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The Effect of Coronavirus Disease 2019 on Retinal Thickness: A Prospective Study COVID-19 and Retina

COVID-19'un Retina Kalınlığı Üzerindeki Etkisi: Prospektif Bir Çalışma COVID-19 ve Retina

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ABSTRACT

Objectives: To prospectively evaluate the effect of coronavirus disease 2019 (COVID-19) on retinal thickness.

Methods: Twenty-six cases of COVID-19 infection confirmed by real-time polymerase chain reaction constituted the study group. The thickness values of the macula, retinal nerve fiber layer (RNFL), and ganglion cell complex (GCC) measured by optical coherence tomography before infection were compared with the thickness values at the 1st and 3rd months after the infection. The control group consisted of 13 cases that were determined not to have the disease by antibody testing. Only the right eyes in all cases were included in the study. For statistical analysis, repeated measures analysis of variance or the Friedman test were used to compare baseline, 1st, and 3rd-month data.

Results: All cases in the COVID-19 group showed mild symptoms. No retinal pathology was observed in any of the cases with COVID-19. There was no difference in retinal thickness measurements at baseline, 1st, and 3rd months in the control group ($p>0.05$). There was no difference at baseline, 1st and 3rd-month RNFL and GCC thickness values in the COVID-19 group ($p>0.05$). The central macular thickness (MT) in the COVID-19 group was thicker at 1 and 3 months than before infection ($p=0.03$).

Conclusion: Coronavirus infection affected the central MT in the first 3 months. RNFL and GCC thicknesses did not change after infection. However, a long-term follow-up of the cases may be required to observe the effects of the virus on retinal thickness.

Keywords: Coronavirus; Coronavirus disease 2019; Ganglion cell complex; Retina; Retinal nerve fiber layer.

ÖZET

Amaç: Bu çalışmanın amacı, koronavirüs hastalığının (COVID-19) retina kalınlığı üzerindeki etkisini prospektif olarak değerlendirmektir.

Yöntem: Gerçek zamanlı polimeraz zincir reaksiyonu ile doğrulanmış COVID-19 enfeksiyonu olan 26 olgu çalışma grubunu oluşturdu. Optik koherens tomografi ile enfeksiyon öncesi ölçülen makula, retina sinir lifi tabakası (RSLT) ve ganglion hücre kompleksi (GHK) kalınlık değerleri, enfeksiyon sonrası birinci ve üçüncü aylardaki kalınlık değerleri ile karşılaştırıldı. Kontrol grubu, antikor testi ile hastalığı olmadığı belirlenen 13 olgudan oluşturuldu. Tüm olguların sadece sağ gözleri çalışmaya dahil edildi. İstatistiksel analiz için, başlangıç, birinci ve üçüncü ay verilerini karşılaştırmak için tekrarlanan ölçümler varyans analizi veya Friedman testi kullanıldı.

Bulgular: COVID-19 grubundaki tüm olgular hafif semptomlar gösterdi. COVID-19 olgularının hiçbirinde retinal patoloji gözlenmedi. Kontrol grubunda başlangıç, birinci ve üçüncü aylarda retina kalınlık ölçümlerinde fark yoktu ($p>0,05$). COVID-19 grubunda başlangıç, birinci ve üçüncü ay RSLT ve GHK kalınlık değerlerinde fark yoktu ($p>0,05$). COVID-19 grubunda merkezi makula kalınlığı enfeksiyon öncesine göre birinci ve üçüncü ayda daha kalındı ($p=0,03$).

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Sonuç: Koronavirüs enfeksiyonu ilk üç ayda santral makula kalınlığını etkiledi. Enfeksiyondan sonra RSLT ve GHK kalınlıkları değişmedi. Ancak virüsün retina kalınlıkları üzerindeki etkilerini gözlemlemek için olguların uzun süreli takibi gerekebilir.

Anahtar sözcükler: Koronavirüs; COVID-19; retina; retina sinir lifi tabakası; ganglion hücre kompleksi.

