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Optical biometric measurements in patients with previous COVID-19 treatment

Tugba Çetinkaya · Muhammed Mustafa Kurt

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Summary
Background We aimed to compare optical biometric measurements using optical biometry in patients with previously received COVID-19 treatment and a control group.
Methods In this cross-sectional study, patients with previously received COVID-19 treatment formed the COVID-19 group and age- and sex-matched healthy participants formed the control group. Optical biometric measurements including keratometry, corneal astigmatism, astigmatic axis, central corneal thickness, anterior chamber depth, and axial length were made using a Nidek optical biometer (AL-Scan; Nidek Co., Ltd., Japan).
Results Measurements of keratometry ($p=0.79$), corneal astigmatism ($p=0.41$), axial length ($p=0.96$), anterior chamber depth ($p=0.59$), and central corneal thickness ($p=0.37$) were similar between the COVID-19 and control groups. The astigmatic axis type taken from 2.4 mm of the cornea showed significant difference between the two groups ($p=0.02$, χ^2), while the measurements taken from 3.3 mm of the cornea were similar ($p=0.10$, χ^2). In the subgroup analysis, axial length, anterior chamber depth, and central corneal thickness measurements were found to be statistically significantly higher in male patients of the COVID-19 group ($p=0.02$; $p=0.001$; $p=0.02$, t test).
Conclusion The changes in optical biometric measurements found in our study were due to the fact that COVID-19 is more frequent and severe in males, SARS-CoV-2 can attach to the cornea via ACE-2 receptors, and favipiravir can reach the aqueous humor. To our knowledge, there is no study on this subject to date, and therefore more research is needed to shed light on this topic.

Keywords ACE-2 receptor · Favipiravir · Cornea · SARS-CoV-2 · Biometry

Optische biometrische Messungen bei Patient*innen mit zuvor erhaltener COVID-19-Behandlung

Zusammenfassung
Hintergrund Es wurden optische biometrische Messungen mittels optischer Biometrie bei Patient*innen mit zuvor erhaltener COVID-19-Behandlung und einer Kontrollgruppe verglichen.
Methodik In dieser Querschnittsstudie wurden Patient*innen mit zuvor erhaltener COVID-19-Behandlung als COVID-19-Gruppe bestimmt. In Bezug auf Alter und Geschlecht angepasste gesunde Proband*innen dienten als Kontrollgruppe. Die optischen biometrischen Messungen wurden mit einem optischen Biometer von Nidek (AL-Scan, Nidek Co., Ltd., Japan) durchgeführt. Sie schlossen die Bestimmung von Hornhautastigmatismus, astigmatischer Achse, zentraler Hornhautdicke, Vorderkammertiefe und Achsenlänge sowie eine Keratometrie ein.
Ergebnisse Die Messergebnisse der Keratometrie ($p=0{,}79$) sowie für Hornhautastigmatismus ($p=0{,}41$), Achsenlänge ($p=0{,}96$), Vorderkammertiefe ($p=0{,}59$) und zentrale Hornhautdicke ($p=0{,}37$) waren in der COVID-19- und der Kontrollgruppe ähnlich. Der astigmatische Achsentyp, der im Bereich von 2,4 mm der Hornhaut ermittelt wurde, zeigte einen signifikanten Unterschied zwischen den beiden Gruppen ($p=0{,}02$, χ^2), während die Messergebnisse aus einem

T. Çetinkaya, MD (✉)
Department of Ophthalmology, Gazi State Hospital, 55070 İlkadım/Samsun, Turkey
mdtubacetinkaya@gmail.com

