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Research Paper

COVID-19 related changes in corneal curvature and endothelium after mild infection

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ABSTRACT

Purpose: To investigate subclinical corneal changes using corneal topography in the evaluation of corneal curvature and specular microscopy in the evaluation of the endothelial layer after mild coronavirus disease 2019 (COVID-19).

Methods: In this prospective study, 112 eyes of 56 individuals with mild COVID-19 who recovered were investigated. Mean cell density (CD), mean coefficient of variation (CV), mean percentage of hexagonal cells, mean cell area (AVG), and central corneal thickness (CCT) were recorded from specular microscopy. K readings, including simulated keratometry flat (K1), simulated keratometry steep (K2), average keratometry (Kmean) and maximum keratometry (Kmax), pachymetric measurement and central corneal thickness (CCT), corneal volume (CV), topographic astigmatism (TA), curvature asymmetry front (CAf) and curvature asymmetry back (CAb) were recorded from corneal topography. Best corrected visual acuity (BCVA), spherical equivalant and biometric measurements were recorded.

Results: The mean time interval between examinations before and after COVID-19 infection was approximately one year. Analysis of specular microscopy data showed a statistically significant change in all endothelial cell parameters ($p<0.001$) except the cell count ($p = 0.358$). The median (range) endothelial cell density (ECD) value was significantly lower after COVID-19 at 2356 (2289–2400) than before, when it was 2596 (2545–2640). Furthermore, CCT values showed a significant increase ($p<0.001$). The topographic values including K2, Kmax and TA and biometric measurements did not change. The Spherical Equivalant (SE) values showed significant myopic progression after COVID-19 ($p<0.001$).

Conclusion: Endothelial parameters changed more than the changes in corneal curvature and ocular biometric measurements after mild COVID-19. The decrease in endothelial cell number and hexagonality and increase in polymorphism after COVID-19 were striking.

Infection

WHAT WAS KNOWN

Many studies have shown that age, genetic make-up, some corneal diseases and anterior segment surgery result in changes to the corneal endothelium and its structure.

WHAT THIS PAPER ADDS

The effects of the COVID-19 pandemic, which has dominated global healthcare concerns for the last 3–4 years, was investigated in the cornea, and found changes in the most refractively active tissue. This study showed that there was a significant change in refraction and endothelial involvement after mild COVID-19 infection. Refractive changes and changes in corneal endothelial

Abbreviations: CD, Cell density; CV, Coefficient of variation; CA, Cell area; AVG, Average cell area; CCT, Central corneal thickness; K1, Keratometry flat; K2, Keratometry steep; Kmean, Average keratometry; Kmax, Maximum keratometry; CV, Corneal volume; TA, Topographic astigmatism; CAf, Curvature asymmetry front; CAb, Curvature asymmetry back; BCVA, Best corrected visual acuity; ECD, Endothelial cell density; SD, Standard deviation; SE, Spherical equivalant; ACE-2, Angiotensin-converting enzyme -2; TMPRSS2, Type II transmembrane serine protease; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; PCR, Polymerase chain reaction; SpO2, Oxygen saturation; PaO2/FiO2, Partial pressure of oxygen to fraction of inspired oxygen; D, Diopter.

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cell number and function should be kept in mind in patients with COVID-19 infection. Procedures involving refractivity should be performed with more caution in such patients. Future large-scale, long-term studies should further investigate these observations.

1. Introduction

Coronavirus disease 2019 (COVID-19), a global pandemic, has been associated with a wide range of symptoms, from minimal viral illness to acute respiratory distress syndrome, multi-organ damage and death [1]. There are many case reports of ocular effects of COVID-19, ranging from conjunctivitis and ocular surface involvement to vasculitic retinal vein occlusion and optic neuritis [2–5]. Angiotensin-converting enzyme-2 (ACE2) receptors that bind viral spike proteins and type II transmembrane serine protease (TMPRSS2), the cell surface-associated protease that binds these proteins to the receptor, have been identified as being central to the viral pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), entry into the host cell. This discovery drew attention to tissues containing these two important structures and, when pathological findings are not evident, these unexpected findings have become a subject of research into sub-clinical changes in these structures [6–8].

