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Original Article

Evaluation of Retinal Microvascular Impairment after COVID-19 and its Clinical Correlates Using Optical Coherence Tomography Angiography

Aslıhan Yılmaz Çebi*, Oğuzhan Kılıçarslan**, Didar Uçar***

*Çerkezköy State Hospital, Clinic of Ophthalmology, Tekirdağ, Turkey
**Ayancık State Hospital, Clinic of Ophthalmology, Sinop, Turkey
***İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: Retinal vascular complications have been described in patients with coronavirus disease 2019 (COVID-19). This study aimed to analyze retinal microvascular changes and their correlations with clinical findings.

Materials and Methods: This case-controlled study was conducted in a university hospital. The right eyes of 52 otherwise healthy patients recovered from COVID-19 and 42 healthy controls were examined with optical coherence tomography angiography. Mann-Whitney U test was used to compare vessel density (VD) and foveal avascular zone (FAZ) parameters. Associations with treatment choices, pneumonia, and laboratory findings were analyzed.

Results: Twenty-nine patients (56%) and 18 healthy controls (43%) were men. Mean age of the COVID-19 group was 39.00±13.04 years. Twenty-two patients had pneumonia, 18 (35%) received hydroxychloroquine (HCQ), 17 (33%) received HCQ plus low-molecular-weight heparin (LMWH), and 10 (19%) received favipiravir. The patient group had lower parafoveal VD in the superficial capillary plexus (SCP) and lower parafoveal VD and perifoveal VD in the deep capillary plexus (DCP) than controls (p=0.003, p=0.004, p=0.001). FAZ area did not differ significantly (p=0.953). Perifoveal VD in the DCP was also significantly lower in the HCQ+LMWH group than the HCQ group (p=0.020) and in the presence of pneumonia (p=0.040). C-reactive protein (CRP) and ferritin levels were negatively correlated with perifoveal VD in the DCP (r=-0.445, p=0.023; r=-0.451, p=0.040). Ferritin was also negatively correlated with parafoveal VD in the SCP (r=-0.532, p=0.013).

Conclusion: Parafoveal and perifoveal VD was found to be lower in the COVID-19 group. Presence of pneumonia, need for LMWH prophylaxis, and levels of CRP and ferritin were found to be negatively associated with retinal VD. Large-scale studies are needed to evaluate the clinical importance.

Keywords: Blood supply, diagnostic imaging, inflammation, retina, thromboembolism

Address for Correspondence: Didar Uçar, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
E-mail: didarucar@gmail.com **ORCID-ID:** orcid.org/0000-0002-3469-7307
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Introduction

Coronaviruses are enveloped positive single-stranded RNA viruses which have surface projections that look like a crown. They can infect humans and usually cause pulmonary tract infections.[1] The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused the recent coronavirus disease-2019 (COVID-19) pandemic.[2]

Interaction between SARS-CoV-2 spike (S) protein and angiotensin-converting enzyme 2 (ACE2) is thought to be a crucial pathway of infection.[3,4] ACE2 and other renin-angiotensin-aldosterone system (RAS) proteins have been demonstrated in the conjunctiva, cornea, aqueous humor, retina, and retinal pigment epithelium.[5,6,7,8,9,10]

Early reports of ocular involvement in COVID-19 have generally mentioned conjunctival hyperemia, conjunctival congestion, tearing, and conjunctivitis.[11] Different studies reported the presence of viral RNA in the tear samples of patients with COVID-19.[12] Wu et al.[13] found severe systemic disease is associated with the frequency of ocular surface symptoms. Viral particles were also detected in the iris, trabecular meshwork, and retinal layers.[14] Recent articles showed a variety of vascular and inflammatory conditions in the retinal layers of patients with COVID-19. Central retinal vein occlusion, paracentral acute middle maculopathy, retinal hemorrhages, papillophlebitis, serpiginous choroiditis, acute viral retinitis, and atypical acute retinal necrosis have all been reported.[15,16,17,18,19,20,21,22,23]

In this study, we aimed to compare the retinal microvasculature between otherwise healthy patients who recovered from COVID-19 and healthy individuals with no history of COVID-19 infection. Associations between retinal vascular parameters and treatment alternatives, imaging, and laboratory findings were analyzed. Spectral domain optical coherence tomography angiography (SD-OCTA) was used to obtain en face angiograms.

