



# Evaluation of choroidal thickness in patients who have recovered from COVID-19

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## Abstract

**Purpose** We aimed to evaluate choroidal thickness (CT) in patients who have recovered from COVID-19 by using enhanced depth imaging optical coherence tomography (EDI-OCT).

**Methods** We included fifty-eight patients who have recovered from COVID-19 (group 1) and fifty healthy control subjects (group 2) in this prospective study. Best corrected visual acuity, anterior segment and posterior segment examinations of all subjects were performed. CT scan and measurements were taken with the EDI mode of the Spectral Domain OCT device.

**Results** Of the 108 subjects included in this study, 57 were female and 51 were male. The mean age was similar in both groups ( $36.10 \pm 7.12$  and  $35.58 \pm 7.29$ , respectively,  $p = 0.276$ ). Group 1 had the following characteristics: the mean time since diagnosis was  $53.18 \pm 2.84$ ; it had been  $38.48 \pm 4.07$  days since the PCR test was negative; and all subjects were outpatients. It was detected that the CT of the patients in group 1 decreased in all areas

compared to group 2, and this decrease was significant in subfoveal, temporal and inferior areas ( $257.48 \pm 32.79$ ,  $273.62 \pm 45.04$ ,  $p = 0.04$ ;  $232.96 \pm 41.79$ ,  $252.76 \pm 46.09$ ,  $p = 0.02$ , and  $245.22 \pm 44.58$ ,  $271.54 \pm 55.07$ ,  $p = 0.01$ , respectively). In the retinal nerve fiber layer analysis for group 1, thickening was detected in all areas, although it was not statistically significant, except in the temporal area where it was (superotemporal, superonasal, nasal, inferonasal, inferotemporal, temporal, and global [ $p = 0.08$ ,  $p = 0.45$ ,  $p = 0.73$ ,  $p = 0.64$ ,  $p = 0.74$ ,  $p = 0.02$ , and  $p = 0.10$ , respectively]).

**Conclusion** For individuals who had recovered from COVID-19, it was found that CT decreased in all areas in these patients. Therefore, this study in which we have demonstrated the decrease in the thickness of the choroidal tissue, a tissue with high blood flow, may contribute to the understanding of the systemic microvascular waste of this disease.

**Keywords** COVID-19 · Optical coherence tomography · Choroidal thickness

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## Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which can be potentially fatal and causes coronavirus disease (COVID-19), a novel disease that affects lungs and airways and is often

manifested by fever, cough, malaise, muscle pain, and shortness of breath, is thought to be transmitted mainly by droplets in the environment as a result of contact with infected patients [1–3].

It has been shown that SARS-CoV-2 infects cells with the angiotensin converting enzyme-2 receptor, which has been reported to be expressed in eye tissues, such as the cornea and conjunctiva, and the presence of RNA of this virus in tear and retinal biopsies has been shown in multiple studies [4–6].

The choroid, which is the vascular layer of the eye, is the region with the highest blood supply in the posterior segment of the eye. It has been reported that choroidal thickness (CT), which is reported to vary depending on age, refractive error, axial length, and diurnal variations, may also change in various retinal diseases and systemic diseases, such as glaucoma and Alzheimer's disease [7–9].

Vasculitis and microembolism have been reported in COVID-19 patients, and studies have also shown that retinal circulation is affected in these patients. Therefore, determining the changes in microcirculation due to COVID-19, especially in tissues with high blood supply in the posterior segment of the eye, such as the choroid, and detecting possible changes in the perfusion of ocular tissues in these patients may contribute to the literature.

Enhanced depth imaging optical coherence tomography (EDI-OCT), which is a noninvasive diagnostic method, enables the evaluation of choroidal morphological features in a cross-sectional manner and in high resolution by reducing the signal strength behind the retinal pigment epithelium [10].

The aim of this study was to evaluate the CT of patients recovering from COVID-19 by EDI-OCT.

