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Photodiagnosis and Photodynamic Therapy 37 (2022) 102674

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Change in retinal vessel diameter and choroidal thickness in patients with severe COVID-19
Change In Retinal Parameters In Patients With Severe COVID-19

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ARTICLE INFO

Keywords:
Choroid
COVID-19
Wall thickness
Choroidal thickness
Retinal vessels
Optical coherence tomography

ABSTRACT

Purpose: : To compare the differences in retinal vascular structure and choroidal thickness between the active disease and post-recovery periods in COVID-19 patients and healthy controls.
Material and Methods: : This prospective, cross-sectional study included 30 eyes from 30 patients with severe COVID-19 and 30 eyes of 30 sex-matched healthy controls. Central macular thickness (CMT), subfoveal choroidal thickness (CT) and retinal vascular changes of patients were measured after positive polymerase chain reaction (PCR) (where the patient had COVID-19-related symptoms) and then three months after two negative PCRs. Laboratory parameters, including C-reactive protein and D-dimer levels, were also recorded.
Results: : The mean age of the patients was 47.90 ± 9.06 years in patients group, 49.07 ± 8.41 years in control goups ($p = 0.467$). In terms of choroidal thicknesses subfoveal, nasal and temporal region were significantly higher in the active disease period than control group ($p = 0.019$, $p = 0.036$, $p = 0.003$, respectively). When the after recovery period was compared with the control group in terms of choroidal thickness, although the choroidal thickness was higher in all regions, this difference was not found statistically significant. There was no statistically significant difference in CMT between groups ($p = 0.506$).The mean venous and arterial wall thicknesses were significantly higher in the active period than after recovery ($p = 0.023$, $p = 0.013$, respectively) but there were no differences between after recovery and control groups in the pairwise comparison ($p = 0.851$, $p = 0.715$, respectively).
Conclusion: : In patients with severe COVID-19, there are changes in thickness of the choroid and retinal vessel walls. While vascular wall thickness increases due to inflammation, the absence of lumen changes may be associated with hemodynamic variables.

1. Introduction

An outbreak of coronavirus disease (COVID-19), which causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2), has emerged in China and has rapidly spread worldwide. In histopathological studies, COVID-19 has been shown to cause endotheliitis and vasculitis in the arterial and venous circulation, mainly in the lung, heart, kidney, intestine and brain; this is caused directly by a viral infection [1,2]. Ultimately, the small vessels' endothelial cell edema, congestion and thrombosis cause ischemia/reperfusion injury, resulting in multiple organ dysfunction. Current information shows that SARS-CoV-2 binds to host cells through a metallopeptidase, angiotensin-converting enzyme 2 (ACE-2) receptor, resulting in the downregulation of cell-surface ACE-2 expression [3]. These receptors are found in all major organs, especially in the lungs, heart, veins, arteries, aqueous humor and retina [4,5]. The downregulation of cell-surface ACE-2 expression can damage the retina either by a direct cytopathic effect through the ACE-2 receptor or indirectly through an inflammatory response.

Extensive endothelial damage and thromboembolic events affecting different body parts other than COVID-19 patients' lungs have been

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https://doi.org/10.1016/j.pdpdt.2021.102674
Received 21 August 2021; Received in revised form 10 November 2021; Accepted 3 December 2021
Available online 5 December 2021

reported in several studies [6,7]. The retina's arteries and vessels, which show changes in many systemic diseases, may indicate when the vascular system undergoes the same pathological processes [8]. Retinal vessel analysis is an emerging technique for the non-invasive assessment of the microvasculature.

Severe proinflammatory cytokine response observed in COVID-19 patients (C-reactive protein (CRP), ferritin, IL-2, IL-6, IL-7, IL-10, IP-10, TNF-α, and even SARS-CoV-2 cytokine storm, which accelerates the onset of systemic inflammatory response syndrome), causes the activation of the hypercoagulable state, leading to a coagulation cascade [9].

In recent years, choroidal thickness and retinal thickness in particular have been considered as potential structural inflammatory markers [10,11]. We aimed to investigate whether retinal vasculature and choroidal thickness as an indicator of systemic inflammation are affected in both patients with severe COVID-19 pneumonia and in recovered patients.