M. M. Kurt, MD
Department of Ophthalmology, Samsun University, Samsun, Turkey

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Bereich von 3,3 mm der Hornhaut ähnlich waren ($p = 0{,}10$, χ^2). In der Subgruppenanalyse waren die Messwerte für Achsenlänge, Vorderkammertiefe und zentrale Hornhautdicke bei männlichen Patienten der COVID-19-Gruppe statistisch signifikant höher ($p = 0{,}02$; $p = 0{,}001$; $p = 0{,}02$, t-Test).
Schlussfolgerung Die Veränderungen in den optischen biometrischen Messungen unserer Studie waren dadurch bedingt, dass COVID-19 bei Männern häufiger auftritt und schwerer verläuft, dass SARS-CoV-2 über ACE-2-Rezeptoren an die Hornhaut binden kann und dass Favipiravir in das Kammerwasser gelangen kann. Unseres Wissens gibt es noch keine Studie zu diesem Thema. Daher sind weitere Forschungsbemühungen erforderlich.

Schlüsselwörter ACE-2-Rezeptor · Favipiravir · Hornhaut · SARS-CoV-2 · Biometrie

Background

In December 2019, an epidemic of pneumonia, which first appeared in Wuhan, China, and caused by SARS-CoV-2, was declared by the World Health Organization as a global pandemic [1–3]. SARS-CoV-2 was reported as the main agent of Coronavirus disease 19 (COVID-19) and the most common symptoms of COVID-19 have been reported to be fever, dry cough, nausea, muscle and joint pain, breathlessness, and diarrhea [4, 5]. Although it was reported that the disease was mainly transmitted by direct contact of respiratory droplets of infected individuals and that it mostly affects the respiratory tract, the effect on many other organs and the presence of virus in tears was also shown [6–10]. It has been suggested that the severity of the disease is related not only to viral infection but also to host response [11]. Previous studies reported that angiotensin-converting enzyme-2 (ACE-2) receptors may be effective in the pathogenesis of COVID-19-related organ failure [8]. As far as we know, corneal tissue also contains ACE receptors [12, 13] and SARS-CoV-2 was found in tear samples [6–10].

Therefore, in the current study, we aimed to compare the optical biometric measurements of patients who previously received COVID-19 treatment and a healthy control group to show the effect of COVID-19 on the cornea.

Material and methods

This study was carried out after the approval of the ethics committee of Samsun Education and Research Hospital in accordance with the tenets of the Helsinki Declaration.

Patients and methods

In this study, 193 eyes of 97 patients (50 men, 47 women) who previously received COVID-19 treatment and 193 eyes of 97 healthy participants (50 men, 47 women; control group) with similar age and gender were examined. The patients in the COVID-19 group were diagnosed according to the clinical and radiological findings as well as polymerase chain reaction (PCR) test results. All patients were hospitalized and received favipiravir and moxifloxacin treatment due to interstitial pneumonia. None of the patients had ocular complaints during COVID-19 infection and none of the patients required intubation.

All patients had a detailed ophthalmic examination including best corrected visual acuity (BCVA), intraocular pressure (IOP, mm Hg) measured with applanation tonometry, anterior and posterior segment examination by slit-lamp biomicroscopy, and optical biometric measurements, including corneal astigmatism, keratometry, astigmatic axis, central corneal thickness (CCT), anterior chamber depth (ACD), and axial length (AL) using a Nidek optical biometer (AL-Scan; Nidek Co., Ltd., Japan). In the COVID-19 group, patients were assessed 1 month after completion of their treatment. Measurements were performed by an experienced assistant after pupil dilation with 1% cyclopentolate drops to avoid errors in optical biometric measurements. In both groups, patients with poor tear film stability, high IOP, >6.0 diopter refraction, glaucoma, ocular inflammation, cataracts, corneal disease, and previous surgical history were excluded from the study. All measurements of the COVID-19 group and the healthy control group were compared.