Since the coronavirus was demonstrated in eye tissues, many studies have reported the effects of the virus on the eye.[1-3] The virus enters the cell using the angiotensin-converting enzyme 2 (ACE2) receptor, and many tissues of the eye have ACE2 receptors.[4] The virus can act on the retina by direct viral invasion by binding to ACE2 receptors expressed in retinal and choroidal vessel endothelium, retinal pigment epithelium, photoreceptors, and Müller cells. In addition, the systemic effects of the virus may cause inflammation in the retina.[5] Inflammation in the retina and the coagulation-enhancing effect of the virus may cause micro occlusions in the retinal vessels.[6] In addition, the protein structure of the virus shows characteristics similar to those of the retinal pigment epithelium. Therefore, in addition to micro occlusions, the autoantibodies formed may affect the retina in the late period and cause neurodegenerative changes.[7]

Optical coherence tomography (OCT) is a non-invasive imaging method used in the cross-sectional evaluation of the retina.[8] Many studies have compared retinal OCT and OCT angiography (OCTA) measurements of coronavirus disease 2019 (COVID-19) cases. Most OCTA studies reported a decrease in macular vascular density in COVID-19 cases.[9,10] Unlike OCTA studies, OCT studies have reported inconsistent results. While some of these studies reported that there was no difference between the retinal thicknesses of COVID-19 cases and the control group, others reported a decrease or increase in retinal thickness in COVID-19 cases.[11-13]

This study aimed to prospectively investigate, using OCT, whether COVID-19 infection affects retinal thickness. For this purpose, retinal thickness measurements of health-care workers in the eye clinic before COVID-19 infection were compared with the 1st and 3rd months post-infection measurements. To our knowledge, this is the first study to prospectively report the effect of COVID-19 on the retina.

Methods

This prospective study conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Research Protocol and Ethics Committee. Informed written consent was obtained from all participants.

A total of 98 health-care professionals working in the eye clinic were included in this study. Health workers were questioned in detail. Of these, 20 cases who had had COVID-19 and/or had close contact with COVID-19 before the start date of the study, had any suspected history of COVID-19 symptoms, had systemic and/or ocular diseases, and/or had eye surgery were excluded from the study. The remaining 78 participants underwent a complete ophthalmologic examination. Retinal nerve fiber layer (RNFL), macula, and ganglion cell complex (GCC) thicknesses were measured in all participants with Fourier-domain OCT (RTVue-100, Optovue, Fremont, CA). After the ophthalmological examination and OCT measurements performed at the very beginning of the pandemic, 26 cases of COVID-19 confirmed by real-time polymerase chain reaction (RT-PCR) were included in the prospective part of the study. The history of pneumonia, fever, loss of taste and smell, and hospitalizations were taken, and the findings were noted. Full ophthalmological examinations and retinal thickness measurements with OCT were performed again in the 1st and 3rd months after the infection of the participants who had COVID-19 and were included in the study group. Only the data from the right eyes of all cases were included in the study. Furthermore, OCT data before infection were compared statistically with the data of the 1st and 3rd months after infection and also with the data of the control group.

The control group was formed as follows: after the initial data collection, 20 participants were accepted as the lead control group. Their OCT measurements were performed again 1 and 3 months after the first data were obtained. In the lead control group, 5 cases with positive RT-PCR tests within 3 months were included in the study group. Two cases were excluded from the study due to suspicious symptoms. The right eyes of 13 cases who were confirmed to have no COVID-19 infection by antibody testing at the end of the 3rd month from the beginning of the study constituted the control group.

A complete ophthalmologic examination, including best-corrected visual acuity (BCVA), corneal thickness measurement, intraocular pressure measurement with Goldman applanation, biomicroscopic examination, and detailed

fundus examination, was performed in all cases. Macular thickness (MT) was measured in the areas of the fovea (central 1 mm circle), parafovea (1–3 mm circle), and perifovea (3–6 mm circle) with OCT. The average, superior, and inferior GCC thickness and average, temporal, superior, nasal, and inferior RNFL thickness values were recorded. All OCT measurements were repeated at least twice. The best measures of signal strength were included in the study. Measurements that were not focused on the fovea or optic disc and had low signal strength were not included in the study.