The cornea expresses ACE2 receptors. In an immunohistochemical study examining the expressions of viral entry factors, ACE2, DC-SIGN/DC-SIGNR and TMPRSS2 expression were detected in both the cornea and conjunctival epithelium. Thus, the authors suggested the ocular surface as a potential route for SARS-CoV-2 transmission and, in corneal transplants, the risk of transmission cannot be ignored [9,10]. A prevalence study reported the presence of SARS-CoV-2 RNA and proteins in the ocular tissues of donors with COVID-19 [11]. It is unclear whether the presence of SARS-CoV-2 RNA and proteins is due to primary ocular surface infection or to the backward transport of viral particles via the nasolacrimal duct and what changes occur in infected ocular surface cells [11]. Since the corneal epithelium and endothelium contain ACE receptors, although pathological findings are not detected in patients with COVID-19, subclinical changes in these structures may have occurred and should be monitored. Early detection of subclinical changes that may have occurred will enable taking early clinical management measures to prevent or avoid risky chronic ophthalmological situations, such as corneal edema due to endothelial insufficiency, corneal graft failures, changes in the course of ectatic diseases, changes in refractive status, and retinal vascular and inflammatory changes. The aim of the present study was to investigate and document these subclinical ocular changes using corneal topography in the evaluation of the corneal curvature and specular microscopy in the evaluation of the endothelial layer after mild COVID-19 in young adults.

2. Materials and methods

This prospective study was conducted in young adults with mild COVID-19 in the ophthalmology department of Recep Tayyip Erdogan University. The study was approved by the local human research ethics committee. The study adhered to the principles of the Declaration of Helsinki and written informed consent was obtained from all participants, consistent with Turkish National Research Ethics Committee resolution for research conducted during the COVID-19 pandemic.

Fifty six patients, aged 23–34 years, who attended our outpatient ophthalmology clinic for routine eye examination, without any known ophthalmic pathology and who did not have any systemic chronic disease, were included in the study. Their ophthalmic examination, biometric measurements, specular microscopy and corneal topograhy results were recorded. All eligible patients were questioned about the symptoms of COVID-19 during the first examination, and those who had no symptoms and had no previous polymerase chain reaction (PCR) positive COVID-19 test and had not yet been vaccinated were included in the study. Participation in the study was on a voluntary basis and the majority of the participants were hospital personnel. The same measurements were repeated during follow-up examinations of the patients, approximately one year after COVID-19 PCR positivity. All participants had a single infection episode which was confirmed by PCR tests. Severe COVID-19 is defined as dyspnoea, respiratory frequency $\geq$ 30 breaths/minute, oxygen saturation (SpO2) $\leq$93 %, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) $<$300 mm Hg and/or lung infiltrates $>$50 % [12]. The active period of the disease is defined as the presence of signs, symptoms and radiological and laboratory investigations consistent with severe COVID-19. Mild COVID-19, on the other hand, is defined as a clinical course in which the condition improves on follow-up, PCR and laboratory findings are positive, without radiological evident involvement and does not require hospitalisation. Recovery was considered as the absence of signs and symptoms of COVID-19 together with normal laboratory results. Among the patient group initially included in the study, those who were vaccinated with any COVID-19 vaccine during follow-up and those who had COVID-19 again during follow-up were subsequently excluded. The study was completed with patients who did not have recurrent PCR positivity in their medical history at a mean of one year follow-up. Patients who required intubation and hospitalization after COVID-19 and whose systemic and ophthalmic complaints continued were excluded. Patients with refractive error more than 4 diopters (D), glaucoma, uveitis, corneal disease, retinal pathology, previous eye surgery, uncontrolled diabetes and systemic uncontrolled pathology were not included in the study.

