Evaluation of the Effect of Covid-19 on Optic Disk and Macula with Oct and Oct-Angiography

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Research Article

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Abstract

PURPOSE: The aim of this study was to investigate changes in the optic nerve, retina, and retinal vessel parameters in recovered COVID-19 patients and compare to the healthy subjects by using optical coherence tomography (OCT), optical coherence tomography angiography (OCT-A).

METHODS: Fiftysix eyes of 29 patients recovered from COVID-19 infection and 47 eyes of 26 healthy subjects were enrolled in this study. COVID-19 patients had to be fully recovered and were evaluated 1-3 months after COVID-19 infection. The primary outcome resulted from OCTA studies of the following vascular structures: vessel density (VD) in the foveal superficial capillary plexus (SFVD), foveal deep capillary plexus (DFVD), parafoveal superficial capillary plexus (SPVD), parafoveal deep capillary plexus (SPVD), radial peripapillary capillaries (RPC), whole disc (WD), inside disc (InD), superior,inferior, nasal, temporal peripapillary retinal VD and foveal avascular zone (FAZ) compared to those of controls. Structural spectral domain (SD)-OCT parameters were also evaluated, foveal macular thickness (FMT), parafoveal macular thickness (PMT), choroidal thickness (CT) and retinal nerve fiber layer (RNFL).

RESULTS: The patients showed a significant reduction in SPVD compared to those in healthy subjects (P=0.008). COVID-19 patients featured an increased CT compared to that in controls (P <0.001). No differences were found in the FMT or PMT between the groups. VD of WD was not significantly different between the groups but InD VD was reduced in patient group (p=0.027). The superior RNFL was increased in the COVID-19 group compared to that in controls (p=0.022).

CONCLUSION: The eye is among the organs affected in COVID-19 infection. OCT and OCTA is a valuable non-invasive method that can be used to monitor the effects of COVID-19 on the retina, choroid and optic disc.

Introduction

Since December 2019, The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outbreak has been a common issue all over the world. On March 11, 2020, the World Health Organization declared a pandemic.[1] This infection can be completely asymptomatic or it can involve several organs and tissues, eyes included. Recent research has demonstrated diffuse endothelial damage that causes ischemic injury to different regions of the body. Such an impairment of the microcirculatory system may lead to functional disorders in multiple organs. [2,3]. Various extrapulmonary symptoms have been described including gastrointestinal, cardiovascular, neurological, dermatological, renal, and ocular complications [4,5]. Ocular symptoms reported during the course of COVID-19 infections were related to the anterior segment of the eye, such as dry eyes, foreign-body sensation, conjunctivitis, redness, and blurry vision [6]. In the eyes, viral RNA has been detected in infected patients' tears as well as in conjunctival tissue. [7-9]. Few studies have reported its manifestations in the posterior segment.[10, 11] Angiotensing converting enzym (ACE) and ACE-2 have been found in the choroid and in different cell types of the retina, including muller cells, ganglion cells, retinal vascular endothelial cells, and photoreceptor cells. [12] It has been

proposed that the retina and choroid could be targets of infection, as the SARS-CoV-2 transmission involves the binding of the virus to ACE-2 receptor. [13]

Optical coherence tomography angiography (OCTA) is a noninvasive, repeatable technique that can provide depth-resolved imaging of blood flow in the retina and choroid with microvascular detail.[14] This study evaluated patients previously infected with coronavirus, using OCTA analysis to assess the retinal and optic disc microvasculature.

The objective of this study was to evaluate whether coronavirus infection has an effect on the retina and optic disc with OCT and OCTA devices. In this context it was measured the vessel density (VD) of the retinal capillary plexuses, radial peripapillary capillaries (RPC), whole disc (WD), inside disc (InD), and the area of the foveal avascular zone (FAZ), peripapillary retinal nerve fiber thickness (PPRNFL) with OCTA. Also, foveal macular thickness (FMT), parafoveal macular thickness (PMT), choroidal thickness (CT) and retinal nerve fiber layer (RNFL) were evaluated by structural spectral domain (SD)-OCT and compared to aged matched normal control group.