2. Materials and methods

2.1. Study population and design

This prospective, cross-sectional study was conducted at the Ophthalmology Department in our pandemic hospital between December 2020 and May 2021. Patients hospitalized due to severe COVID-19 were asked to participate in the study. The local ethics committee approved the study, and oral and written informed consent was obtained from all participants. The procedures used conformed to the tenets of the Declaration of Helsinki. This study included 30 eyes of 30 patients who were diagnosed with severe COVID-19 and 30 eyes of 30 age and sex-matched healthy controls. Healthy controls were selected from individuals with no prior COVID-19 history and confirmed PCR negativity during the study. The inclusion criteria were as follows: 1) having a positive polymerase chain reaction (PCR) and COVID-19 related symptoms; 2) being classified as having severe COVID-19; 3) being able to sit in front of the OCT; and 4) having onset of symptoms within one week before the evaluation. We determined severe COVID-19 based on the following findings: oxygen saturation <93% for room air (or PaO2/FiO2 <300 mmHg); respiratory rate >30 breaths per minute; more than 50% involvement of the lung parenchyma in chest imaging [12]. For all patients, the exclusion criteria were as follows: 1) refractive error $\geq \pm 3$ D; 2) other previous or concomitant retinal diseases; 3) any history of ocular surgery within 6 months; 4) uncontrolled systemic hypertension or other systemic diseases; 5) eyes with low-quality OCT image scores (quality scores <25).

All participants underwent a complete ophthalmic examination, including visual acuity measurement, Goldman applanation tonometry, autorefraction (Nidek Co. Ltd.), slit-lamp biomicroscopy, dilated funduscopy, fundus fluorescein angiography and Spectralis OCT + HRA (Heidelberg Engineering, Inc., Heidelberg Germany). The patients' duration of symptoms and laboratory parameters, including CRP and D-dimer levels, were recorded.

2.2. OCT imaging and measurements

Retinal vessel diameters were evaluated using Spectralis OCT+HRA with infrared reflectance (IR) images (Fig. 1). IR images were obtained by scanning a circular region with a diameter of 3.42–4.04 mm centered on the optic disk and then analyzed using Spectralis software. Firstly, all OCT and IR images of the eyes were reviewed by a single retina specialist. Retinal vessels were then classified as arteries and veins, according to an experienced retinal specialist's anatomical features in IR images. Retinal artery and vein diameters, including the vertical vessel outer diameter (VOD), vertical vessel inner diameter (VID), and vessel wall thickness (VWT), within each of the four quadrants around the optic disk, were measured from IR images using the manual caliper tool (Fig. 1). Central macular thickness (CMT), subfoveal choroidal thickness (CT) and retinal vessel diameters of patients were measured after a positive PCR with COVID-19-related symptoms and three months after two negative PCRs. Two experienced retinal specialists independently measured the vessel diameters in each IR image according to a published method, and intraclass correlation coefficients (ICC) were calculated [13]. The average inner, outer diameter and wall thickness of the retinal artery and vein were calculated using the average of the data in the four quadrants.

Central macular thickness (CMT) was defined as the mean thickness of the central 1 mm zone of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid and measured by spectral-domain OCT (Fig. 1). Subfoveal choroidal thickness (CT) was described as the distance between the RPE line base and the scleral layer's inner surface. CT was manually measured at nasal and temporal regions of 1500 μm from the center of the fovea using the SD-OCT software's caliper tool (Fig. 1).

For all OCT images, each scan was averaged 100 times during acquisition to reduce speckle noise, and was evaluated for analysis if ART averaging $\geq$ 75 times. According to signal strength, the OCT images with a quality score $\geq$ of 25 dB (range: 0–40 dB) were assessed for analysis.

