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Original Article

Assessment of the optic nerve, macular, and retinal vascular effects of COVID-19

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Objective: To evaluate the effects of SARS-CoV-2 infection on the optic nerve, macula, and retinal vascular structures.

Methods: This study included 129 participants recovering from COVID-19 and 130 healthy control subjects aged 18 to 55 years. The study was designed as observational and cross-sectional and was conducted between June 2020 and February 2021. The average thicknesses of the retinal nerve fibre layer (RNFL), ganglion cell complex (GCC), and macula also were measured using a spectral domain optical coherence tomography analysis. The vessel densities of the superficial and deep capillary plexuses of the macula, foveal avascular zone, and radial peripapillary capillary plexus of the optic disc were quantified by optical coherence tomography angiography.

Results: In all quadrants, the RNFL and GCC were thinner in patients with neurologic symptoms of COVID-19 ($p < 0.05$). None of the measurements of the Early Treatment Diabetic Retinopathy Study regions significantly differed between patients with and without COVID-19 symptoms ($p > 0.05$). The foveal avascular zone area, perimeter, circularity index, and vessel densities (%) of the global and inner and outer circles of superficial capillary plexuses and deep capillary plexus and global and superior and inferior halves of the radial peripapillary capillary plexus measurements were found to significantly differ between the symptomatic COVID-19 group and the asymptomatic COVID-19 and control groups ($p < 0.05$).

Conclusion: RNFL and GCC thickness evaluation with optical coherence tomography and vessel density evaluation with optical coherence tomography angiography can be considered remarkable diagnostic methods for retinal neurovascular abnormalities and a biomarker for microvascular abnormalities after infection with SARS-CoV-2.

The pathogen of COVID-19, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an RNA virus that primarily affects the upper and lower respiratory tracts.[1–3] The novel type of coronavirus disease (COVID-19), first detected in Wuhan, China, in December 2019, was declared a pandemic by the World Health Organization in March 2020.[4] As is known, COVID-19 is a disease that has effects on the central nervous and cardiovascular systems as well as the respiratory system.[5–7] In individuals who have had COVID-19 disease, retinal tissue also may vary depending on the effects on the central nervous or vascular system.[8,9]

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on cell surfaces, and the virus–receptor interaction is thought to reduce ACE2 action and increase levels of angiotensin II, a strong capillary vasoconstrictor, which propagates microvascular damage.[10]

This study aimed to investigate the possible effects of COVID-19 disease on the optic nerve, macula, and retinal vascular structure.

Methods

This study was designed as observational and cross-sectional study and was conducted in the Ophthalmology, Pulmonology and Infectious Diseases Departments of the Erzincan Binali Yildirim University Faculty of Medicine between June 2020 and February 2021. Ethical approval was obtained from the local ethics committee (Approval Number E-21142744-804.99-70916), and detailed informed consent was taken from all participants. The principles of the Declaration of Helsinki were adhered to throughout this study.

Study design and participants

Patients diagnosed with COVID-19 confirmed by laboratory-confirmed SARS-CoV-2 infection based on a positive polymerase chain reaction (PCR) test by an infectious diseases specialist and (or) a pulmonologist were included in the study. All patients in the COVID-19 group included in the study were called for ophthalmologic examinations after PCR negativity was observed. All the patients were included in this study at the earliest 29 and the latest 45 days after COVID-19 PCR positivity was detected. The participants with COVID-19 were divided into 3 groups according to their admission symptoms as neurologic, non-neurologic (e.g., respiratory, cardiovascular, and gastrointestinal), and asymptomatic or paucisymptomatic. Asymptomatic patients included in the study consisted of patients who had a history of contact with patients with COVID-19 and who wanted to have a PCR test without