Materials and Methods

Study Population

This case-controlled study was conducted in accordance with the Declaration of Helsinki. It was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee for Registering Clinical Trials (approval date: July 2020, number: 92001). Informed consent was obtained from all patients and healthy participants.

Patients with confirmed COVID-19 history from the database of İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty in Istanbul, Turkey from 20 July to 20 September 2020 were enrolled in the study. The diagnosis of COVID-19 was defined as two positive reverse transcriptase polymerase chain reaction (RT-PCR) results for SARS-CoV-2 in nasopharyngeal swabs. Patients who received mechanical ventilation or were admitted to the intensive care unit were excluded. Patients were interviewed by telephone and initially questioned about the selection criteria. Eligible patients were invited to the hospital for examination. In order to eliminate confounding factors, patients with chronic systemic diseases affecting the vascular system, such as hypertension, diabetes mellitus, coronary artery disease, and obstructive or restrictive pulmonary disease, were excluded. Patients with body mass index between 18 and 25 were included and those with smoking history were excluded. Eyes with prior ocular surgery, history of ocular trauma, known ocular diseases such as uveitis, glaucoma, retinal disorders, optic nerve abnormalities, and refractive error greater than ±2 diopters spherical equivalent were excluded. None of the patients reported having any ocular symptoms during the active disease period. The right eyes of age- and gender-matched never-smokers with no systemic or ocular diseases were included as healthy controls. None of the controls had jobs or behaviors associated with increased risk of COVID-19.

Data Collection and Image Analysis

Demographic, epidemiological, clinical, laboratory, and radiologic data were obtained from the patients' medical records. All the patients underwent a complete eye examination including dilated fundus examination. Each subject underwent pupil dilation with 1% tropicamide and 2.5% phenylephrine eye drops. En face angiograms were obtained with RTVue XR Avanti (Optovue, Inc., Fremont, CA, USA). SD-OCTA is an innovative technology which allows non-invasive, dye-free imaging of retinal vessels by detecting motion contrast from flowing erythrocytes. SD-OCTA works with an A-scan rate of 70,000 per second and an 840 nm light source.

The built-in split-spectrum amplitude decorrelation angiography (SSADA) algorithm and AngioVue Analytics software (Optovue, Inc., Fremont, CA, USA) were used to process the images, reduce artefacts, and generate indices for automatically segmented en face angiograms. Fovea-centered 6x6 mm HD Angio Retina images were obtained. Parafoveal and perifoveal values were calculated in the areas between the inner and outer ring diameters of 1 to 3 mm and 3 to 6 mm, respectively. Foveal avascular zone (FAZ) measurement was based on the retina slab (internal limiting membrane to outer plexiform layer + 9 µm). Flow areas of the outer retina and choriocapillaris were calculated in a circular area 1 mm in diameter. Images with inadequate quality (signal strength index <40), discontinuous vessel pattern, haziness, and inaccurate retinal segmentation were excluded.

Statistical Analysis

Shapiro-Wilk test was used to evaluate the distribution of continuous variables. Student's t-test was used for comparison between two independent groups when continuous variables were normally distributed; otherwise, the Mann-Whitney U test was used. Kruskal-Wallis test was used for comparison between three independent groups when continuous variables were not normally distributed. Continuous variables were summarized using mean and standard deviation. Comparison of categorical valuables was performed with chi-square test. Categorical

variables were presented as frequencies and percentages. Spearman rank correlation was used to measure the association between non-normally distributed scaled variables. P values below 0.05 were defined as statistically significant. SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) was used for biostatistical analysis.

Results

The medical records of 150 consecutive patients were evaluated. Ninety-seven patients were contacted by phone. Eleven of them could not come to hospital for personal reasons. Of the remaining 86 patients, another 34 were excluded because of previously unknown ocular or systemic diseases and confounders detected during history-taking and examination. Finally, the right eyes of 52 patients and 42 healthy controls were included in the study. The interval between the first positive SARS-CoV-2 RT-PCR result and the dilated eye examination ranged from 67 to 86 days. Of 52 patients, 29 (56%) were male and 23 (44%) were female, and of 42 controls, 18 (43%) were male and 24 (57%) were female. The mean ages of the COVID-19 and control groups were 39.00±13.04 years (range: 20-62) and 36.81±9.29 years (range: 22-58), respectively. The groups did not differ significantly in age (p=0.34) or sex (p=0.30).