## Methods

### Study design and subject

This prospective study included 58 patients who had recovered from COVID-19 (group 1) and 50 healthy control patients (group 2) of a similar age and gender. We obtained approval from the ethics committee. All study participants gave written consent before measurements were taken, and the study was carried out according to the Declaration of Helsinki.

The study group consisted of people who had contracted COVID-19 and had recovered from it for at least one month (group 1) and individuals who applied to our outpatient clinic for a routine eye examination and did not have any eye disease (group 2).

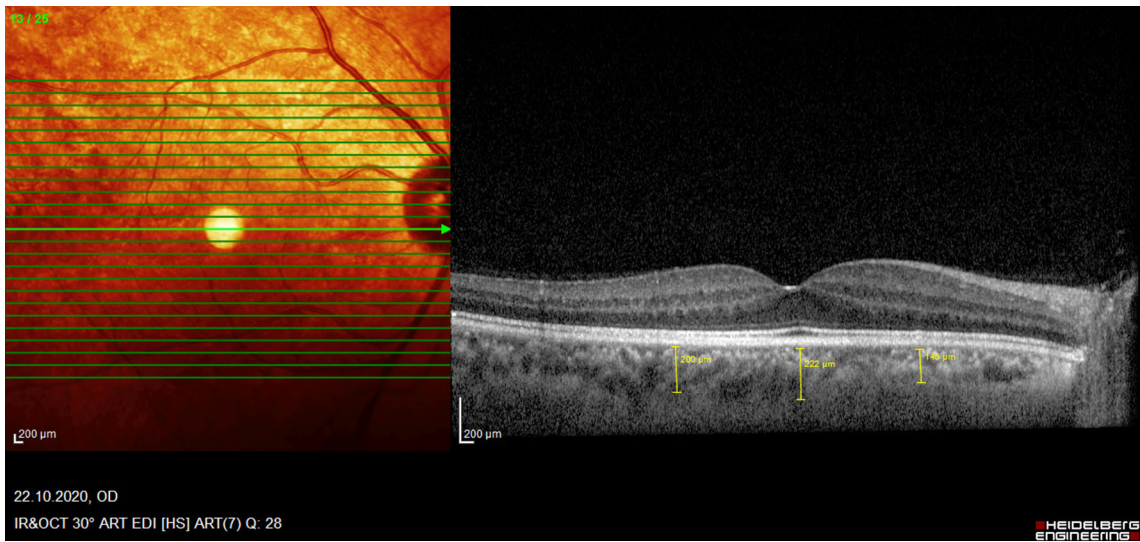
All subjects in the study had best corrected visual acuity, refractive error detection, anterior segment, and posterior segment examinations performed. In both groups, subjects with previous ocular surgery, spherical equivalent diopters of more than  $\pm 4$  diopters, other ocular diseases (corneal opacity, glaucoma, uveitis, amblyopia, retinal disease, etc.), and systemic diseases, such as diabetes and hypertension, were not included in the study.