Ophthalmic examination included best corrected visual acuity (BCVA), refractive data as spherical equivalant was obtained after cycloplegia with an auotorefractometer (Topcon KR-8800, Tokyo, Japan), biomicroscopic findings of anterior and posterior segment evaluation, non-contact ocular biometry findings (Lenstar LS 900, Haag-Streit Inc., Kaeniz, Switzerland), topographic parameters and specular microscopic findings.

3. Ethics statement

The study adhered to the principles of the Declaration of Helsinki and written informed consent was obtained from all participants consistent with Turkish National Research Ethics Committee resolution for research conducted during the COVID-19 pandemic. 2020/245.

4. Corneal topography and specular microscopy evaluation

Scheimpflug camera combined with placido-disk corneal topography (Sirius, CSO Inc, Florence, Italy) was used for assessing the corneal surface. From topographic records, K readings, simulated keratometry flat (K1), simulated keratometry steep (K2), average keratometry (Kmean) and maximum keratometry (Kmax), pachymetric measurement, central corneal thickness (CCT, in mm), corneal volume (CV, in mm^3), topographic astigmatism (TA), curvature asymmetry front (CAf) and curvature asymmetry back (CAb) were recorded.

Corneal endothelial evaluation was performed using Tomey EM-4000 specular microscopy (Tomey GmbH, Germany). All measurements were made by the same experienced trained technician. On proper alignment on the center of the cornea, endothelial cells were imaged at least three times in a non-contact fashion. Endothelial cell density (ECD, cell numbers/mm^2), counted endothelial cells (Num: the number of cells that remained in the evaluation frame), average cell area (AVG, [μm^2], the mean cell area), minimum cell area (CAmin, [μm^2], the smallest cell area measured in the evaluation frame), maximum cell area (CAmax, [μm^2], the largest cell area within the evaluation frame), standard deviation of the mean cell area (SD), coefficient of variation in cell area (CV, [%], SD of cell area/average cell area $\times$ 100), 6 A (the percentage of hexagonal endothelial cells was determined as an

indicator of pleomorphism, [%]) and central corneal thickness (CCT, in mm) were noted. Each measurement was calculated from images with at least 100 cells (Fig 1).

5. Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows, version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov test was used to assess the assumption of normality. Variables that did not have normal distribution were expressed as medians (25th percentile-75th percentile). The 95 % confidence interval for the mean difference was also given. Comparisons of dependent samples were carried out using Wilcoxon Signed Ranks test. A p-value <0.05 was considered as statistically significant.

6. Results

This study was conducted in 112 eyes of 56 patients and their before and after COVID-19 examination results were compared. The mean age was 27.9 ± 2.9 years and all participants were between 23 and 34 years old and all were working. The gender distribution of the patients was 52 (46.4 %) male, 60 (56.3 %) female. The mean interval between before COVID-19 examination and COVID-19 positivity was 29.58±10.21 days and the mean interval between COVID-19 PCR positivity and the post-COVID-19 examination was 344.46±33.95 days. The mean time between the first measurements and the follow-up measurements after contracting SARS-Cov-2 was approximately one year. The mean spherical equivalant was −0.75 (−1.0–0.25) before COVID-19 and was −1.25 (−1.75–−1.0) on the post-infection examination (p<0.001). The presence of myopic progression was evident. On the BCVA evaluation there was no significant difference between the pre- and post-infection measurement, all patients had 1.0 Snellen visual acuity, both before and after COVID-19. The changes in the biometrical and topographical data of the patients are shown in Table 1. While a significant decrease was observed in K1 (p = 0.008) and Kmean (p = 0.006), which was remarkable in the topographical examination, no significant change was observed in Kmax (p = 0.307) or topographical astigmatism (p = 0.472).