2.3. Statistical analysis

All statistical tests were performed using the SPSS program (Version 26.0, Armonk, NY: IBM Corp). Quantitative descriptive variables were presented as the mean ± standard deviation and qualitative descriptive variables were expressed as frequencies and percentages. The normal distribution of all variables was determined with the Kolmogorov-Smirnov test. The differences among active disease period, after recovery, and healthy controls were compared with a one-way analysis of variance for parametric data. When a significant result was obtained, the Scheffe test was performed for post hoc comparisons. Pearson's chi-square test was used for the comparison of categorical variables. Kruskal-Wallis test was used to compare the differences in non-parametric data and applied Bonferroni corrections in cases of significant differences. The intraclass correlation coefficient (ICC) was calculated to determine the interobserver reliability of retinal vessel diameters, and ICC values of greater than 0.80 were accepted as good agreement. A p-value less than 0.05 was accepted as significant.

3. Results

Thirty eyes of 30 patients with COVID-19, confirmed both clinically and by the laboratory, were enrolled in this study. The mean age of patients was 47.90 ± 9.06 years (range: 29–65 years), and 18 (60%) patients were male and 12 (40%) patients were female. The mean age of controls was 49.07 ± 8.41 years (range: 31– 65 years), and 19 (63.3%) patients were male and 11 (36.6%) patients were female. The two groups were statistically similar in age and gender ($p = 0.467$ and $p = 0.802$, respectively). Demographics and laboratory parameters of the patients are shown in Table 1. Nineteen (63.3%) of patients had a fever, 24 (80%) of patients had a cough, 25 (83.3%) of patients had respiratory distress and 6 (20%) of patients had ocular findings (hyperemia, epiphora, episcleritis and follicular conjunctivitis). The mean duration of hospital admission was 3.7 ± 1.8 days, while the time from onset of symptoms to the time ophthalmologic examinations was 8.3 ± 2.3 days.

There was a statistically significant difference between groups in terms of choroidal thickness. Although the choroidal thickness increased in all regions when the active disease period was compared with the recovery period, there was a significant difference only in subfoveal choroidal thickness ($p = 0.036$). In terms of choroidal thicknesses subfoveal, nasal and temporal region were significantly higher in the active disease period than control group ($p = 0.019$, $p = 0.036$, $p = 0.003$ respectively). When the recovery period was compared with the control group in terms of choroidal thickness, although the choroidal thickness