### Optical coherence tomography measurement

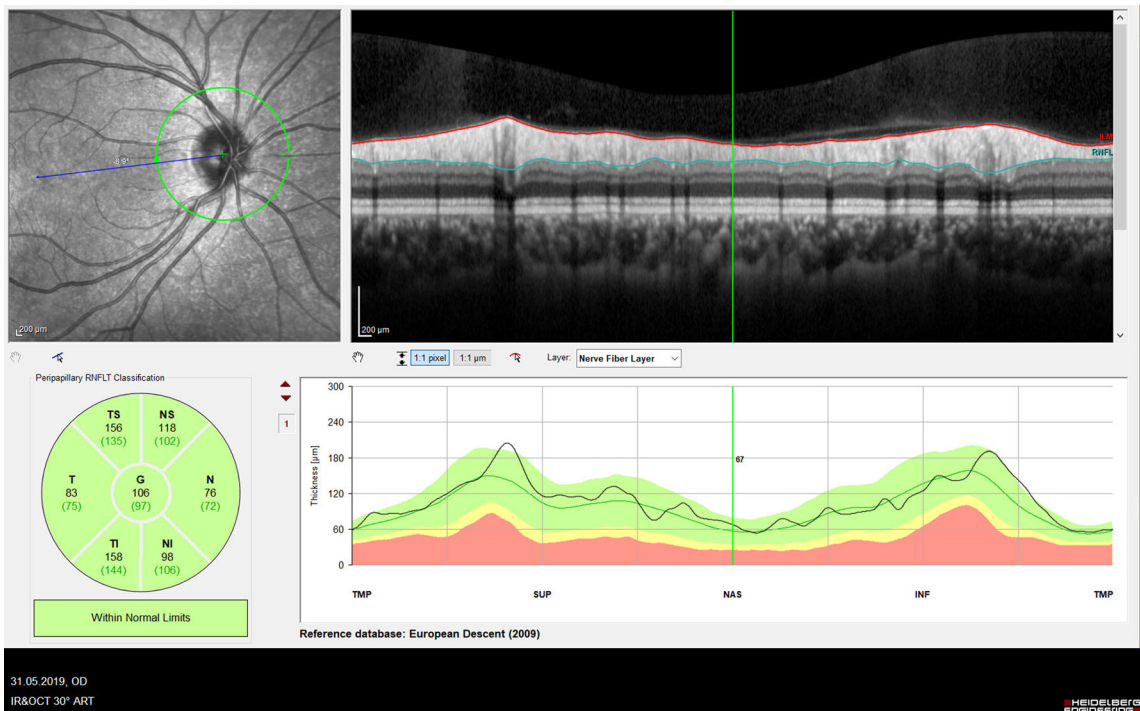
In all included subjects, measurements were taken at the same time interval to prevent diurnal changes. CT was obtained with the EDI mode of the Spectral Domain OCT device (Heidelberg Engineering, Heidelberg, Germany). In the horizontal section image passing through the fovea, measurements were taken in the nasal and temporal regions at a distance of 1500  $\mu\text{m}$  from the central fovea and fovea center. The measurement of CT, which was manually measured and defined as the vertical distance from the outer surface of the retinal pigment epithelium to the choroid-scleral interface, was performed by a single trained technician (Fig. 1). A circular scan centered on the optic disk was used to evaluate the RNFL thickness measurement of the patients (Fig. 2).

### Statistical analysis

SPSS version 26.0 (Chicago, IL, USA) was used for all statistical analyses. Demographic data were calculated using descriptive statistics. Mean and standard deviations were used to describe the data. After all measurements were entered into the SPSS program, a normality test was applied. The student t test was used to compare the continuous variables of the two groups according to the normality test results. Comparison of categorical variables was made using the chi-square test.



**Fig. 1** Measurement of the subfoveal, nasal and temporal (1500 μm away from the fovea) choroidal thickness taken in the enhanced depth imaging mode of the choroidal layer in the subjects included in the study



**Fig. 2** Retinal nerve fiber layer (RNFL) thickness measurement with a circular scan centered on the optic disk of the subjects included in the study

**Results**

This study included 57 females and 51 males. The mean age was similar in both groups ( $36.10 \pm 7.12$

and  $35.58 \pm 7.29$ , respectively,  $p = 0.276$ ). For group 1, the mean time since diagnosis of COVID-19 was  $54.25 \pm 6.36$  days, the number of days since the PCR

test was negative was  $38.45 \pm 6.87$ , and all the subjects were outpatients (Table 1).

It was detected that the CT of the patients in group 1 decreased in all areas compared to group 2, and this decrease was significant in subfoveal, temporal and inferior areas ( $257.48 \pm 32.79$ ,  $273.62 \pm 45.04$ ,  $p = 0.04$ ;  $232.96 \pm 41.79$ ,  $252.76 \pm 46.09$ ,  $p = 0.02$ , and  $245.22 \pm 44.58$ ,  $271.54 \pm 55.07$ ,  $p = 0.01$ , respectively). (Table 2).