Table 2 shows the specular microscopy findings, both before and after COVID-19. Analysis of specular microscopy data showed a significant change in all endothelial cell parameters (p<0.001) except for the number of cells (p = 0.358). The median ECD value was significantly lower after COVID-19 at 2356 (2289–2400) than before COVID-19 when it was 2596 (2545–2640). The decrease in ECD between the two measurements taken almost one year apart was remarkable (mean difference −241.34 cell/mm^2; 95 % CI −251.55 to −231.13 cell/mm^2 and mean difference −9.29 %; 95 % CI −9.69 to −8.90 %). The mean CV value was 39 (38–42) before COVID-19 and 42 (40–44) after COVID-19. The mean 6A value was 50 (48.2–52) before COVID-19 and 48 (46–49) after COVID-19. Besides that, CCT values showed a remarkable increase after COVID-19 (p<0.001). Corneal parameters before and after COVID are shown by box plot graph (Fig. 2).

Table 1
Biometrical and topographical evaluation of before and after COVID-19 infection measurements.

	Before COVID-19	After COVID-19	p value
Biometrical data			
AL (mm)	23.86 (23.38–24.08)	23.87 (23.36–24.10)	0.070
ACD (mm)	3.20 (3.13–3.52)	3.21 (3.14–3.51)	0.123
LT (mm)	3.55 (3.48–3.66)	3.55 (3.49–3.68)	0.121
WTW (mm)	12.13 (11.89–12.33)	12.12 (11.89–12.34)	0.376
Corneal topographical data			
K1 (D)	42.78 (42.52–43.24)	42.77 (42.52–43.22)	**0.008**
K2 (D)	43.27 (42.89–43.67)	43.29 (42.87–43.56)	0.272
Kmean (D)	43.09 (42.84–43.33)	43.05 (42.81–43.23)	**0.006**
Kmax (D)	44.64 (44.27–45.02)	44.62 (44.22–44.96)	0.307
Cyl (D)	−0.70 (−0.90–−0.44)	−0.64 (−0.88–−0.46)	0.472
CCT (mm)	529 (520–538)	542 (537–549)	**<0.001**
HVID (mm)	11.94 (11.65–12.58)	11.96 (11.66–12.28)	0.236
ICA (°)	48.50 (46.0–51.0)	48.0 (46.0–51.0)	0.354
CV (mm^3)	56.47 (55.78–57.03)	56.50 (55.82–57.03)	**0.017**

AL: Axial length, CCT: Central corneal thickness, ACD: Anterior chamber depth, LT: Lens thickness, WTW: white to White, Cyl: Korneal astigmatism, HVID: Horizontal visibl iris diameter, ICA: Iridocorneal angle, CV: corneal volume, D: diopter.

Table 2
Specular microscopy findings between before and after COVID-19 infection.

	Before COVID-19	After COVID-19	p value
ECD (cell numbers/mm^2)	2596 (2545–2640)	2356 (2289–2400)	**<0.001**
NUM	278 (267–293)	279 (267–293)	0.358
AVG (µm^2)	362 (358–364)	371 (368–374)	**<0.001**
CAmax (µm^2)	819 (769–846)	841 (790–870)	**<0.001**
CAmin (µm^2)	102 (95.2–110)	114 (106–119)	**<0.001**
SD	117 (110–124)	122 (114–129)	**<0.001**
CV (%)	39 (38–42)	42 (40–44)	**<0.001**
6 A (%)	50 (48.2–52)	48 (46–49)	**<0.001**
CCT (µm)	533 (526–538)	548 (545–555)	**<0.001**

ECD: endothelial cell density, NUM: number of cells, AVG: average cell area, CAmax: maximum cell area, CAmin: minimum cell area, SD: standard deviation, CV: coefficient of variation in cell area. 6 A: the percentage of hexagonal endothelial cells, CCT: central corneal thickness.