https://doi.org/10.1016/j.jcjo.2022.06.016
ISSN 0008-4182

Table 1—Systemic examination results of the COVID-19 group at presentation

Symptom	n (%)
Respiratory symptoms	
Cough	21/129 (16.3%)
Sore throat	14/129 (10.9%)
Rhinorrhea, sneezing	7/129 (5.4%)
Pneumonia	20/129 (15.5%)
Dyspnea	12/129 (9.3%)
Hypoxemia	11/129 (8.5%)
Neurologic symptoms	
Hyposmia/anosmia	7/129 (5.4%)
Hypogeusia/ageusia	7/129 (5.4%)
Visual disturbance	4/129 (3.1%)
Fatigue, somnolence	11/129 (8.5%)
Headache	18/129 (14%)
Dizziness	9/129 (7%)
Myalgia	12/129 (9.3%)
Tinnitus	6/129 (4.7%)
Diplopia	3/129 (2.3%)
Cardiovascular symptoms	
Chest pain	10/129 (7.8%)
Arrhythmia	7/129 (5.4%)
Sinus tachycardia	5/129 (3.9%)
Blood coagulation	13/129 (10.1%)
Arterial or venous thromboembolism	10/129 (7.8%)
Pulmonary embolism	7/129 (5.4%)
Gastrointestinal symptoms	
Nausea and vomiting	11/129 (8.5%)
Diarrhea	9/129 (7%)
Loss of appetite	10/129 (7.8%)
Abdominal pain	8/129 (6.2%)
Bloating	7/129 (5.4%)
Heartburn	5/129 (3.9%)

any complaints. Systemic examination results of the COVID-19 group at presentation are shown in Table 1. Patients were also divided into symptomatic and asymptomatic in the COVID-19 group.

The demographic and clinical data of 184 patients who recovered completely from COVID-19 were evaluated. Fifty-five participants were excluded from the study based on the criteria given in the following section. The final sample included 129 participants recovering from COVID-19 and 130 control subjects aged between 18 and 55 years with a visual acuity of ≥20/20, axial length of 22−24.5 mm, refractive error spherical equivalent of ±3 D or less, and intraocular pressure (IOP) of 21 mm Hg or less. All the control subjects were evaluated between 2018 and 2019 for the normative data assessment of vessel density and foveal avascular zone metrics using AngioScan software study in our clinic. Only the right eyes of all the participants were included.

Exclusion criteria

Individuals who had systemic diseases, such as hypertension, diabetes, and cardiovascular and neurologic problems; those with ocular disorders such as glaucoma, cataract, retinal vascular, and (or) macular diseases; those with previous ocular surgery and/or trauma; and those who had 2 or more of the neurologic, cardiovascular, respiratory, and gastrointestinal admission symptoms, were excluded from the study.

Ophthalmological examinations

A detailed ophthalmologicalal examination was performed, including autorefractometry (Tonoref III, Nidek Co Ltd, Bunkyo City, Japan), best-corrected visual acuity analysis, slit-lamp biomicroscopy, and IOP measurement with a Goldmann applanation tonometer. The axial length was measured with the ALSCAN (Nidek Co. Ltd) device in all patients.

Pulmonological examinations

The patients' complaints, such as cough, fever, weakness, fatigue, joint pain, shortness of breath, headache, sore throat, chest pain, back pain, decreased sense of smell and taste, and diarrhea, were questioned. Respiratory system examinations (i.e., inspection, percussion, palpation, and auscultation) were performed. Laboratory examinations that could suggest macrophage activation syndrome (e.g., hemogram, routine biochemistry, acute-phase reactants, and parameters such as ferritin, D-dimer, and fibrinogen) also were examined. In addition, the patients were radiologically evaluated in terms of COVID-19 using thoracic computed tomography (16-slice computed tomography canner; Sensation 16, Siemens Medical Systems, Erlangen, Germany), posteroanterior chest radiography, and PCR.

Infectious disease examinations

Patients were evaluated in terms of oral cavity mucosal involvement, cervical lymphadenopathies, thyroid sensitivity, cardiac murmurs, abdominal sensitivity, and rashes. The complete blood count, serum C-reactive protein, procalcitonin, D-dimer, and ferritin levels were measured.