In the RNFL analysis of group 1, thickening was detected in all quadrants, although it was not statistically significant, except in the temporal area where it was (superotemporal, superonasal, nasal, inferonasal, inferotemporal, temporal, and global [ $p = 0.08$ ,  $p = 0.45$ ,  $p = 0.73$ ,  $p = 0.64$ ,  $p = 0.74$ ,  $p = 0.02$ , and  $p = 0.10$ , respectively]) (Table 3).

## Discussion

For group 1, it was found that CT decreased in all areas, especially in the subfoveal, temporal, and inferior areas. In addition, although it was not statistically significant in the RNFL analysis of these patients, thickening was detected in all quadrants.

Although the potential transmission of SARS-CoV-2 from the ocular surface is thought to be important,

the route of virus transmission to ocular tissue is still controversial because the presence of SARS-CoV-2 RNA in blood samples has been demonstrated. It has also been reported that conjunctival symptoms range from 0.8 to 32% [11, 12].

Studies have reported that COVID-19 caused by SARS-CoV-2 causes tissue hypoperfusion and thrombosis by causing endothelitis, resulting in neurovascular events and pulmonary artery thrombosis [13–16]. In addition, the presence of cotton wool exudates associated with retinal vascular occlusion and retinal ischemia has been reported in patients with COVID-19 [17–19]. There are studies examining the retinal microcirculation changes in these patients with optical coherence tomography (OCTA). In a study examining patients recovering from COVID-19, significant decreases in superficial capillary plexus vessel density (SCP-VD) and deep capillary plexus vessel density (DCP-VD) were reported in both foveal and parafoveal regions of the macula. Another study reported that moderate and severe COVID-19 patients had decreased central retinal VD [20, 21]. Similarly, patients with COVID-19 have been reported to have lower radial peripapillary plexus perfusion density [22]. However, one study reported that the SCP-VD and DCP-VD of patients recovering from moderate COVID-19 were similar to those of healthy controls.

**Table 1** Demographic and clinical characteristics of the subjects included in the study

Characteristics	Patients recovered from COVID-19 ( $N = 58$ )	Healthy control ( $N = 50$ )	Significance ( $p$ value)
Age (years) (mean $\pm$ SD)	$36.10 \pm 7.12$	$35.58 \pm 7.29$	0.276
Sex, $n$ (%)			
Female	31 (53.44)	26 (52.0)	0.88
Male	27 (46.56)	24 (48.0)	
WBC ( $10^3/\mu\text{L}$ )	$7.16 \pm 2.69$ (3.66–21.93)	–	–
Neutrophil ( $10^3/\mu\text{L}$ )	$4.16 \pm 2.44$ (1.84–19.99)	–	–
Lymphocyte ( $10^3/\mu\text{L}$ )	$4.16 \pm 2.44$ (1.84–19.99)	–	–
CRP (mg/dl)	$1.39 \pm 1.97$ (0.09–7.48)	–	–
D Dimer (mg/l)	$0.31 \pm 0.23$ (0.08–0.96)	–	–
Ferritin ( $\mu\text{g/l}$ )	$74.66 \pm 91.23$ (3.70–552)	–	–
Time elapsed since the diagnosis of the disease (days), (mean $\pm$ SD)	$53.18 \pm 2.84$	–	–
Time elapsed since the PCR test was negative (days), (mean $\pm$ SD)	$38.58 \pm 4.07$	–	–