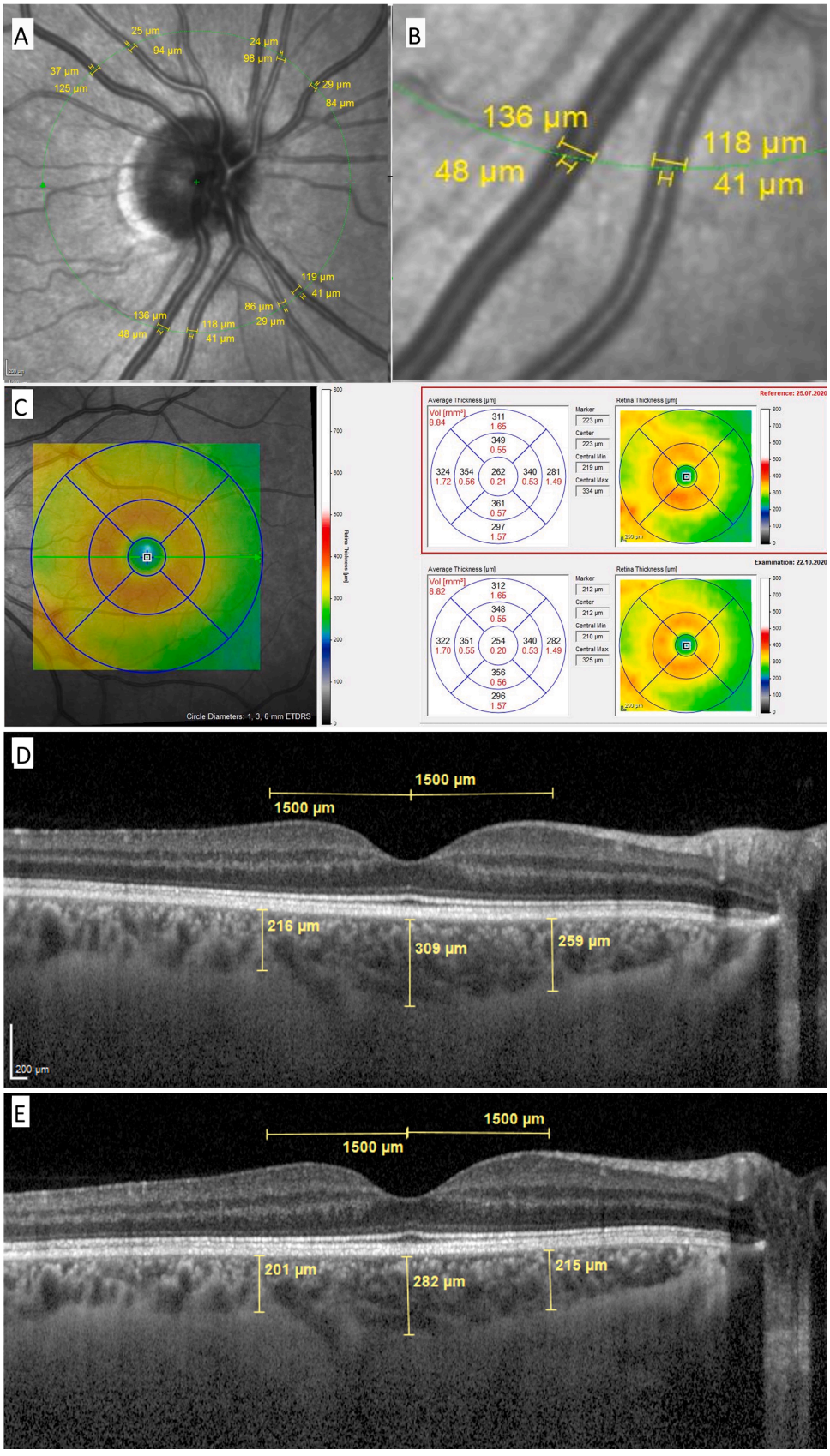

Fig. 1. Measurements of a patient's retinal parameters. Illustration of the measurement of the inner and outer diameters of the retinal arteries and veins from the four quadrants (a, b). Illustration of measurement of CMT by spectral-domain OCT in the active disease period and after recovery (c). Measurement of choroidal thickness from central subfoveal area and nasal and temporal 1500 µm using the SD-OCT software's caliper tool in active disease period and after recovery (d, e).

Table 1
Demographics and laboratory parameters of the patients.

Age	47.90 ± 9.0 years (29–65 years)*
Gender, n, (%) males	18 (60%)
Fever, n, (%)	19 (63.3%)
Cough, n, (%)	24 (80%)
Dispne, n, (%)	25 (83.3%)
Ocular findings, n, (%)	6 (20%)
C-Reactive Protein (mg/L)	46.93 ± 56.5*
D-dimer(μg/L)	1175.00 ± 1985.6*
Symptoms onset	8.03 ± 2.3 days (4–15 days)*
Hospital admission	3.70 ± 1.8 days (0–7 days)*

*The variables were expressed as mean ± standard deviation (range).

was higher in all regions, this difference was not found statistically significant. There was no statistically significant difference in CMT between groups ($p = 0.506$) (Table 2).

Table 3 presents the artery and vein diameters with the average inner, outer diameter and wall thickness within each of the four quadrants of the controls' and the patients' eyes at admission to the hospital and in the third month of follow-up. While the mean venous and arterial wall thicknesses were significantly higher in the active period than after recovery ($p = 0.023$, $p = 0.013$ respectively) but there were no differences between after recovery and control groups in the pairwise comparison ($p = 0.851$, $p = 0.715$ respectively). The mean venous and arterial outer diameter were statistically different between the groups ($p = 0.002$, $p = 0.022$ respectively). The venuler and arterial outer diameters were higher in the active disease period than after recovery ($p = 0.010$, $p = 0.044$ respectively), but there was no difference between after recovery and control groups in the pairwise comparison ($p = 0.783$, $p = 0.817$ respectively). Also the mean venous and arterial VID values were not significantly different between groups ($p = 0.865$, $p = 0.074$ respectively), (table 3). The graphs in Figs. 2 and 3 present the mean inner, outer diameter and wall thickness of the artery and vein in all groups comparatively.