SPSS Version 22 (IBM SPSS, Türkiye) was used for the statistical analysis. The data were initially tested with the Kolmogorov–Smirnov test to determine whether the distribution of variables was normal. Parametric tests were used for normally distributed data, and nonparametric tests were used for non-normally distributed data. Pearson's chi-square test was used to compare the categorical variables in different groups. An independent t-test or Mann–Whitney U test was used to compare the baseline values of the groups. Repeated measures of analysis of variance, or the Friedman test, were used to compare the baseline, 1st, and 3rd-month measurements within the groups. The Wilcoxan test with Bonferroni correction was used for pairwise comparison of statistically significant results. A $p<0.05$ was considered statistically significant.

Results

The mean age of the COVID-19 group was 37.92±9.13 years, and the mean age of the control group was 35.84±10.18 years (p=0.523). The BCVA of all cases was 10/10 with a Snellen chart (decimal system). No ocular or retinal pathology was observed before or after infection in any of the cases.

None of the cases with COVID-19 were hospitalized, and none of them developed pneumonia. Loss of taste and smell occurred in nine cases.

The demographic characteristics of both groups are shown in Table 1. There was no difference between the groups in terms of age, gender, intraocular pressure, refraction values, or axial length ($p>0.05$).

There was no difference between the groups in terms of the baseline retinal thickness values ($p>0.05$) (Table 2).

In the control group, there was no difference in the macula, RNFL, and GCC values in the baseline, 1st, and 3rd-month comparisons ($p>0.05$). In the COVID-19 group, central MT was significantly higher in the 1st, and 3rd months compared to baseline (p=0.001, p=0.013, respectively) (Table 3).

Discussion

This study compared the retinal thicknesses of the cases before COVID-19 with the retinal thicknesses of the 1st and 3rd months after the infection. In our study, the central MT of the cases was significantly higher in the 1st and 3rd months after COVID-19 compared to the baseline. No significant differences were observed in the RNFL and GCC values after COVID-19. To the best of our knowledge, our study is the first to prospectively evaluate retinal thickness in COVID-19 cases with pre-infection data.

Coronavirus-19 was demonstrated in postmortem biopsies of retinal tissue.[14] The virus can cause inflammation in the retina by directly invading the retina or through systemic inflammatory mediators. In addition, the inflammation in the retinal vascular endothelium and the microthrombi formed by the coagulation-enhancing effect of the virus may cause edema in the retina.[15] Therefore, the effects of COVID-19 on the retina were mostly reported in OCTA studies. Many OCTA studies have shown decreased retinal plexus density in the macular area.[9,10,16] This result does not seem unexpected because of the inflammation and microthrombi that occur in the acute phase. However, some studies have failed to show this decrease.[17] Furthermore, OCTA does not show

Table 1. Comparison of baseline characteristics of participants between groups

	COVID-19 group (n=26) eyes	Control group (n=13) eyes	p
Age (year)	37.92±9.13	35.84±10.18	0.523
Sex (female/male)	17/9	8/5	0.813
Spherical equivalent	−0.39±1.04	0.33±0.09	0.086
Axial length (mm)	23.28±0.56	23.16±0.65	0.549
Intraocular pressure (mmHg)	13.53±2.17	14.30±1.97	0.291

Statistically significant, $p<0.05$.