Twenty-two patients (42%) in the COVID-19 group had pneumonia on computed tomography and 14 (27%) were hospitalized. Eighteen patients (35%) were given hydroxychloroquine (HCQ), 17 (33%) were given HCQ plus low-molecular-weight heparin (LMWH), and 10 (19%) were given favipiravir. Seven patients (13%) did not receive any treatment. None of the patients were given corticosteroids or tocilizumab. The patients' mean white blood cell count was 6073±1556/µL (range: 3800-9000), mean lymphocyte count was 1838±634 /µL (range: 900-2900), mean C-reactive protein (CRP) level was 14.2±26.4 mg/L (range: 0.6-100.8), mean lactose dehydrogenase (LDH) level was 232±106 U/L (range: 133-543), mean ferritin level was 93±65 µg/L (range: 13-216), and mean D-dimer level was 0.86±1.50 µg/mL (range: 0.19-5.31).

Continuous variables were non-normally distributed according to the results of the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the OCTA parameters of patients and healthy individuals (Table 1). Vessel density (VD) of the superficial parafoveal, deep parafoveal, and deep perifoveal capillary plexus was significantly lower in the COVID-19 group than in healthy individuals (p=0.003, p=0.004, and p=0.001, respectively). Within the COVID-19 patient group, the Mann-Whitney U test was used to determine if there was a difference in VD based on the presence of pneumonia, and the Kruskal-Wallis test was used to see whether there was a difference based on treatment alternatives. The presence of pneumonia had no effect on the VD of the superficial parafoveal or deep parafoveal capillary plexus (p=0.124 and p=0.071, respectively), but VD in the deep perifoveal capillary plexus was significantly lower in patients who had COVID-19 pneumonia (p=0.040). VD of the superficial parafoveal and deep parafoveal capillary plexus did not differ between the HCQ, HCQ+LMWH, and favipiravir subgroups (p=0.182 and p=0.214, respectively). VD of the deep perifoveal capillary plexus, on the other hand, was significantly lower in the HCQ+LMWH subgroup than in the HCQ subgroup (p=0.020). When comparisons were made between the 35 patients who were given HCQ and 17 patients who were given favipiravir or no treatment, there were no differences in the VD of the superficial parafoveal, deep parafoveal, or deep perifoveal capillary plexus (p=0.868, p=0.385, and p=0.640, respectively).

Spearman correlation analysis was used to investigate the correlations between microvascular changes and continuous variables in the COVID-19 group (Table 2). VD in the deep

Table 1. Vessel density, foveal avascular zone area, and choriocapillaris flow area values of patients with COVID-19 history and healthy controls (Mann-Whitney U test)

	COVID-19 group (n=52) mean ± SD	**Control group (n=42) mean ± SD**	**p value**
Foveal VD of SCP (%)	21.68±6.04	22.36±7.66	0.858
Parafoveal VD of SCP (%)	**51.89±3.90**	**54.14±3.20**	**0.003**
Perifoveal VD of SCP (%)	51.14±3.36	52.36±3.03	0.059
Foveal VD of DCP (%)	38.97±5.89	41.22±7.29	0.179
Parafoveal VD of DCP (%)	**55.99±4.29**	**58.32±3.46**	**0.004**
Perifoveal VD of DCP (%)	**53.83±6.34**	**70.76±8.28**	**0.001**
FAZ area (mm^2)	0.255±0.068	0.257±0.101	0.953
Flow area of CC (mm^2)	2.127±0.109	2.101±0.097	0.166

CC: Choriocapillaris, COVID-19: Novel coronavirus disease 2019, DCP: Deep capillary plexus, FAZ: Foveal avascular zone, SCP: Superficial capillary plexus, SD: Standard deviation, VD: Vessel density. Significant p values (p<0.05) are marked in bold.