COVID-19 treatment algorithm

The treatment algorithm recommended by the Ministry of Health of the Republic of Turkey was followed for the symptomatic patients diagnosed with COVID-19 based on PCR positivity. This algorithm includes favipiravir 1600 mg/day for 3 days, 600 mg/day for 5 days for maintenance, and enoxaparin 4000 mIU/mL per day (body mass index <30 kg/m^2) or 8000 mIU/mL per day (body mass index >30 kg/m^2) for 1 week. In severe cases, the maintenance dose of favipiravir was extended to 10 days and enoxaparin to 14 days.

Optical coherence tomography and optical coherence tomography angiographyscan procedures

The macular and peripapillary thicknesses were measured using a spectral-domain Optical coherence tomography (SD-OCT) device (Nidek Co Ltd). The Nidek RS-3000 Advance OCT system was used to evaluate the SD-OCT images. The average thicknesses of the retinal nerve fibre layer (RNFL), ganglion cell complex (GCC), and macula

also were determined with SD-OCT analysis. The RNFL measurements for the mean, superior, inferior, temporal, and nasal quadrants were performed from a 6×6 mm^2 ring centred on the optic nerve head and recorded. From the 6×6 mm^2 macular map, macular thicknesses were measured from the 9 zones described by the Early Treatment Diabetic Retinopathy Study (ETDRS), and the superior and inferior GCC thicknesses also were recorded. The subfoveal choroidal thickness was measured at 3 points (central foveal, 500 μm nasal, and temporal of the central foveal), and the average of these 3 values was determined as the final thickness.

The vessel densities of the superficial (SCP) and deep capillary plexuse (DCP) of the macula, foveal avascular zone (FAZ), and the vessel density of the radial peripapillary capillary plexus (RPCP) for the optic disc were quantified using OCT- angiographyscan (OCT-A; RS-3000 Advance, Nidek Co Ltd). Updated AngioScan software (version 1.8.0; Navis, Gamagori, Japan). of Nidek's RS-3000 Advance system was used to evaluate the OCT-A images. This software automatically calculates the macular and peripapillary vessel densities as well as the FAZ. The fovea was focused on using an OCT-A prototype internal fixation lamp, and 3×3 mm^2 macular cubes, each consisting of 256 B-scans, were generated. For the retinal peripapillary capillary plexus, the scans included a 2.4×4 mm^2 disc map centred on the optic nerve head. The updated software of Nidek's RS-3000 Advance device allows removing the projection artifacts of OCT-A scans through the ALL Layers projection artifact removal feature. From the macular OCT-A scans, the FAZ circularity index (values closer to 1 indicate higher circularity), area and perimeter, and the vessel densities of the global whole-image SCP and DCP, outer and inner superficial capillary plexuses, deep capillary plexus rings, and 9 ETDRS regions were evaluated.

SD-OCT and OCT-A measurements were performed by an experienced ophthalmologist after pupil dilation with a 1% tropicamide eye drop (Tropamid, Bilim Ilac Ltd, Istanbul, Turkey). In cases where the signal strength index quality was <7/10, scanning was repeated. FAZ (with a 3×3 mm^2 OCT-A measurement field) and the vessel densities of the SCP and DCP were measured. Automated segmentation was performed to determine the en face slab for the superficial and deep retinal layers extending from the internal limiting membrane to 13 μm below the inner nuclear layer and from 8 μm below the inner nuclear layer to 13 μm below the outer nuclear layer, respectively. Vessel densities were calculated as the percentage area filled by flowing blood vessels in the selected region. The vessel density of RPCP for the superior/inferior (S/I) and temporal superior nasal inferior temporal (TSNIT) sectors was obtained from the OCT-A scans of the peripapillary area. In the study, all the numerical values of the vessel densities were obtained automatically by the OCT-A device. The segmentation algorithm also was selected automatically by the device.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, Ill.) version 23.0 was used for statistical analysis of the data. G-Power analysis was not performed because the study was exploratory. Data on continuous variables were expressed as mean ± SD and those of categorical variables as frequency and percentages. Whether the data were normally distributed was determined with the Shapiro–Wilk test. In the analysis comparing the groups, the analysis of variance test with the Bonferroni correction was performed for continuous variables with a normal distribution and the Mann–Whitney U test for the comparison of quantitative data without a normal distribution. The Pearson and Spearman correlation tests were used to evaluate the correlations between variables. After checking collinearity diagnostics, a multivariate regression analysis corrected for age, sex, image quality, intraocular pressure, and axial length was used to determine the associations between the RNFL and GCC thicknesses as dependent variables and the vessel densities of the SCP, DCP, and RPCP as independent variables in the COVID-19 group. Statistical results were stated at the 95% CI and given with the regression coefficient (β) in the regression analysis. Statistical significance was evaluated at the level of $p < 0.05$.