**Table 2** Choroidal thickness of the subjects included in the study ( $\mu\text{m}$ )

Characteristic	Patients recovered from COVID-19 (Group 1)	Healthy control (Group 2)	Significant ( $p$ )
Subfoveal CT	257.48 $\pm$ 32.79	273.62 $\pm$ 45.04	<b>0.04</b>
CT 1500 $\mu\text{m}$ nasal	225.64 $\pm$ 45.43	241.44 $\pm$ 47.89	0.09
CT 1500 $\mu\text{m}$ temporal	232.96 $\pm$ 41.79	252.76 $\pm$ 46.09	<b>0.02</b>
CT 1500 $\mu\text{m}$ superior	254.42 $\pm$ 43.72	264.08 $\pm$ 46.28	0.28
CT 1500 $\mu\text{m}$ inferior	245.22 $\pm$ 44.58	271.54 $\pm$ 55.07	<b>0.01</b>

Bold values indicate statistically significant

**Table 3** Retinal nerve fiber layer (RNFL) thickness of the subjects included in the study ( $\mu\text{m}$ )

RNFL thickness	Patients recovered from COVID-19	Healthy control(Group 1)	Significant ( $p$ )(Group 2)
Superotemporal ( $\mu\text{m}$ )	147.68 $\pm$ 18.78	142.60 $\pm$ 17.88	0.08
Superonasal ( $\mu\text{m}$ )	120.02 $\pm$ 27.88	117.44 $\pm$ 17.10	0.45
Nasal ( $\mu\text{m}$ )	81.86 $\pm$ 13.40	80.80 $\pm$ 13.48	0.73
Inferonasal ( $\mu\text{m}$ )	122.24 $\pm$ 20.13	120.86 $\pm$ 22.08	0.64
Inferotemporal ( $\mu\text{m}$ )	144.62 $\pm$ 31.56	144.58 $\pm$ 17.24	0.74
Temporal ( $\mu\text{m}$ )	73.18 $\pm$ 12.48	69.20 $\pm$ 9.85	<b>0.02</b>
Global ( $\mu\text{m}$ )	105.50 $\pm$ 9.56	103.20 $\pm$ 9.47	0.10

Bold values indicate statistically significant

Possible reasons for this change in VD were that the study may have been limited only to patients severely affected by COVID-19 or a possible return of damage to the macular capillary plexuses after acute infection [23].

It has been reported that hypoxia may increase circulating proinflammatory cytokine levels, leading to vascular leakage and consequently edema [24]. In addition, it has been reported that this value increased in four out of five patients whose RNFL thicknesses before and after COVID-19 infection were compared [25]. The result of this study may have resulted from the hypoxia-related inflammation and edema caused by the decrease in the choroidal blood supply that we obtained in our study.

The limitations of this study were the relatively small number of participants, the use of a cross-sectional study conducted in a single center, and a lack of long-term follow-up of choroidal thickness change as an indicator of choroidal blood supply with the subjects. The potential strength of this study is that, to our knowledge, it is the first study to examine choroidal blood supply, which plays an important role in eye blood supply in patients recovering from COVID-19 using EDI-OCT.

In conclusion, individuals in group 1 showed decreased CT in all areas in these patients. Therefore, the results of our study may contribute to the understanding of the systemic microvascular waste of this disease. However, these findings should be demonstrated and supported by multicenter, long-term, high case series studies.

**Author contribution** Study design: S.E., B.B.Ş., M.K., S.A., M.E.D.; Study intervention: S.E., B.B.Ş., M.E.D., M.K., U.K., B.D Methodology: S.E., B.B.Ş., M.K., U.K.; Formal Analysis: S.E., S.A., M.K., U.K., B.D., B.B.Ş.; Writing–Original Draft Preparation: S.E., B.B.Ş., M.K., B.D., S.A. Writing–Review and Editing: S.E., U.K., L.H., M.E.D., S.A.; Visualization: S.E., B.D., B.B.Ş., U.K., L.H., S.A.; Supervision: S.E., M.E.D., B.B.Ş., L.H., M.K., U.K., M.E.D.

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**Data availability** Data and material are available.

**Declarations**

**Conflict of interests** The authors declare that they have no conflict of interest.

**Consent to participate** Informed consents were obtained from the participants.

**Consent to publish** Participants signed informed consent regarding publishing their data.

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