Methods

This prospective study was carried out with the approval of the Adana City Training and Research Hospital Ethics Committee and in compliance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Volunteers from patients who applied to the ophthalmology clinic for any complaints were invited to the study. Patients who were infected with COVID-19, whose positive PCR of a nasopharyngeal swap sample test and who were in the postinfection 1-3 months period were included in the study. The PCR positive tests and also the hospitalization necessary or the medication history during the isolation time were checked from the medical history of each patient. Patients with diabetes, uncontrolled hypertension, any known chronic vascular or neurodegenerative disease were excluded from the study. Participants with previously diagnosed ocular disease such as congenital eye disease, high myopia and high hyperopia (greater than 6 diopters), retinal vascular diseases, macular diseases, previous ocular surgery, optic neuritis were excluded from the study. Significant lens opacity was also an exclusion criteria to avoid low-quality OCTA images. We used the data collected before the pandemic of COVID -19 for age matched control group. All individuals underwent complete ophthalmic examination, including a best corrected visual acuity test, intra ocular pressure (IOP) measurement, slit-lamp examination, SD-OCT and OCTA of the macula and optic nerve.

All subjects underwent SD-OCT and OCTA scanning (Optovue RTVue XR Avanti; version 2017.1.0.151, Optovue Inc., Fremont, California, USA). The system is based on a split-spectrum amplitude decorrelation algorithm (SS-ADA). Each OCTA volume was acquired in 3 seconds, and two orthogonal OCTA volumes were acquired to perform motion correction to minimize motion artifacts due to microsaccades and fixation changes. The software (AngioAnalytic) automatically calculated the VD in different retinal vascular networks: superficial capillary plexus (SCP) and deep capillary plexus (DCP) in a 3 × 3-mm

quadrant scan centered on the fovea. FAZ area (mm²), superficial foveal and parafoveal VD (%), and deep foveal and parafoveal VD (%) were evaluated. Parafoveal VD was calculated for the ring-shaped area between a 0.3 and 1.25 mm radius from the center of the macula. Parafoveal VD, defined as the percentage of total area occupied by vessels and microvasculature, was quantified in the SCP and DCP. All the images were checked for segmentation errors.

The peripapillary images were acquired with a 4.5 x 4.5-mm scanning area centered on the optic disc. The eye tracking function was activated. Motion correction to minimize motion artifacts arising from microsaccades and fixation changes was applied. The peripapillary capillary vascular density (PPCVD) was measured at a 1.00-mm-wide elliptical annulus extending outward from the optic disc boundary in the RPC zone. The RPC layer extends from the internal limiting membrane to the nerve fiber layer.

The capillary VD percentages were automatically calculated as the proportion of the area with flowing blood vessels, defined by pixels with decorrelation values above the SS-ADA threshold level. The software version we used provides separate information on peripapillary capillary VD. For analyses, VD is automatically calculated for the WD, InD and the peripapillary area, respectively.

PPRNFL was also measured using the AngioVue (Optovue, Inc.). The PPRNFL thickness was assessed at a 3.45-mm-diameter circle around the optic disc.

All images in the study were carefully reviewed by the authors to ensure sufficient quality and resolution. Poor quality images were defined as scans with quality index <7 or images with residual motion artifacts, segmentation errors were excluded from the analysis.

Statistical Analysis

Power analysis of the study was performed with GPower 9.1.2 (Universitaet Kiel, Germany). The effect size was calculated using the measurements obtained in the pilot study for the patient and control groups. Since the effect size of the superficial parafoveal density measurement was minimal according to five different measurement parameters, the value of d=0.834 was used in the sample calculation. One-way t-test was chosen as test family and two independent group Mann-Whiney U test was chosen as analysis. The sample size for each group was determined as 45, with a margin of error of 5% and power of the test as 90%. In order to increase the power of the study, 47 eyes for the control group and 56 eyes for the patient group were randomly selected in accordance with the inclusion criteria, and the study was completed with a total of 103 eyes. Descriptive measures were presented as mean±SD (median; min-max) and frequency (percentage ratio). Normality test was performed using the Shapiro-Wilk method. It was observed that the measurement results did not generally comply with the normal distribution. Mann-Whitney U test analysis was used for comparisons between patient and control groups and right and left eyes. Chi-square test was used in the analysis of categorical data. Univariate Logistic Regression model was established to determine the measurement parameters that were effective on the patient group. A p

value of <0.05 was considered statistically significant in the analyses. All analyzes were performed with the SPSS 20.0 (IBM Inc, Chicago, IL, USA) program.