Results

Demographic and clinical data

The demographic and clinical data of the participants are presented in Table 2. A total of 129 participants recovering from COVID-19 and 130 control subjects were enrolled in the study. Only the right eyes of all the participants were included in the evaluations. All the participants were white. Sixty-seven of the individuals in the COVID-19 group and 68 in the control group were female ($p > 0.05$). The mean age was 42.3 ± 13.8 years (range, 18–55 years) in the COVID-19 group and 44.9 ± 12.4 years (range, 18–55

Table 2—Demographic, ophthalmologic, and clinical data on the study participants

Factor	COVID-19	Control	*p* Value
Number of participants	129	130	—
Sex (F/M)	64/60	68/62	>0.05
Mean age ± SD (y)	42.3 ± 13.8	44.9 ± 12.4	>0.05
Mean BCVA ± SD (logMAR)	−0.07 ± 0.06	−0.06 ± 0.05	>0.05
Average IOP ± SD (mm Hg)	15.2 ± 4.5	15.1 ± 4.3	>0.05
Mean AL ± SD (mm)	23.05 ± 1.1	23.12 ± 0.92	>0.05
Asymptomatic/paucisymptomatic	32/129	—	—
Neurologic symptoms	38/129	—	—
Cardiovascular symptoms	17/129	—	—
Respiratory symptoms	29/129	—	—
Hospitalization	58/129	—	—
Oxygen therapy	42/129	—	—
Intensive care requirement	8/129	—	—

F = female; M = male; BCVA = best-corrected visual acuity; IOP = intraocular pressure;
AL = axial length

years) in the control group. There were no differences between the 2 groups in terms of mean age, best-corrected visual acuity, IOP, and axial length ($p > 0.05$). And in addition, there were no significant differences between the subgroups in patients with COVID-19 in terms of age and sex ($p > 0.05$). Severe cases were hospitalized. Hospitalization rates were 18 of 38 (47.4%) in patients with neurologic symptoms and 40 of 59 (67.8%) in patients with nonneurologic symptoms. In patients with neurologic symptoms, 8 (21%) were taking oxygen therapy, whereas in patients with nonneurological symptoms, 34 (57.6%) were taking oxygen therapy. Only the patients who needed intensive care were intubated. All patients needing intensive care were admitted with nonneurological symptoms.

Systemic examination and laboratory results

The results of the systemic examination are shown in Table 1. Thirty-two of the patients with COVID-19 were asymptomatic or paucisymptomatic at the time of admission. Of the remaining patients in the COVID-19 group, 38 had predominantly neurological symptoms, and 59 had predominantly nonneurological symptoms (respiratory in 29, cardiovascular in 17, and gastrointestinal in 13 patients) at the time of admission. Laboratory findings of the study participants with COVID-19 at first visit are presented in Table 3.

Optical coherence tomography and optical coherence tomography angiographyscan measurement results

The results of the OCT measurements are shown in Table 4. In all quadrants, the RNFL and GCC were thinner in patients with neurologic COVID-19 symptoms ($p < 0.05$). None of the measurements of the ETDRS regions significantly differed between the COVID-19 and control groups ($p > 0.05$).