No significant relationship was found between the reduction in choroidal thickness and the retinal vessel diameter change and patients' laboratory parameters. There was excellent interobserver reproducibility for 20 randomly selected images in the measurement of VID and VWT thickness. Interobserver intraclass correlation coefficient values for VID and VWT thickness were 0.812 (0.788–0.940) and 0.843 (0.802–0.895), respectively.

4. Discussion

Our study found that retinal artery and vein wall thickness, in addition to central macular and choroidal thickness, increased in patients with severe COVID-19. Previous studies showed that COVID-19 attacks tissues with ACE receptors and causes pathologies through this receptor (3). The blood retina barrier, RPE and blood endothelial cells formed by the endothelial cells of retinal vessels and epithelial cells with retinal pigment express ACE2 [14,15]. These findings suggest that vessels in the eye (retinal, choroid) and vitreous containing ACE receptors may also have pathologies because of COVID-19 infection.

Animal studies have shown that in the conjunctiva of feline (feline infectious peritonitis virus or FIPV), infection with coronavirus is common and can cause conjunctivitis, anterior uveitis, retinal vasculitis and choroiditis with retinal detachment [16]. Endothelial changes and endotheliitis are essential determinants of microvascular dysfunction since this process activates vasoconstriction, ischemia, tissue edema and procoagulant tendency. It is not fully understood whether the virus directly activates this process and results from local and systemic inflammatory processes [9]. However, these findings suggest a close relationship between inflammation and the coagulation cascade [9]. Alfredo Insausti-García et al. described papillophlebitis presenting with dilated and tortuous retinal vessels, disk edema, macular edema and retinal hemorrhages in a patient with COVID-19 [17]. Studies have shown that more than 30% of COVID-19 patients develop venous and arterial thrombotic events, especially venous thromboembolic events (27%) [9,18]. Vascular occlusion associated with thrombotic susceptibility and changes such as chorioretinitis or vasculitis directly mediated by the virus can be observed in the retina, a privileged site for non-invasive and in vivo evaluation of systemic diseases [17]. Similarly, we detected vascular structure, choroid and retinal changes in patients with COVID-19, a systemic disease affecting many organs.

Subsegmental vascular enlargement has been reported on computed tomography of the chest in COVID-19 patients, which may be due to an inflammatory response or increased blood flow due to direct endothelial damage [19,20]. Invernizzi et al. investigated alterations of the retina and its vasculature in patients with COVID-19 within 30 days of onset of symptoms [21]. The authors found that retinal arteries and veins were larger in COVID-19 patients than in the non-infected group. In more severe cases, the vessel diameter was larger and inversely correlated with the onset of symptoms. However, in this study, the total vessel diameter was measured, and lumen and wall thickness were not evaluated in detail. It is unknown whether the increase in total wall diameter is due to lumen enlargement or increased wall thickness. Our study performed retinal analysis within the first week after hospitalization, and we evaluated both lumen diameter and wall thickness in arteries and veins in detail. We found that while the lumen diameter did not change in either artery or vein, the vessel wall thickness increased. In another study evaluating retinal vessel diameters, vasodilation was demonstrated during active disease compared to control and after recovery, but detailed vessel analysis was not evaluated [22]. In stress situations such as a decrease in O2 or an increase in CO2, and with an increase in inflammatory mediators, the retinal arteries actively enlarge, while the veins are passively enlarged [23–25]. The absence of a significant change in vessel lumen diameters despite the increased vessel wall thickness, hemodynamic stimuli caused by shear stress and the negative effect of endothelial-induced vessel wall edema may have caused the lumen diameter to not increase as expected. We think that the increase in the vessel walls' thickness is due to edema associated with inflammation and endotheliitis in a severe COVID-19 period.

Retinal arteries and vein diameters, which are significantly associated with various systemic factors, have been studied with concern to systemic diseases and conditions [25–27]. Retinal vascular changes may be seen in patients with viral diseases such as HIV. HIV targets the vascular endothelium and causes retinopathy to damage the microvasculature [28]. Similarly, COVID-19 is systemically involved throughout the vascular system and the primary pathology is vasculitis. Our study showed that COVID-19 could affect the entire vascular system regardless of the artery and vein.