Table 2. Comparison of baseline retinal thicknesses between groups

	COVID-19 group	Control group	p
RNFL (µm)			
Average	108.80±10.58	111.15±13.25	0.552
Temporal	87.19±10.51	85.69±9.57	0.668
Superior	136.11±17.07	142.92±20.44	0.279
Nasal	78.46±13.24	78.76±10.04	0.964
Inferior	133.46±16.43	136.92±25.73	0.664
GCC (µm)			
Average	100.28±6.64	101.76±5.52	0.494
Superior	99.71±6.71	100.54±5.77	0.705
Inferior	100.87±6.93	102.98±5.68	0.350
Makula (µm)			
Fovea	239.92±20.70	244.69±22.89	0.520
Parafovea	321.72±15.24	319.30±14.16	0.639
Perifovea	281.88±12.49	282.30±13.31	0.923

RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; µm: Micrometer; statistically significant, p<0.05.

occlusions in vessels smaller than 20 µ, and therefore, microthrombi were not excluded in these studies.[18] Sim et al.[19] reported retinal vascular changes in one of nine eyes with COVID-19. In our study, no ocular or retinal findings were observed in any patient who recovered from COVID-19. However, the mean age of our cases was low, and they did not have comorbid diseases. They also experienced mild symptoms during the infection. For these reasons, retinal vascular findings may not have been observed in our cases.

There are conflicts in the results of OCT studies investigating the retinal thicknesses of patients who recovered from COVID-19. Oren et al.[3] found the central MT to be higher in COVID-19 cases compared to controls during the acute recovery period. Another study reported that the retinal thickness was not different from the controls, despite the difference in choroidal thickness in COVID-19 cases in the acute phase.[12] Naderi Beni et al.[20] compared the retinal thickness of COVID-19 cases 40–95 days after recovery with healthy controls. They reported that MT was higher in the parafoveal and perifoveal areas in patients who recovered from COVID-19 compared to healthy controls. Brantl et al.[17] did not detect any changes in the retina 3 months after infection. These conflicting results in the literature may be because the studies are cross-sectional studies and the cases were included in the study at different time sections after infection due to different reasons, such as mild or severe disease. In our study, we found that the central MT was higher than the initial values 1 month after infection. This thickness increase continued in the 3rd month.

Studies investigating GCC and RNFL thicknesses using OCT in cases with COVID-19 have also shown different results. Naderi Beni et al.[20] reported an increase in peripapillary RNFL thickness. Burgos-Blasco et al.[21] also reported an increase in peripapillary RNFL thickness in recovered COVID-19 patients. However, there was a decrease in macular RNFL and an increase in GCC thickness. Oren et al.[3] reported that despite the increase in MT, there was a thinning of the GCC thickness. González-Zamora et al.[22] reported thicker RNFL and thinner GCC thicknesses in cases with COVID-19. Unlike studies reporting increased RNFL thickness, Ornek et al.[11] reported localized peripapillary RNFL thinning in cases of COVID-19. Cennama et al.[23] reported that in the measurements performed 6 months after the patients recovered from COVID-19, pneumonia, retinal vascular changes were still observed compared to the control group; the RNFL thickness decreased, but the GCC thickness did not change. Savastano et al.[24] did not find that the RNFL and GCC thicknesses of cases with COVID-19 were different from those of the control group. However, there was a linear relationship between radial peripapillary capillary plexus perfusion density, flow index, and RNFL. In the study of Abrishami et al.,[25] average GCC thickness and average, superior, and inferior RNFL thicknesses did not change 3 months after infection. However, RNFL thinning occurred in the nasal quadrant. Although this study was a prospective, it did not have pre-infection data on the cases. A review reporting the results of imaging modalities in cases

Table 3. Comparison of retinal thicknesses baseline, 1st and 3rd month in COVID-19 and control groups