Table 2. Spearman correlation analysis for laboratory findings and the interval between diagnosis and optical coherence tomography angiography imaging in the COVID-19 group

N=52	Parafoveal VD of SCP	Parafoveal VD of DCP	Perifoveal VD of DCP
WBC	r =-0.059 p= 0.776	r=0.221 p=0.277	r=0.145 p=0.481
Lymphocytes	r=0.225 p=0.269	r=-0.077 p=0.709	r=0.026 p=0.900
CRP	r=-0.170 p=0.405	r=-0.233 p=0.251	**r=-0.445** **p=0.023**
LDH	r=-0.049 p=0.812	r=0.080 p=0.698	r=0.036 p=0.861
Ferritin	r =-0.175 p=0.448	**r=-0.532** **p=0.013**	**r=-0.451** **p=0.040**
D-dimer	r=0.090 p=0.699	r=0.249 p=0.277	r =-0.036 p=0.877
Time since COVID-19 diagnosis	r =-0.023 p=0.871	r =-0.019 p=0.896	r =-0.085 p=0.548

CRP: C-reactive protein, DCP: Deep capillary plexus, LDH: Lactate dehydrogenase, SCP: Superficial capillary plexus, VD: Vessel density, WBC: White blood cells. Significant p values (p<0.05) are marked in bold

parafoveal capillary plexus was found to be negatively correlated with ferritin level (r=-0.532, p= 0.013). VD in the deep perifoveal capillary plexus was found to be negatively correlated with CRP and ferritin levels (r=-0.445, p=0.023 and r=-0.451, p=0.040, respectively). The interval between the diagnosis of COVID-19 and OCTA imaging did not significantly correlate with the decrease in parafoveal and perifoveal VD in the superficial or deep capillary plexus (p>0.05).

Discussion

Involvement of the retinal microvasculature is important because the retinal circulation is an end-arterial system, thus microvascular complications have the potential to cause visual impairments.[24] In our study, VD of the superficial parafoveal, deep parafoveal, and deep perifoveal capillary plexus were reduced in patients with a history of COVID-19 (Table 1).

Similarly, Turker et al.[25] found that VD in the superior and nasal superficial parafoveal capillary plexus and all quadrants of the deep capillary plexus were lower in patients with COVID-19 history. However, they examined eligible patients as soon as PCR negativity was demonstrated. Moreover, the inclusion of both eyes of the patients may be considered a confounder. In our study, the time between COVID-19 diagnosis and examination was 67 to 86 days. The decreased VD observed in our patient group suggests that COVID-19 might cause long-term microvascular impairment.

SARS-CoV-2 viral RNA was detected in the retinal layers of three deceased patients with COVID-19.[26] Nucleocapsid protein antigens of SARS-CoV-2 were described in the iris and trabecular meshwork of another patient.[27] The main pathogenesis of SARS-CoV-2 is thought to be the interaction between the S protein of viral spikes and ACE2 receptor.[28] Therefore, endothelial ACE2 expression in the retina could be a possible target for viral antigens.[29,30] Hematogenous spread of the viral load may cause the destruction of ACE2 receptors. Diminished ACE2 expression in neurosensory retinal cells and the retinal vasculature may cause inflammation and oxidative stress, both of which could result in the impairment of neurovascular autoregulation, and may alter flow regulation in the retina, retinal pigment epithelium, choroid, and optic disc through the intraocular local RAS.[31-33]

Recent articles emphasized the thromboembolic effects of COVID-19 on the retinal layers. Outer retinal abnormalities, acute macular neuropathy, paracentral acute middle maculopathy, and central retinal vein occlusion were reported.[15,16,17,34] In a meta-analysis, D-dimer levels greater than 0.5 µg/mL on admission were found to be associated with more severe disease course.[35] Anticoagulant and antiplatelet agents have been given to prevent or treat thromboembolic complications.[36,37] In our study, 17 patients needed LMWH prophylaxis. Although higher levels of D-dimer did not correlate with microvascular changes, VD of the deep perifoveal capillary plexus was significantly lower in the HCQ+LMWH subgroup than in the HCQ subgroup (p=0.020). Also, Guemes-Villahoz et al.[38] found that patients with D-dimer levels higher than 0.5 µg/mL showed lower macular VD. Thus, COVID-19 related risks for microangiopathy and microthrombi may explain the underlying mechanism for decreased VD. Reperfusion injury following an ischemic episode could be another explanation for the persistence of microvascular alterations.[39]