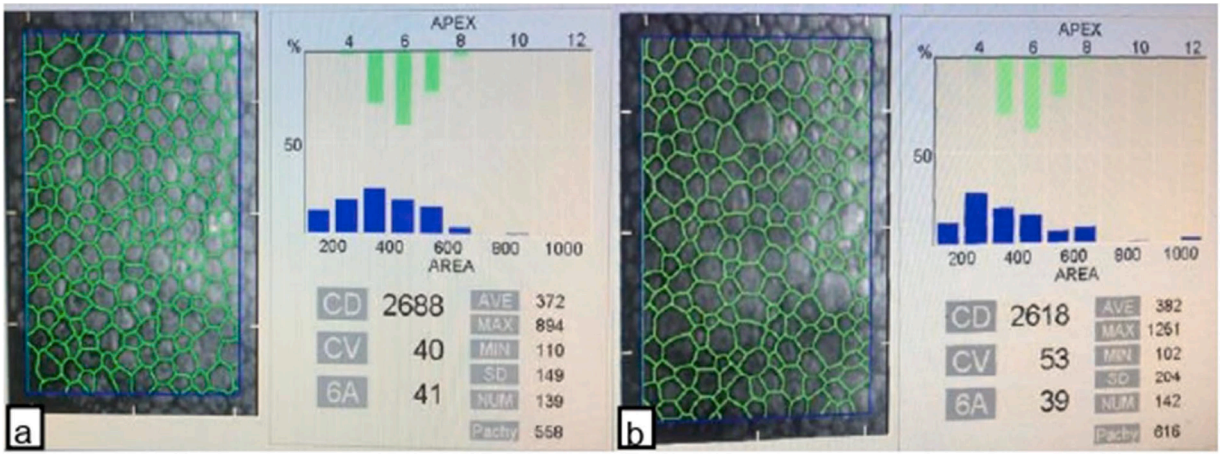

Fig. 1. Specular microscopic findings of an individual a) before mild COVID-19; and b) approximately one year after mild COVID-19 are seen.