	Baseline (1)	1. Month (2)	3. Month (3)	p
Average RNFL (µm)				
COVID-19	108.80±10.58	107.76±10.54	108.53±9.65	0.308
Control	111.15±13.25	110.46±11.28	111.07±11.39	0.801
Temporal RNFL (µm)				
COVID-19	87.19±10.51	86.80±8.32	85.76±10.06	0.733*
Control	85.69±9.57	87.92±11.05	87.00±10.58	0.625
Superior RNFL (µm)				
COVID-19	136.11±17.07	134.19±17.34	135.46±16.51	0.380
Control	142.92±20.44	137.15±14.61	140.30±18.91	0.323
Nasal RNFL (µm)				
COVID-19	78.46±13.24	77.73±11.17	79.65±11.39	0.297
Control	78.76±10.04	76.53±6.29	83.23±12.45	0.210*
Inferior RNFL (µm)				
COVID-19	133.46±16.43	132.34±17.61	133.30±16.11	0.630
Control	136.92±25.73	140.23±25.22	135.30±20.09	0.125
Average GCC (µm)				
COVID-19	100.28±6.64	102.30±9.11	101.33±6.77	0.120
Control	101.76±5.52	106.03±8.00	105.83±7.96	0.184
Superior GCC (µm)				
COVID-19	99.71±6.71	102.12±9.46	100.98±7.21	0.100
Control	100.54±5.77	104.51±8.11	104.21±8.07	0.143
Inferior GCC (µm)				
COVID-19	100.87±6.93	102.46±9.16	101.69±6.69	0.237
Control	102.98±5.68	107.52±8.15	107.21±7.82	0.117
Fovea (µm)				
COVID-19	239.92±20.70	245.92±21.87	248.07±26.22	**0.03*†** **1–2 0.001** **1–3 0.013** 2–3 0.821
Control	244.69±22.89	242.69±20.59	243.61±20.63	0.481
Parafovea (µm)				
COVID-19	321.72±15.24	322.69±15.53	323.19±16.14	0.585
Control	319.30±14.16	320.23±13.81	321.30±13.11	0.061
Perifovea (µm)				
COVID-19	281.88±12.49	284.23±12.14	284.03±12.69	0.558
Control	282.30±13.51	283.07±13.56	283.07±13.54	0.077

RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; µm: Micrometer; *, Friedman test; others, repeated measures analysis of variance; †, p<0.05; statistically significant results are shown in bold.

with COVID-19 summarized the OCT findings in all these studies as follows: thinner GCC layer, thicker RNFL layer, and thicker central macula.[26]

Because of its high resolution and advanced scanning systems, OCT provides repeatable and reliable data. While macular measurements show the highest reproducibility rates, peripapillary RNFL measurements should be carefully considered. However, the reproducibility of OCT measurements in different segments in macular and peripapillary RNFL assessments depends on the scan direction, and the agreement between scans varies according to the measured sector.[27] Horizontal scanning corresponds to fewer blood vessels in the horizontal segments (nasal and temporal) and reduces repeatability variation. The opposite is true for vertical segments.[28] For this reason, studies investigating the retinal thickness of cases with COVID-19 should be carefully

evaluated in terms of variations based on the scanning programs of the devices used.

In addition, studies in the literature differ from each other in terms of time of inclusion after infection and severity of disease. Zapata et al.[10] emphasized the relationship between the severity of the disease and a decrease in central vascular density. The second study conducted with the same case group showed that the decrease in vascular density continued 8 months after the infection.[29] In our study, unlike in the literature, we did not observe any difference in RNFL and GCC thicknesses before and after infection. This result may be due to the mild COVID-19 symptoms in our cases and the short follow-up period. In the long term, thinning of retinal thickness may occur because of ischemia from retinal microocclusions and autoantibodies. Longer follow-ups on the cases may shed light on this issue.

The strength of this study is its prospective nature. Data for all cases were collected before infection. In addition, we created a control group with cases determined by antibody testing not to have COVID-19. However, the number of cases in both groups was limited. In addition, all the COVID-19 cases had mild diseases. Therefore, this study did not report retinal findings in severe cases. There may also be variations in the repeatability of the OCT measurements.

Conclusion

The current study compared pre-COVID-19 retinal thicknesses with post-infection thicknesses. While the central MT did not change in the control group, it was higher in the COVID-19 group in the 1st and 3rd months compared to the baseline. RNFL and GCC values did not change after infection. However, long-term follow-up may better elucidate the effects of infection on the retinal layers.

Disclosures

Ethics Committee Approval: This prospective study conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Research Protocol and Ethics Committee (HNEAH-KAEK 2021/KK/166). Informed written consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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