Results

The study was completed with 56 eyes of 29 individuals recovered from COVID-19 as patient group and 47 healthy eyes of 26 individuals as control group. 42.7% of the cases were male and 57.3% were female. There was no significant difference between the genders according to the study groups (p=0.975). The mean age was 56.08±8.54 years in the patient group, 57.57±8.45 years in control group, and there was no significant difference between groups (p=0.376).

Superficial foveal vessel density (SFVD) was slightly lower in the patient group (14.58±6.68%), but it was not significantly lower than the control group (p=0.756). The superficial parafoveal vessel density (SPVD) was significantly lower as 47.25±6.45% in the patient group and 50.01±3.45% in the control group (p=0.008).

DFVD and DPVD values were not significantly different between the groups. FAZ measurement results were higher in the patient group, but the difference was not significant (p=0.483).

CT was found to be significantly higher in the patient group (386.98±67.76 μm) (p<0.001).

FMT and PMT were not significantly different between groups.

The WD VD was 49.38±2.85% in the control group and 48.85±3.17% in the patient group (p=0.491). On the other hand, the rate of InD VD was significantly lower in the patient group (48.61±6.60), while it was 51.48±4.97% in the control group (p=0.027).

PPCVD mean and related superior, inferior, nasal and temporal density components were all measured very closely between the groups. There was no significant difference between the groups.

PPRNFL thickness mean values did not differ significantly between the groups (p=0.266). Among the RNFL components, only superior PPRNFL was found to be significantly higher in the patient group (p=0.022). Superior RNFL was measured as 112.82±15.97 (median 112) μm in the control group, and 120.71±119.76 (median 103.5) μm in the patient group. Inferior, nasal and temporal RNFL thickness measurements were not significantly different between the groups (Table 1).

Table 1

Optical coherence tomography and optical coherence tomograph angiography findings

	Control Group (n=47)	Patient Group (n=56)	*p*
	0,29±0,11	0,31±0,11	
FAZ (µm)			*0,483*
SFVD (%)	15,06±5,68	14,59±6,69	*0,756*
SPVD (%)	50,01±3,45	47,26±6,45	***0,008****
DFVD (%)	31,34±8,57	30,76±7,51	*0,665*
DPVD (%)	55,03±3,08	53,80±4,19	*0,113*
CT (µm)	247,38±62,03	386,98±67,77	***<0,001****
FMT (µm)	217,19±12,81	216,75±15,31	*0,824*
PMT (µm)	277,34±14,92	279,54±16,86	*0,285*
WD VD (%)	49,39±2,86	48,85±3,18	*0,491*
InD VD (%)	51,48±4,97	48,61±6,60	***0,027****
PPCVD (%)	52,71±4,82	51,61±3,85	*0,368*
Superior-PPCVD (%)	52,36±4,74	51,91±6,11	*0,737*
Inferior- PPCVD (%)	52,94±4,19	52,70±5,49	*0,881*
Nasal- PPCVD (%)	52,96±6,12	53,91±8,06	*0,309*
Temporal- PPCVD (%)	51,19±5,80	50,55±6,69	*0,645*
PPRNFL mean (µm)	95,60±10,95	93,79±13,91	*0,266*
Superior-PPRNFL (µm)	112,83±15,98	120,71±119,77	***0,022****
Inferior-PPRNFL (µm)	120,49±16,31	121,11±17,12	*0,385*
Nasal-PPRNFL (µm)	85,83±13,92	87,45±22,09	*0,939*
Temporal-PPRNFL (µm)	65,15±10,22	62,27±11,55	*0,100*

**: significant at 0.05 level according to Mann-Whitney U test*

FAZ: foveal avascular zone ;SFVD: superficial foveal capillary plexus vessel density, SPVD: superficial parafoveal capillary plexus vessel density; DFVD: deep foveal capillary plexus vessel density; DPVD: deep parafoveal capillary plexus vessel density; CT:choroidal thickness; FMT: foveal macular thickness; PMT:parafoveal macular thickness; WDVD: whole disc vessel density ; InD VD: inside disc vessel density; PPCVD: peripapillary capillary vessel density; PPRNFL: peripapillary retinal nerve fiber layer