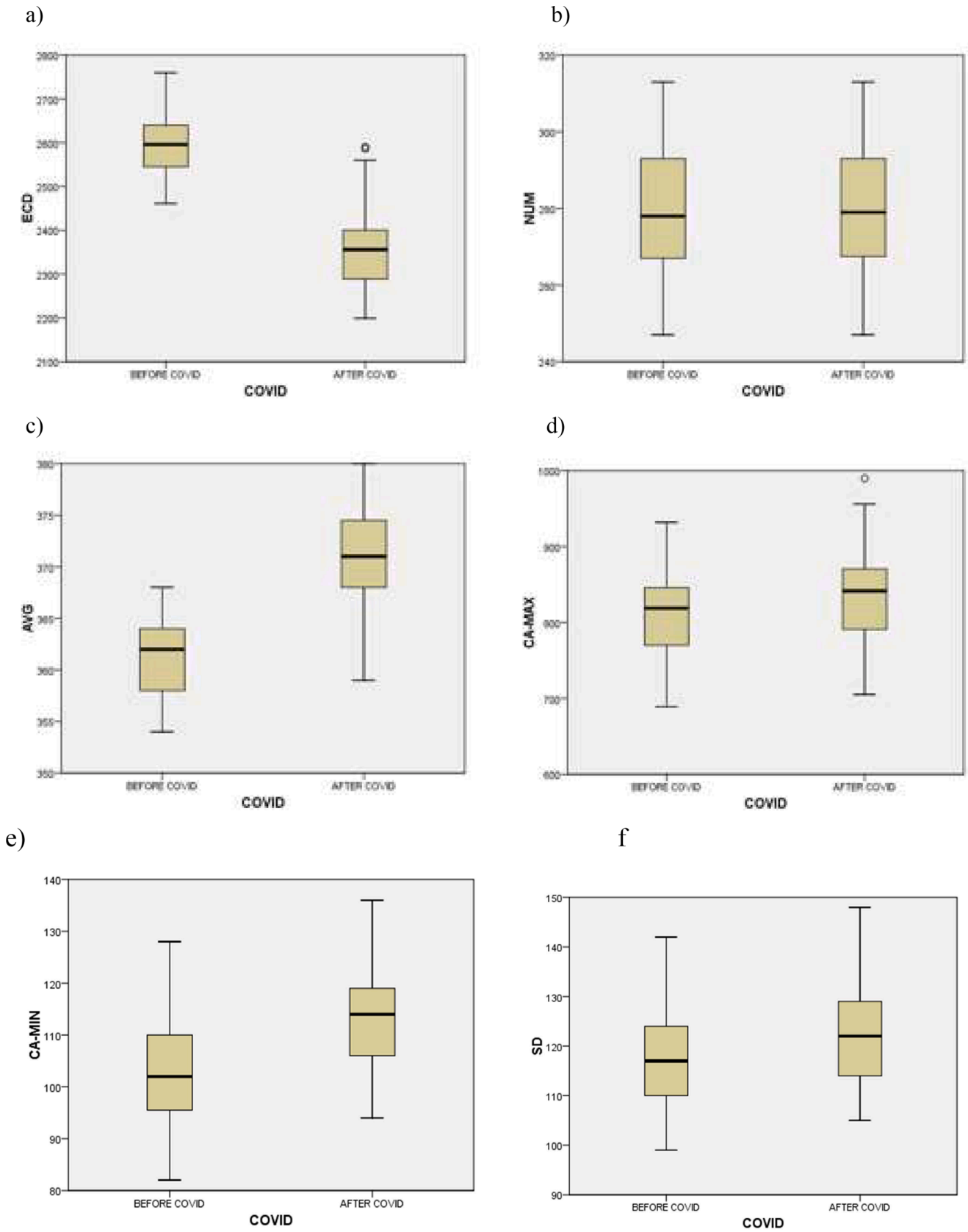

Fig. 2. Compare box plot graphics before and after COVID; a) Before and after endothelial cell density (ECD) findings, b) Before and after number of cells findings (NUM), c) Before and after average cell area findings (AVG), d) Before and after maximum cell area findings (CA-max), e) Before and after minimum cell area (CA-min) findings f) Before and after standard deviation (SD) findings g) Before and after coefficient of variation in cell area (CV) findings h) Before and after the percentage of hexagonal endothelial cells (6A) findings ı) Before and after central corneal thickness (CCT) findings.