Casagrande et al. detected CoV-2-SARS viral RNA in the retina of COVID-19 patients in a biopsy study [29]. Marinho et al. described

Table 2
The mean central macular thickness and choroidal thickness at active disease period, in period after recovery and control group.

	Active disease period	After recovery	Control group	p[a]
CMT*	275.77 ± 26.93	270.20 ± 26.39	268.03 ± 25.79	0.506
Subfoveal CT*	376.30 ± 50.26[a]	343.50 ± 50.79[b]	340.47 ± 50.09[b]	0.012
Temporal CT*	324.00 ± 67.02[a]	308.27 ± 50.07[ab]	277.77 ± 38.30[b]	0.004
Nasal CT*	314.80 ± 53.49[a]	291.90 ± 63.92[ab]	279.30 ± 45.04[b]	0.044

CMT: Central macular thickness, CT: choroidal thickness, a: One-way analysis of variance.
Different superscripts in the same row indicate a statistically significant difference between groups.
*The variables were expressed as mean ± standard deviation.

Table 3
The mean vessel diameter measurements of patients' eyes at active disease period , in period after recovery and control group.

	Active disease period	After recovery	Control group	p[a]
Venular parameters (μm)*	167.07±21.17[a] 166.93±26.65	147.77±18.29[b] 156.13±25.04	148.50±22.55[b] 154.83±22.06	<0.001 0.120 0.375
Superior-Temporal VOD	116.33±19.25 125.37±22.41	112.03±17.88 118.53±25.26	110.00±16.06 117.67±19.51	0.354 0.002 0.806 0.966
Inferior-Temporal VOD	143.92±15.24[a] 65.27±13.37	133.61±13.34[b] 62.90±13.62	132.75±11.09[b] 63.87±14.95	0.937 0.849 0.865 0.001
Superior-Nasal VOD	61.57±12.84 49.87±10.22	61.60±12.90 49.07±8.92	60.87±10.39 49.80±9.27	0.153 0.360 0.403 0.006
Inferior-Nasal VOD Mean	47.50±7.20 56.05±7.47	47.03±7.65 55.15±7.19	46.80±10.41 55.33±5.69	0.278 0.046 0.387 0.458
VOD Superior-Temporal	101.80±18.65[a] 105.37±26.11	84.87±21.00[b] 94.53±23.71	84.63±18.87[b] 93.97±26.28	0.022 0.176 0.759 0.854
VID Inferior-Temporal VID	66.47±18.57 77.87±22.06	62.97±16.49 71.50±22.98	60.20±15.55 70.87±21.33	0.022 0.074 0.032 0.084
Superior-Nasal VID	87.87±15.93[a] 117.53±14.44	78.46±13.54[b] 113.30±12.91	77.41±10.54[b] 112.37±12.22	0.180 0.011 0.001
Inferior-Nasal VID Mean	118.33±11.82[a] 95.73±14.66	112.13±12.74[ab] 91.77±12.95	110.60±13.02[b] 91.37±12.79	
VID Superior-Temporal	104.40±18.08 109.00±8.34[a]	98.67±17.01 103.96±7.33[b]	101.30±18.00 103.90±8.30[b]	
VWT Inferior-Temporal	47.10±10.11 47.73±9.81	45.83±9.94 46.43±10.08	50.30±8.25 48.23±9.10	
VWT Superior-Nasal VWT	42.47±10.81 39.30±7.79[a]	43.27±8.49 45.97±7.88[b]	43.80±8.16 45.70±8.02[b]	
Inferior-Nasal VWT Mean	44.15±5.20 70.43±11.71[a]	45.37±5.15 67.47±12.07[ab]	47.00±3.89 62.07±13.02[b]	
VWT Arteriolar parameters	70.60±13.29 53.27±16.76	65.70±14.71 48.50±10.16	62.37±14.59 47.57±9.87	
(μm)* Superior-Temporal	65.10±15.28[a] 64.85±9.68[a]	52.70±14.66[b] 58.59±7.70[b]	55.60±18.72[ab] 56.90±7.55[b]	
VOD Inferior-Temporal				
VOD Superior-Nasal				
VOD Inferior-Nasal				
VOD Mean VOD Superior-				
Temporal VID Inferior-				
Temporal VID Superior-				
Nasal VID Inferior-Nasal				
VID Mean VID Superior-				
Temporal VWT Inferior-				
Temporal VWT Superior-				
Nasal VWT Inferior-Nasal				
VWT Mean VWT				

VOD: Vertical vessel outer diameter, VID: Vertical vessel inner diameter, VWT: Vertical vessel wall thickness, a: One-way analysis of variance Different superscripts in the same row indicate a statistically significant difference between groups *The variables were expressed as mean ± standard deviation .