COVID-19-related cytokine storm is widely recognized and addressed in treatment algorithms.[40,41] Recent studies reported inflammatory conditions like papillophlebitis, serpiginous choroiditis, acute viral retinitis, and acute retinal necrosis in patients with COVID-19.[20,21,22,23] In our study, CRP levels were

found to be negatively correlated with perifoveal VD of the deep capillary plexus (r=-0.445, p=0.023), and ferritin levels were found to be negatively correlated with both parafoveal and perifoveal VD in the deep capillary plexus (r=-0.532, p=0.013 and r=-0.451, p=0.040, respectively). Hazar et al.[42] found that VD values were negatively correlated with the white blood cell and neutrophil counts of patients who recovered from COVID-19. Therefore, a hyperinflammatory state may cause endothelial dysfunction that results in reduced VD in the retinal microvasculature. Considering the high vascularity of the ocular tissues and the endothelial ACE2 expression, localized vasculitis can decrease VD.[43]

A cross-sectional study examining the eyes of 46 patients hospitalized with severe COVID-19 pneumonia showed that there were no retinal pathologies except for one opportunistic chorioretinal infection.[44] In our study, we found the VD of the perifoveal deep capillary plexus was significantly lower when the pneumonia was present (p=0.040). To the best of our knowledge, there is no previous study about the possible effects of community- or hospital-acquired pneumonia on retinal vessels.

Long-term HCQ treatment was found to be related to reduced VD and larger FAZ in previous OCTA studies.[45,46] However, these patients had chronic rheumatologic diseases and needed immunomodulatory therapy for more than 5 years. In our study, none of the patients had comorbidities, they received HCQ for 5 to 10 days, and Kruskal-Wallis analysis revealed no differences between patients who did and did not receive HCQ. Currently, there is no consistent evidence regarding HCQ-related retinal toxicity in patients with COVID-19.[47]

To summarize, our study demonstrated impairment of the retinal microvascular circulation of patients with a history of COVID-19, even though they had no baseline comorbidities. These alterations may be associated with the presence of pneumonia, higher CRP and ferritin levels, and the need for LMWH therapy. Reduced VD might occur due to the ACE2-related vascular tropism of SARS-CoV-2, intraocular RAS dysregulation, thrombosis predisposition, reperfusion injury, and inflammation. Further research must be done to establish the role of these theories in the pathogenesis of ocular and vascular involvement.

Study Limitations

We would like to acknowledge the limitations of our study. Regarding the ongoing spread of the virus, we did not include patients with active COVID-19 infection. Due to the restricted clinical labor, we were only able to investigate a relatively small sample size. Another possible confounder is the heterogenous severity of COVID-19. Because of the small sample size, we were not able to thoroughly analyze the relationships between disease severity, systemic indicators, different treatment choices, and OCTA parameters. In addition, it was a cross-sectional study. As a result, it is unclear how long these changes will be evident. Large-scale prospective cohort studies with proper post-hoc analysis of subgroups can be helpful to understand the vascular impact of COVID-19. On the other hand, the presence of a healthy control group, the rarity of systemic confounding factors, and exclusion of the fellow eyes can be regarded as strengths of our study design.

Conclusion

In our study, patients who recovered from COVID-19 had lower VD in the parafoveal superficial capillary plexus and in both the parafoveal and perifoveal deep capillary plexus. Presence of pneumonia, need for LMWH prophylaxis, and higher levels of CRP and ferritin may be associated with these changes. More investigation is needed to evaluate the clinical importance of these microvascular changes.

Ethics

Ethics Committee Approval: Approval was obtained from the İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine (approval date: 17 July 2020, number: 92001). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed Consent: Written and oral informed consent was obtained from all individual participants included in the study. The participants have consented to publishing their data.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y.Ç., O.K., Concept: A.Y.Ç., O.K., D.U., Design: A.Y.Ç., O.K., D.U., Data Collection or Processing: A.Y.Ç., O.K., Analysis or Interpretation: A.Y.Ç., O.K., D.U., Literature Search: A.Y.Ç., O.K., Writing: A.Y.Ç., O.K., D.U.

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