The mean and SD values of the FAZ area, perimeter and CI, and vessel densities of the SCP, DCP, and RPCP are shown in Table 5. The FAZ area, perimeter, and CI and the vessel densities (%) of the global, inner, and outer circles of SCP and DCP and global, superior, and inferior parts of the RPCP measurements were found to significantly differ between the symptomatic COVID-19 group and the asymptomatic COVID-19 and control groups ($p < 0.05$).

Multiple regression analyses showed in symptomatic COVID-19 patients a significant relationship between reduced average thickness of the RNFL and GCC and impaired OCT-A parameters ($r = 0.894$ and $r = 0.799$; p

Table 3—Laboratory findings of participants with COVID-19 at first visit

Laboratory test	Asymptomatic	Neurologic	Nonneurologic	*p* Value
Neutrophils ($\times 10^3/\mu$L)	6.22 ± 2.15	8.19 ± 3.74	10.36 ± 4.98	**<0.001**
Lymphocytes ($\times 10^3/\mu$L)	2.17 ± 0.92	1.06 ± 2.56	0.68 ± 0.57	**<0.001**
Platelets ($\times 10^3/\mu$L)	417.45 ± 58.16	421.87 ± 52.8	419.75 ± 60.32	0.297
Monocytes ($\times 10^3/\mu$L)	0.6 ± 0.25	1.2 ± 0.52	1.19 ± 0.65	**<0.001**
Serum C-reactive protein (mg/L)	2.14 ± 1.56	7.8 ± 5.9	8.2 ± 6.8	**<0.001**
Procalcitonin (ng/mL)	0.04 ± 0.02	0.18 ± 0.09	0.23 ± 0.11	**<0.001**
D-Dimer (quantitative)	167.81 ± 99.54	415.68 ± 164.3	521.67 ± 178.95	**<0.001**
Fibrinogen (mg/dL)	321.54 ± 102.87	408.27 ± 97.64	423.38 ± 115.78	**0.014**

Note: Significant *p* values are shown in boldface.

Table 4—Optical coherence tomography measurements of the study groups

Measurement	Neurologic COVID-19	Nonneurologic COVID-19	Asymptomatic COVID-19	Control	*p* Value
RNFLT (μm), mean	104.18 ± 12.48	112.85 ± 14.27	112.48 ± 14.58	113.72 ± 13.42	**<0.001*/0.789†**
RNFLT (μm), superior	125.78 ± 17.52	133.27 ± 16.44	134.64 ± 18.54	135.38 ± 17.79	**0.001**/0.352
RNFLT (μm), nasal	72.8 ± 10.1	78.2 ± 7.54	79.13 ± 8.15	79.27 ± 7.98	**<0.001**/0.458
RNFLT (μm), inferior	136.7 ± 19.45	145.87 ± 30.84	144.54 ± 32.46	145.29 ± 33.55	**0.002**/0.528
RNFLT (μm), temporal	72.04 ± 13.16	75.23 ± 11.45	76.83 ± 12.88	76.14 ± 12.74	**0.004**/0.744
MT (μm), outer ring superior	339.54 ± 17.82	335.4 ± 19.21	336.62 ± 19.81	338.64 ± 19.82	0.141/0.214
MT (μm), outer ring inferior	343.19 ± 18.59	346.78 ± 17.89	344.22 ± 16.79	343.25 ± 16.87	0.605/0.389
MT (μm), outer ring nasal	324.76 ± 18.28	326.24 ± 18.54	325.88 ± 19.23	326.76 ± 18.95	0.334/0.457
MT (μm), outer ring temporal	328.44 ± 16.12	328.88 ± 19.67	325.78 ± 18.23	328.44 ± 17.99	0.298/0.197
MT (μm), inner ring superior	352.36 ± 17.26	350.26 ± 18.43	352.16 ± 16.94	349.76 ± 17.83	0.117/0.274
MT (μm), inner ring inferior	343.82 ± 16.55	345.82 ± 16.77	346.74 ± 14.28	342.82 ± 15.37	0.159/0.091
MT (μm), inner ring nasal	344.74 ± 17.29	342.88 ± 16.28	341.48 ± 15.55	342.64 ± 17.16	0.798/0.925
MT (μm), inner ring temporal	328.29 ± 14.57	327.48 ± 15.72	329.4 ± 14.84	328.49 ± 15.58	0.682/0.547
CFST (1 mm)	256.92 ± 18.75	257.6 ± 14.66	259.04 ± 12.4	256.91 ± 14.85	0.125/0.243
GCCT (μm), upper quadrant	95.86 ± 9.11	111.24 ± 8.75	110.4 ± 7.2	108.96 ± 8.1	**<0.001**/0.324
GCCT (μm), lower quadrant	98.77 ± 6.44	111.21 ± 7.13	109.9 ± 6.5	108.51 ± 7.2	**<0.001**/0.278
Subfoveal choroidal thickness (μm)	276.9 ± 54.28	278.11 ± 47.34	279.54 ± 52.5	277.98 ± 54.1	0.317/0.385