The control group was accepted as a reference and the factors that were significant on the patient group were determined. Binary logistic regression model was established by accepting the patient group as the dependent variable. Some measurements that had a significant difference between the study groups or that we thought could be significant were determined as independent variables. The model's goodness-of-fit results and the model's significance level were found to be quite high (p<0.001 and RNagelkerke2=0.707). The prediction success rate of the model was determined as 90.3%. Parameters that would cause multicollinearity problems were not added to the model. Among the contributing factors, only CT (p<0.001) and InD VD ratio (p=0.020) were found to have a significant effect. CT was found to have an effect on increasing the disease, and the rate of InD VD was found to have a reducing effect on the disease. OR = 1.028 for CT and OR = 1.091 for InD VD ratio. (Table 2).

Tablo 2

Logistic regression model of measures effective on COVID-19 patient group

Patient Group	-2LL=64,43	R^2=0,707	X^2=77,56; *p<0,001*
	Beta	***p***	**OR (95% CI)**
FAZ (mm²)	7,046	*0,054*	1148 (0,89-1468857)
SFVD (%)	-0,099	*0,279*	0,906 (0,758-1,083)
CT (µm)	0,027	***<0,001****	1,028 (1,018-1,038)
InD VD (%)	-0,088	***0,020****	0,916 (0,851-0,986) 1,091 (1,014-1,175)
PPCVD (%)	-0,082	*0,413*	0,921 (0,756-1,122)
PPRNFL (µm)	-0,029	*0,256*	0,972 (0,925-1,021)

**: significant at 0.05 level according to Univariate Logistic Regression*

FAZ: foveal avascular zone; SFVD: superficial foveal capillary plexus vessel density; CT: coroidal thickness; InDVD: inside disc vessel density; ;PPCVD: peripapillary capillary vessel density; PPRNFL: peripapillary retinal nerve fiber layer

Discussion

In this study we analysed the OCTA and SD-OCT findings of recovered COVID-19 patients in early 3 months and compared to the control group.

The presence of the SARS-CoV-2 virus in tears of infected patients has been demonstrated, and the pathogen is known to cause ocular surface disorders, in different studies. [6,7,15] . Marinho et al were among the first to publish results suggesting retinal findings that could be associated with COVID-19. They reported nonspecific finding such as cotton wool spots, microhemorrhages. They also reported hyper-reflective changes in the inner retina that can be related to the COVID-19 [10]. However a number of other authors have questioned these findings, raising the possibility that these hyper-reflective changes can be attributed to normal retinal structures, namely retinal blood vessels. [16-18] . Studies by Caporossi et al, Pereira et al, and Pirraglia et al included retinal examinations of patients with severe COVID-19, many of whom were at the time admitted in the intensive care unit. [19-21] While the first two groups reported evidence of microvascular disease such as retinal hemorrhages, cotton wool spots, retinal microaneurysms, and tortuous retinal vessels. Pirraglia et al did not see any of these changes in their cohort. It remains unclear if these microvascular changes can be attributed directly to COVID-19 or if they are a consequence of COVID-19 patients who needs intensive care unit, hemodynamic instability, increased inflammatory response. None of participants in our study were needed intensive care unit or positive pressure ventilation. The course of COVID- 19 was relatively mild with a none of patients requiring hospitalization in our study.

Abrishami et al reported decreased SFVD, DFVS, SPVD and DPVD on OCTA of patients with history of COVID-19 infection. [22] They analyzed the patients 2 weeks after recovery, we analyzed at least 4 to 12 weeks after recovery. Turker et al reported significantly lower SPVD in the the superior and nasal quadrants and also significantly lower DPVD in all quadrants of 6x6 mm macular images of OCTA in the COVID-19 patient group .[23] The study group had significantly higher choriocapillaris flow area values and similar FAZ measurements. Their measurements were done within 1 week of discharge after complete recovery and the patient group all were hospitalized. Low oxygen saturation, severe lung involvement, impaired blood values such as high procalcitonin, D-dimer were among the indications for hospitalization. Within 1 week after discharged the findings in OCTA may be effected from the systemic situation. Therefore in this study we included the nonhospitalized mild COVID-19 patients. Differently from their study we analayzed the measurment of 3x3 mm macular images of OCTA in this study. Abrishami et al. reported decreased VD in SCP and DCP in an other study with the patients in a longitudinal midterm follow-up. They mentioned that changes were more pronounced in DCP. [24] In this study, we showed the SPVD was significantly lower in the COVID-19 patient group. DFVD, DPVS, SFVD were not significantly different between the groups.