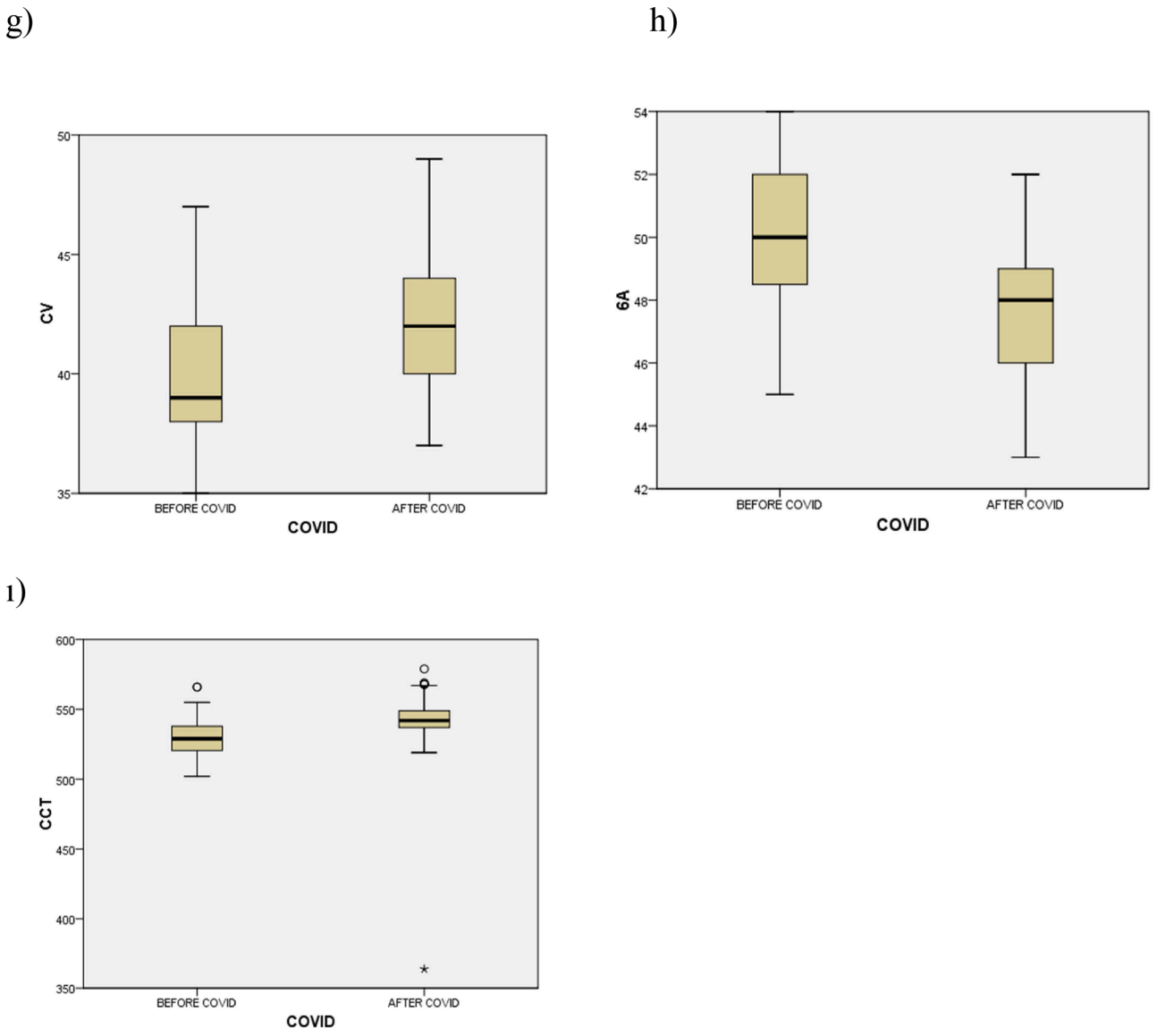

Fig. 2. (*continued*).

7. Discussion

In the present study, the aim was to examine the long-term corneal topographic changes and both number and morphological differences of endothelial cells after mild COVID-19 disease. When the topographic parameters were examined, it was seen that there was no significant change in the step keratometry and Kmax values, and stabilization was detected in topographic astigmatism. The absence of a significant change in the corneal curvature and the stable course of corneal astigmatism were detected after mild COVID-19 disease.

Although it is not clear how SARS-CoV-2 infection reaches the ocular surface and through which mechanisms it affects the ocular surface, studies have shown that there is an effect on the ocular surface [2]. In a study summarising the evidence for ocular transmission of SARS-CoV-2, it was found that both the ACE2 receptor and TMPRSS2 protein form the basis for ocular susceptibility, that SARS-CoV-2 can be detected on the ocular surface of COVID-19 patients, with or without ocular symptoms, and that the isolated virus is infectious. This is evidence that the ocular surface can be not only a reservoir but also a source of transmission. In the same study, it was argued that SARS-CoV-2 may reach the ocular surface through hand-eye contact and aerosol, and once SARS-CoV-2 reaches the ocular surface, it may be transferred to other systems via the nasolacrimal system or haematogenous metastasis [13].

In a study investigating the effect of COVID-19 infection on ocular biometric parameters, COVID-19 patients were evaluated approximately one month after completing their treatment, and the results were similar to the control group in terms of keratometry, corneal astigmatism, axial length and anterior chamber depth [14]. Further and comprehensive studies are needed to determine the course of ectatic diseases during and after COVID-19. In addition, the statistically significant increase in myopia progression in SE values. The increase in the SE may be due to several reasons, such as achange in habits or close working activity, rather than being a pathological process of COVID-19 disease. This needs to be examined in comprehensive and detailed studies. In the long term, these changes in refraction and ocular structures may increase the need for treatment.