RNFLT, retinal nerve fibre layer thickness; MT, macular thickness; CFST, central foveal subfield thickness; GCCT, ganglion cell complex thickness

Note: The significant *p* values are shown in boldface.

*Difference compared with all remaining groups (ANOVA test).

†Difference compared with 3 (nonneurological, asymptomatic, and control) groups (ANOVA test).

Table 5—Measurements of the FAZ area, perimeter and CI, and the vessel densities of SCP, DCP, and RPCP in the study groups

Area	Neurologic COVID-19	Nonneurologic COVID-19	Asymptomatic COVID-19	Control	*P* (*/¥/ϕ)
FAZ area (mm^2)	0.38 ± 0.21	0.37 ± 0.12	0.32 ± 0.11	0.31 ± 0.15	<0.001*/0.021†/<0.001‡
FAZ perimeter (mm)	2.99 ± 0.58	2.97 ± 0.62	2.88 ± 0.54	2.9 ± 0.6	<0.001/0.001/<0.001
FAZ CI	0.37 ± 0.17	0.38 ± 0.16	0.49 ± 0.2	0.52 ± 0.15	<0.001/<0.001/<0.001
SCP, global VD (%)	38.22 ± 3.75	39.1 ± 3.24	41.9 ± 2.82	42.9 ± 2.3	0.001/<0.001/0.001
SCP, inner circle VD (%)	34.33 ± 4.11	35.24 ± 4.84	38.98 ± 4.78	39.6 ± 4.2	0.001/<0.001/<0.001
SCP, outer circle VD (%)	47.85 ± 5.19	49.23 ± 5.82	51.79 ± 5.9	52.01 ± 5.25	0.001/0.001/0.001
DCP, global VD (%)	34.56 ± 4.75	35.22 ± 4.73	38.49 ± 4.24	38.6 ± 3.98	<0.001/<0.001/<0.001
DCP, inner circle VD (%)	27.74 ± 4.89	28.25 ± 4.92	33.82 ± 4.84	33.9 ± 5.18	<0.001/<0.001/<0.001
DCP, outer circle VD (%)	46.8 ± 4.71	47.5 ± 4.8	53.2 ± 3.52	53.75 ± 3.79	<0.001/0.001/<0.001
RPCP, global VD (%)	50.78 ± 6.12	51.39 ± 5.82	56.98 ± 5.27	57.4 ± 5.19	0.001/0.002/.001
RPCP, superior half VD (%)	51.68 ± 5.88	52.54 ± 4.82	57.32 ± 4.85	56.98 ± 4.78	0.001/0.001/<0.001
RPCP, inferior half VD (%)	50.19 ± 5.23	52.87 ± 4.35	56.83 ± 4.36	57.21 ± 4.15	<0.001/0.001/<0.001

FAZ = foveal avascular zone; CI = circularity index; SCP = superficial capillary plexus; VD = vessel density; DCP = deep capillary plexus; RPCP = retinal peripapillary capillary plexus

Note: Significant *p* values are shown in boldface.