Statistical analysis

Statistical analysis was performed using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to evaluate whether the variables were normally distributed. Continuous variables are described as mean ± standard deviation. Statistical analysis for the data of optical biometric measurements (keratometry, corneal astigmatism, central corneal thickness, axial length, and anterior chamber depth) were analyzed using the Student *t* test. Values less than 0.05 were considered to be statistically

Table 1 Optical biometric results for the patients in the COVID-19 group and the healthy control group

Parameters	COVID-19 group	Control group	*p*
K_2.4 mm (D)	43.18 ± 1.45	43.09 ± 1.69	0.79
K_3.3 mm (D)	43.14 ± 1.44	43.04 ± 1.68	0.77
Corneal astigmatism_2.4 mm (D)	0.78 ± 0.44	0.70 ± 0.37	0.41
Corneal astigmatism_3.3 mm (D)	0.72 ± 0.41	0.71 ± 0.36	0.95
AL (mm)	23.37 ± 0.77	23.36 ± 0.73	0.96
ACD (mm)	3.36 ± 0.33	3.32 ± 0.22	0.59
CCT (μm)	552.80 ± 36.77	559.25 ± 26.83	0.37

K_2.4 keratometric measurements obtained from central 2.4 mm of the cornea, *K_3.3* keratometric measurements obtained from central 3.3 mm of the cornea, *COVID-19* Coronavirus disease 19, *AL* axial length, *ACD* anterior chamber depth, *CCT* central corneal thickness, *D* diopter

Table 2 Chi-square correlation test between COVID-19 and healthy individuals for keratometric measurements obtained from 2.4 mm of the cornea

			The type of astigmatism_2.4			Total	χ^2	SD	*p*
			With the rule	Against the rule	Oblique				
Classification of individuals	*COVID-19*	*N*	99	31	63	193	7.449	2	0.024
		%	44.9	100	51.9	51.8			
	Healthy	*N*	130	0	63	193			
		%	55.1	0	48.1	48.2			
	Total	*N*	229	31	126	386			
		%	100	100	100	100			

COVID-19 Coronavirus disease 19, *SD* standard deviation

Table 3 Chi-square correlation test between COVID-19 and healthy individuals for keratometric measurements obtained from 3.3 mm of the cornea

			The type of astigmatism_3.3			Total	χ^2	SD	*p*
			With the rule	Against the rule	Oblique				
Classification of individuals	*COVID*	*N*	103	18	72	193	4.528	2	0.104
		%	46	100	55.2	51.8			
	Healthy	*N*	130	0	63	193			
		%	54	0	44.8	48.2			
	Total	*N*	233	18	135	193			
		%	100	100	100	100			

COVID-19 Coronavirus disease 19, *SD* standard deviation

significant. The type of astigmatism between the two groups was compared with the chi-square test.

Results

In the COVID-19 group, there were 50 male and 47 female patients with a mean age of 48.12 ± 14.29 years (19–66). The PCR test results were positive in 82% of the patients. All patients also had diffuse interstitial pneumonia. In the healthy control group, 50 male and 47 female patients with a mean age of 47.58 ± 6.24 years (35–61) were evaluated. The visual acuity was 1.0 (in decimal) and IOP values were in the normal range in both groups. The optical biometrical measurements obtained from the COVID-19 and healthy control groups are shown in Table 1 and Fig. 1. There were no significant differences between the two groups ($p > 0.05$ in all). Although there were no significant differences in the measurements of keratometry, corneal astigmatism, axial length, anterior chamber depth, and central corneal thickness, the type of astigmatism was different between the two groups (Tables 2 and 3). The distribution of optical biometrical measurements with male and female gender in patients with COVID-19 is shown in Fig. 2. In the COVID-19 group, there was a lower percentage of with-the-rule (WTR) astigmatism on the central 2.4 mm and 3.3 mm of the cornea than in the healthy control group, while there was a higher percentage of against-the-rule (ATR) astigmatism on the central 2.4 mm and 3.3 mm of the cornea compared with the healthy control group. According to the results of the chi-square test, the astigmatic axis type obtained from the central 2.4 mm of the cornea was significantly different between two groups ($\chi^2_{(2)} = 7.449$, $p = 0.02$), and the measurements obtained from the central 3.3 mm of the cornea were similar ($p = 0.10$). According to the frequency and percentage distribution, while the WTR astigmatism was low in the COVID group, the ATR astigmatism was higher.