Corneal sensitivity has been another parameter studied in the cornea after COVID-19. In a study examining the effect of infection on corneal sensitivity in the early period, esthesiometry measurements performed on average 4.2 $\pm$ 2.1 days after the onset of symptoms were repeated after an average of 32.5 $\pm$ 17.8 days, and it was reported that no change was observed in corneal sensitivity in the acute period [15]. In a study in which corneal cellular and ultrastructural parameters were evaluated by *in vivo* confocal microscopy, a decrease in posterior stromal keratocyte

density, an increase in the number of central corneal dendritic cells, and a change in sub-basal nerve fiber morphology were found when comparing patients with severe COVID-19 and a control group [16]. Although ophthalmoscopic changes were not detected on examination, it was reported that COVID-19 causes neuroinflammatory changes in the cornea [17]. These studies show that the corneal tissue is a target tissue for this infection, and although there is no change detected in the gross examination in the relatively short term, microscopic effects have begun.

Although the cornea is the most refractory surface of the eye, it provides this function by maintaining its transparency. Corneal endothelial cells are responsible for maintaining corneal transparency by providing controlled hydration to the stroma. As corneal endothelial cells have no ability to undergo mitosis, the ECD decreases by an average annual amount of 0.3–0.5 % as age progresses [18,19]. In addition to the ECD, the morphological changes also give important clues about stress on the endothelial cells because repair of damage in endothelial cells is provided by expansion, migration and amitotic nuclear division in the remaining intact cells. On morphological examination, this is observed as a change in the size of the cells (polymegatism), a change in the maximum and minimum cell areas, and a change in their shape (hexagonality). Therefore, average cell area, pleomorphism and hexagonality of these cells are used to evaluate the functional capacity of endothelial cells [20,21]. Due to the presence of ACE2 receptors, the corneal endothelium is thought to be one of the target tissues for COVID-19 and clinical studies are needed to observe the changes in the endothelium. In two published case-control studies in which the corneal endothelium was examined in the early period after COVID-19 infection and compared with healthy controls, a significant decrease in ECD and changes in morphology supporting this decrease were observed [22,23]. To the best of our knowledge, the present study is the first to compare the change in corneal curvature, ECD and morphology before and after approximately one year of COVID-19 infection in the same group of subjects. The present study shows that there was a significant decrease in ECD after COVID-19, along with a morphological change, including an increase in AVG, CAmax, CAmin and CV values and a decrease in 6A to compensate for this. As a result of all these changes, a significant increase was observed in CCT. All these changes took place without any clinically observed pathology and the decrease in ECD in approximately one year was found to be 9.29 %. As this decrease is much higher than expected, it is a change that needs to be monitored, and long-term follow-up studies with more patients are needed to monitor its long-term course.

The strength of the present study is the absence of the effect of age, gender, disease level and additional systemic diseases due to the monitoring of pre- and post-disease changes in the same population. Some limitations should also be noted. Firstly, the study lacked an uninfected control group and there was a lack of detailed analysis of the COVID-19 disease severity, although none of th eparticipants required hospitalization. Another limitation was the lack of further detailed examinations of corneal microstructural parameters, such as confocal microscopy esthesiometry. Finally, there is a need for detailed clinical studies with longer follow-up periods in which the long-term effects of changes in the corneal endothelium are reported.

In conclusion, the present study showed that there was a significant change in some refractive data and endothelial involvement while topographical data did not show remarkable changes after mild COVID-19 disease. Those with COVID-19 should be closely monitored for changes in refractive data, endothelial number and function. Future large-scale, long-term studies must further investigate these observations.

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CRediT authorship contribution statement

Fatma Sümer: Project administration, Investigation, Conceptualization. **Sevgi Subaşi:** Writing – review & editing. **Süleyman Karaman:** Validation.

Declaration of Competing Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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