*Difference compared with all the remaining groups (ANOVA test).

†Difference compared with 3 (nonneurologicl, asymptomatic, and control) groups (ANOVA test).

‡Difference compared with symptomatic (neurologic and nonneurologic) groups and nonsymptomatic (asymptomatic and control) groups (*t* test).

= 0.001 and $p = 0.002$, respectively), particularly with DCP, RPCP, and FAZ measurements (Table 6).

Discussion

In this study, RNFL and GCC measurements were significantly lower in the patients who presented with the neurologic symptoms of COVID-19 disease. In addition, the SCP, DCP, and RPCP measurements of the patients with symptomatic COVID-19 were significantly lower than those of the asymptomatic COVID-19 and control groups. In the participants with symptomatic COVID-19, the FAZ area and perimeter measurements were significantly higher, and the FAZ CI measurements were significantly lower.

Table 6—Multiple linear regression model between the RNFL and GCC and OCTA parameters in the symptomatic COVID-19 group

Factor	*r* Value	ANOVA *p* value	*β* value	*p* value
RNFL average	0.894	0.001	—	—
FAZ perimeter (mm)			2.584	0.003
FAZ CI			−1.911	0.001
SCP, global VD (%)			0.618	0.124
SCP, inner circle VD (%)			0.297	0.387
SCP, outer circle VD (%)			0.465	0.215
DCP, global VD (%)			2.978	0.001
DCP, inner circle VD (%)			−1.984	0.001
DCP, outer circle VD (%)			2.112	0.002
RPCP, global VD (%)			−1.499	0.015
RPCP, superior half VD (%)			0.785	0.003
RPCP, inferior half VD (%)			−3.147	0.005
GCC AVERAGE	0.799	0.002	—	—
FAZ perimeter (mm)			−1.768	0.001
FAZ CI			3.678	0.002
SCP, global VD (%)			0.714	0.687
SCP, inner circle VD (%)			0.692	0.341
SCP, outer circle VD (%)			0.315	0.246
DCP, global VD (%)			1.147	0.003
DCP, inner circle VD (%)			1.548	0.002
DCP, outer circle VD (%)			2.479	0.001
RPCP, global VD (%)			−1.984	0.001
RPCP, superior half VD (%)			−2.596	0.007
RPCP, inferior half VD (%)			2.687	0.003

ANOVA = analysis of variance; RNFL = retinal nerve fibre layer; GCC = ganglion cell complex; VD = vessel density; FAZ = foveal avascular zone; CI = circularity index; SCP = superficial capillary plexus; DCP = deep capillary plexus; RPCP = retinal peripapillary capillary plexus

Note: Significant *p* values are shown in boldface. Multiple linear regression model, statistically significant $P < 0.05$.

COVID-19 disease has been found to cause prothrombotic status in patients, but its long-term outcomes remain unknown.[11–13] In COVID-19 disease, many organs and systems are involved because of the direct and indirect effects of the SARS-CoV-2 virus. Therefore, theoretically, COVID-19 can be expected to affect all organs in the body that contain vessels. In patients with symptomatic COVID-19, subnormal oxygenation levels are present, and therefore, supplemental oxygen is required for an extended period. This also can account for retinal vessel density decreases in patients with symptomatic COVID-19. However, this study was performed after patients had completely recovered from COVID-19 disease, and therefore, the acute effects of hypoxia or hyperoxia on retinal vessel density in SARS-CoV-2 infection remain uncertain. Different studies have shown that oxygen status has effects on retinal vessel density lasting from a few minutes to a few days.[14–16]