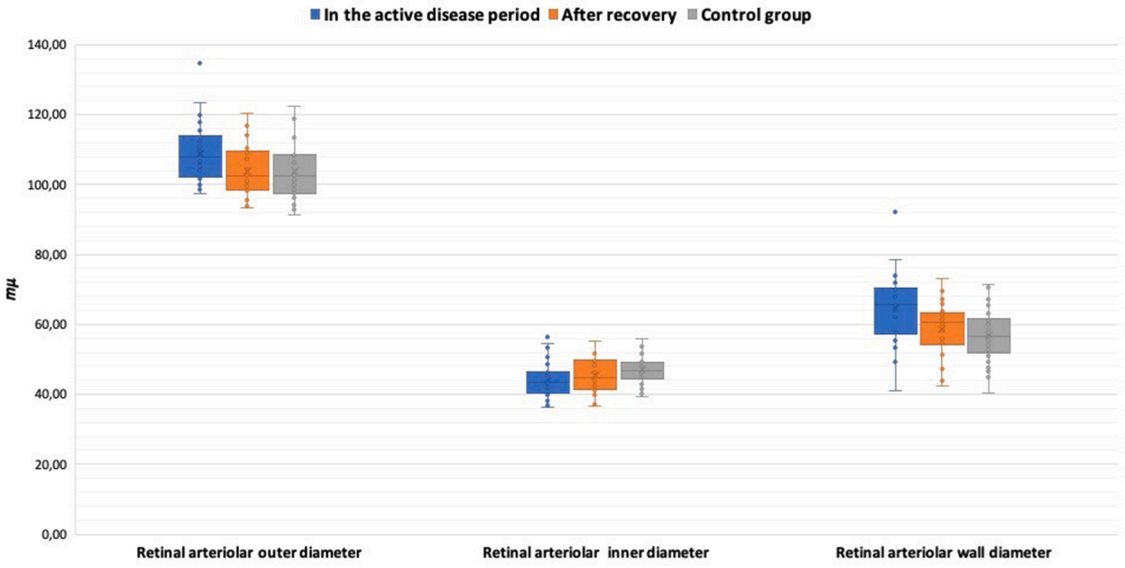

Fig. 2. Graphs of retinal artery diameter in the active period, after recovery and control group.

subtle cotton wool spots and microhemorrhages on the retinal surface in four of 12 patients (aged 25- 69 years) with COVID-19 and hyperreflective lesions that can be observed with OCT in the ganglion cell and inner plexiform layer in all patients [30]. Our study did not find any retinal lesions, such as cotton wool spots, microhemorrhages, or hyperreflective lesions, so we think these findings are likely related to other medical conditions prior to infection.

Choroidal thickness and retinal thickness are considered potential inflammatory markers for inflammatory diseases accompanied by vascular pathologies [10,31]. Agarwal et al. reported that patients with HIV infection, especially HIV microangiopathy, had thicker choroids than healthy control subjects matched for age and sex. These changes may be choroidal changes associated with vascular dysfunction caused by HIV. Similarly, Luhtala et al. demonstrated that the pathophysiology of COVID-19 is due to complement-mediated vascular injury in the lung [32]. Also, COVID-19 has been described as a multi-organ dysfunction characterized by multisystem inflammatory syndrome (MIS) [33]. Subclinical choroidal involvement has been shown in multisystem inflammatory diseases, even without any evidence of ocular involvement [34]. It is thought that choroidal pathologies may also occur because COVID-19 causes both vascular damage and systemic inflammatory syndrome. Indeed, it has been shown that choroidal thickness is increased in severe COVID-19 patients in a recent study [35]. In our study, the increased in choroidal thickness in the active disease period