Savastano et al identified reduced perfusion density of the PPCVD in recovered COVID-19 patients versus age-matched controls using OCTA analysis. The patient group they worked with was not homogeneous and consisted of participants who received various treatments like antiviral or anticuagulation or hydroxychloroquin and also had diseases such as diabetes and arterial hypertension, systemic autoimmune or inflammatory diseases.[25] In this study PPCVD mean and related superior, inferior, nasal and temporal density components were all similar between the groups.

Abrishami et al found a trend towards increased retinal thickness in patients with history of COVID-19, though their comparison to age-matched controls did not reach statistical significance.[24] Yıldız et al reported increased FMT but presence of comorbidities, including diabetes and hypertension, might have influenced retinal thickness measurements in their study.[26] In this study we detected that FMT and PMT were not significantly different between the groups.

The choroid is the layer of the eye with the highest vascularization and also the tissue with the highest blood flow per unit weight in the body. [27] It also provides vascularization to the outer retina, the RPE, and some parts of the optic nerve and responsible for feeding the avascular fovea [28,29]. Hepokur et al reported that CT and total choroidal area were reduced in the early postinfectious period (15-40 days) of the disease and increased 9 months after the initial infection. [30]. Fırat et al reported that there was no statistically significant difference between the groups in terms of FMT and CT in a period of 14-60 days after the onset of the first COVID-19 symptoms. [31] In this study we demonstrated significantly increased CT in COVID-19 patients group. The analyzed autopsy cohort of eyes from COVID-19 patients demonstrates an impairment of the microvessels mainly in the choroid. [32]. Destruction of ACE2 receptors has been associated with multiorgan dysfunction owing to increased levels of reactive oxygen species, induction of fibrosis, hypertrophy, and inflammation. Therefore, decreased ACE2 expression in the neurosensory retinal cells and retinal vasculature could result in inflammation and oxidative stress, The increase in CT in the patient group was considered as a finding indicating that the inflammation continued even after 3 months.

In the present study we detected that InD VD was significantly decreased and superior PPRNFL was found to be significantly higher in the patient group. In a recently published case series, seven out of eight patients recovered from COVID-19 demonstrated an increase in PPRNFL thickness compared to their own available previous examinations. The only patient with decreased PPRNFL thickness had glaucoma. [30] Abrishami et al reported no significant difference in COVID-19 recovered patients at least a two week recovery period. [33] The measurements of the patient groups were taken at least 2 weeks after the recovery and it was not stated how long after the symptoms started or the PCR was positive, the measurements were taken. The fact that the patient group could not be analyzed within the same period may have affected the result. In this study İnD VD was significantly lower in the patient group. We think that the presence of microthrombus or endothelitis in microvascular structures that contribute to optic disc nutrition, similar to diseases such as glaucoma, optic neuropathy affecting the optic disc, cause this result.

The control group was consisting age and gender matched individuals. Ingrid Arevalo-Rodriguez et al reported the need for repeated testing in patients with suspicion of being infected because up to 54% of COVID-19 patients may have an initial negative RT-PCR result. They analysed information from 34 studies collecting information from 12,057 patients confirmed to have SARS-CoV-2 infection and 1060 cases with RT-PCR negative findings in their initial assessment. False-negative rates ranged from 0.018 to 0.58. [34] Considering the possibility of including the participants that have unknowingly recovered from COVID-19 asymptomatically, without having PCR, or the recovered cases, who were not accepted as

COVID-19 according to false negative PCR results although they showed symptoms and tested, we analaysed the data obtained before december 2019, the begining of pandemic COVID-19, as control group .As the superiority of our study, the patient group consists of individuals who are homogeneous, with similar periodic intervals in terms of disease onset and recovery time. The control group consists of healthy participants who are known to have not actually encountered the COVID- 19.

Limitations of our study; the small sample and the short and long-term measurements of the patients have not been compared.

In conclusion; In the present study, we evaluate COVID- 19 patients with OCT and OCT A. Microvascular changes occure in both the macula and optic disc. Also it seems that this vascular changes continue overtime. Large-scale studies are needed to guide the long-term follow-up of these patients.

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