The reduction in vessel densities can be explained by multiple mechanisms due to COVID-19 infection, including thromboinflammatory microangiopathy and angiotensin-converting enzyme 2 (ACE-2) disruption.[17,18] SARS-CoV-2-related microvascular damage is assumed to occur due to complement activation.[19] Complement-mediated thrombotic vasculopathy activates platelet and leukocyte recruitment, coagulation, and endothelial cell dysfunction.[20,21] Impairment in the local renin-angiotensin system due to endothelial injury causes the high endothelial expression of ACE-2 receptors that are used by SARS-CoV-2 to enter into the cell. Then endothelial damage results in the hypercoagulopathy and microvessel occlusion seen in COVID-19 infection.[20] An important finding that has been reported previously is that the human eye structures, including the ciliary body, choroid, retina, and retinal pigment epithelium, have significant levels of ACE-2 receptors.[22] Thus COVID-19 infection is considered to damage the chorioretinal vasculature.

Cennamo et al.[23] investigated changes in the retinal vessel density in the macular and papillary regions in patients with post-SARS-CoV-2 pneumonia using OCT-A and found a decrease in the vessel density of the retina in those who had recovered from the disease. Zapata et al.[24] showed that patients with moderate and severe SARS-CoV-2 pneumonia had decreased central retinal vessel densities compared with asymptomatic or paucisymptomatic patients or control subjects. Similarly, in this study, the vessel densities of the SCP, DCP, and RPCP were significantly lower in the symptomatic COVID-19 group. Savastano et al.[25] reported a reduction in the RPCP vessel densities of patients 1 month after they had recovered from COVID-19. However, Abrishami et al.[26] found that the SCP and DCP vessel densities were reduced in COVID-19 patients versus normal control subjects and that the FAZ was enlarged. In this study, the vessel densities of the SCP, DCP, and RPCP were reduced in the COVID-19 group according to the OCT-A measurements.

In this study, OCT and OCT-A showed a significant relationship between the RNFL and GCC thicknesses and the DCP and RPCP in symptomatic COVID-19 patients. Yu et al.[27] reported a positive correlation between RPCP density and RNFL thickness in the same healthy human eyes in their study. There was no relationship between OCT parameters and SCP values in symptomatic COVID-19 patients in that study. The vascular structure of the DCP is characterized by a fine capillary network that makes it more vulnerable to thrombotic events than to the greater vascular diameter of the SCP.[28] These previous studies support the multiple regression analyses results of our study.

This study has certain limitations. First, because the patients were not evaluated in the acute period of the infection, we did not have the chance to observe the possible retinal findings of any patient in the active phase of COVID-19. Second, patients with cardiovascular symptoms were not examined as a separate group, and potential retinal vascular effects were not examined. Third, because of the low number of patients requiring intensive care with very severe COVID-19 findings, we were not able to determine whether OCT-A findings are affected more seriously in this subgroup. Fourth, long-term follow-up data were not available because the disease is caused by a novel coronavirus, and more time is needed to perform a long-term evaluation. Lastly, this study analyzed only the macular and peripapillary retinal vessel densities, and fluorescein angiography was not undertaken to investigate the peripheral retina.

In conclusion, retinal microvascular changes were observed with OCT-A following COVID-19 infection in clinically asymptomatic eyes. Vessel density evaluation with OCT-A can be considered a remarkable diagnostics method for retinal neurovascular abnormalities and a biomarker for microvascular abnormalities after a SARS-CoV-2 infection. Further studies are needed to evaluate the relationship between the OCT-A parameters and both the onset and the duration of COVID-19 infection.

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Footnotes and Disclosure

The authors state that they have no conflicts of interest concerning the publication of this article. This study was not funded, and the authors accept responsibility for the entire contents of this article and approve its submission.

Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of restrictions, for example, their containing information that could compromise the privacy of research participants.

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Originally received Jan. 7, 2022. Final revision Apr. 10, 2022. Accepted Jun. 23, 2022.

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