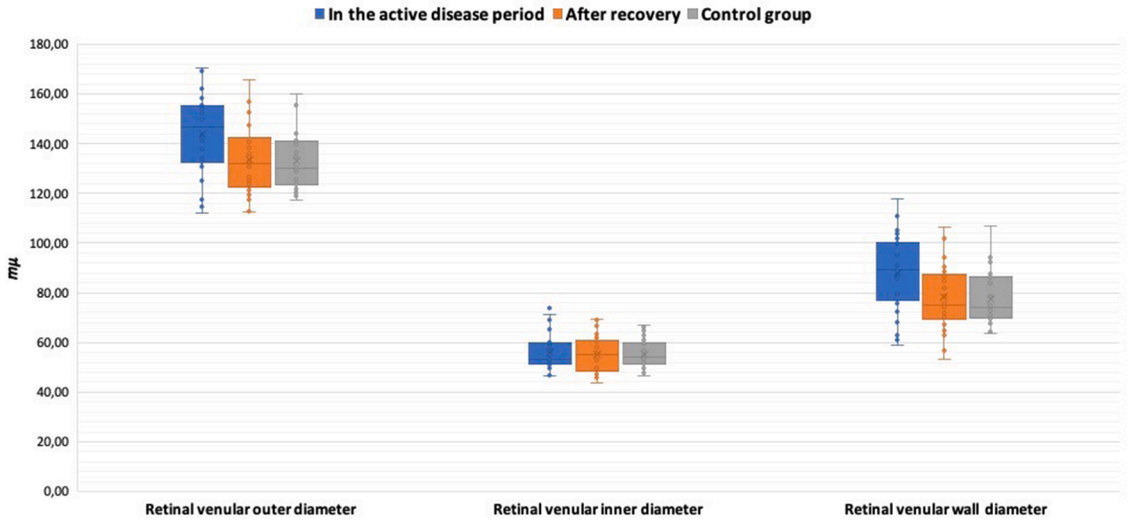

Fig. 3. Graphs of retinal vein diameter in the active period, after recovery and control group.

compared to the after recovery and control group supports this study. In our study evaluating the 3rd month after the disease, it was shown that most findings were reversible and in a study with a longer follow-up period of 9 months, all available findings were found to be similar to the control group [36].

Blood retina barrier consists of endothelial cells of retinal vessels and RPE cells and expresses ACE2 due to this endothelial cell component. It has been shown in the literature that SARS-CoV-2 triggers a peripheral immune response by increasing the release of proinflammatory cytokines that can disrupt the blood retina barrier [37]. Thus, it can damage the retina either by a direct cytopathic effect through the ACE-2 receptor or indirectly through an inflammatory response. In our study, increased central retinal thickness during the disease period supports the presence of retinal involvement. However, decreased retinal thickness after recovery suggests that it is a temporary finding.

One of the limitation of this study is that retinal vessel diameters were measured by manuel caliper tool. In this study, ICC values of greater than 0.80 were accepted as good agreement in all manual measurements. When the examiners' measurements were not consistent, they were repeated until good agreement was obtained and the average of both measurements was used for the statistical analysis. Despite all these measures, it should be taken into account that retinal vessel diameters were measured on IR images using manuel caliper tool, the errors caused by the manual technique may not be completely eliminated. Another point to be noted is that the retinal vessel diameters may differ between the participants. Another limitation is that we included only severe cases, so we could not examine the correlation between disease severity and vessel diameter changes. Therefore, there is a need for larger and subgroup studies that classify disease severity.

In conclusion, in patients with severe COVID-19, there may be structural changes in the retinal vessels and choroid level, but the findings regress after the disease heals. While vascular wall thickness increases due to inflammation, the absence of lumen changes may be due to hemodynamic variables. However, more advanced physiopathological studies are needed.

Disclosures financial support

No financial support was received for this submission.

Ethic

Our prospective study conducted in accordance with the Declaration of Helsinki

Conflict of Interest

None of the authors has conflict of interest with this submission

The authors haven't used any sources of public or private financial support and they have no conflict of interest

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