In the subgroup analysis performed according to gender, the AL, ACD, and CCT measurements were significantly increased for male gender in the COVID-19 group ($p = 0.02$; $p = 0.001$; $p = 0.02$, t test), while all other parameters were similar between both genders

Table 4 Subgroup analysis by gender for all measured values in patients with COVID-19

Parameters	Mean ± SD		
	Female	Male	*p*
Patients with COVID-19			
K_2.4 (D)	43.38 ± 1.53	42.74 ± 1.37	0.33
C_ast_2.4 (D)	0.71 ± 0.43	0.69 ± 0.54	0.93
K_3.3 (D)	43.31 ± 1.56	42.75 ± 1.41	0.39
C_ast_3.3 (D)	0.77 ± 0.36	0.60 ± 0.50	0.39
AL (mm)	23.01 ± 0.79	24.12 ± 0.67	0.02
ACD (mm)	3.18 ± 0.28	3.54 ± 0.31	0.001
CCT (μm)	540.70 ± 27.20	571.40 ± 32.00	0.02

K_2.4 keratometric measurements obtained from central 2.4 mm of the cornea, *C_ast_2.4* corneal astigmatism obtained from central 2.4 mm of the cornea, *K_3.3* keratometric measurements obtained from central 3.3 mm of the cornea, *C_ast_3.3* corneal astigmatism obtained from central 3.3 mm of the cornea, *COVID-19* Coronavirus disease 19, *AL* axial length, *ACD* anterior chamber depth, *CCT* central corneal thickness, *D* diopter

Table 5 Subgroup analysis by gender for all measured values in the healthy individuals

Parameters	Mean ± SD		*p*
	Female	Male	
K_2.4 (D)	43.65 ± 1.89	42.24 ± 0.98	0.07
C_ast_2.4 (D)	0.80 ± 0.36	0.83 ± 0.16	0.08
K_3.3 (D)	43.59 ± 1.83	42.18 ± 1.00	0.06
C_ast_3.3 (D)	0.83 ± 0.38	0.82 ± 0.20	0.76
AL (mm)	23.05 ± 0.63	23.21 ± 0.64	0.46
ACD (mm)	3.30 ± 0.18	3.37 ± 0.29	0.55
CCT (μm)	560.25 ± 20.99	556.37 ± 35.54	0.76

K_2.4 keratometric measurements obtained from central 2.4 mm of the cornea, *C_ast_2.4* corneal astigmatism obtained from central 2.4 mm of the cornea, *K_3.3* keratometric measurements obtained from central 3.3 mm of the cornea, *C_ast_3.3* corneal astigmatism obtained from central 3.3 mm of the cornea, *AL* axial length, *ACD* anterior chamber depth, *CCT* central corneal thickness, *D* diopter

in the healthy control group (Tables 4 and 5). The distribution of optical biometrical measurements with male and female gender for the healthy control group is shown in Fig. 3.

Discussion

Coronaviruses are single-stranded RNA viruses that encode structural and non-structural proteins in their genome. Structural proteins are responsible for viral infection and replication, while non-structural proteins (S protein) provide attachment between the coronavirus and the host cell [14]. The angiotensin-converting enzyme-2 (ACE) receptor [8],cell surface protease enzyme (TMPRSS2), and CD147 transmembrane protein have also been reported to be effective in enabling SARS-CoV-2 to enter the host cell [15]. Previous studies showed the ACE-2 receptor in the conjunctiva, cornea [12, 13], aqueous humor [6, 16], limbus, ciliary body [13], choroid, retinal Müllerian cells, ganglion cells, retinal vascular endothelial cells, photoreceptor cells [17], and retinal pigment epithelium [13], as well as in the respiratory tract, gastrointestinal system, and endothelial cells [17]. TMPRSS2 has not been demonstrated in tear, cornea, and con-

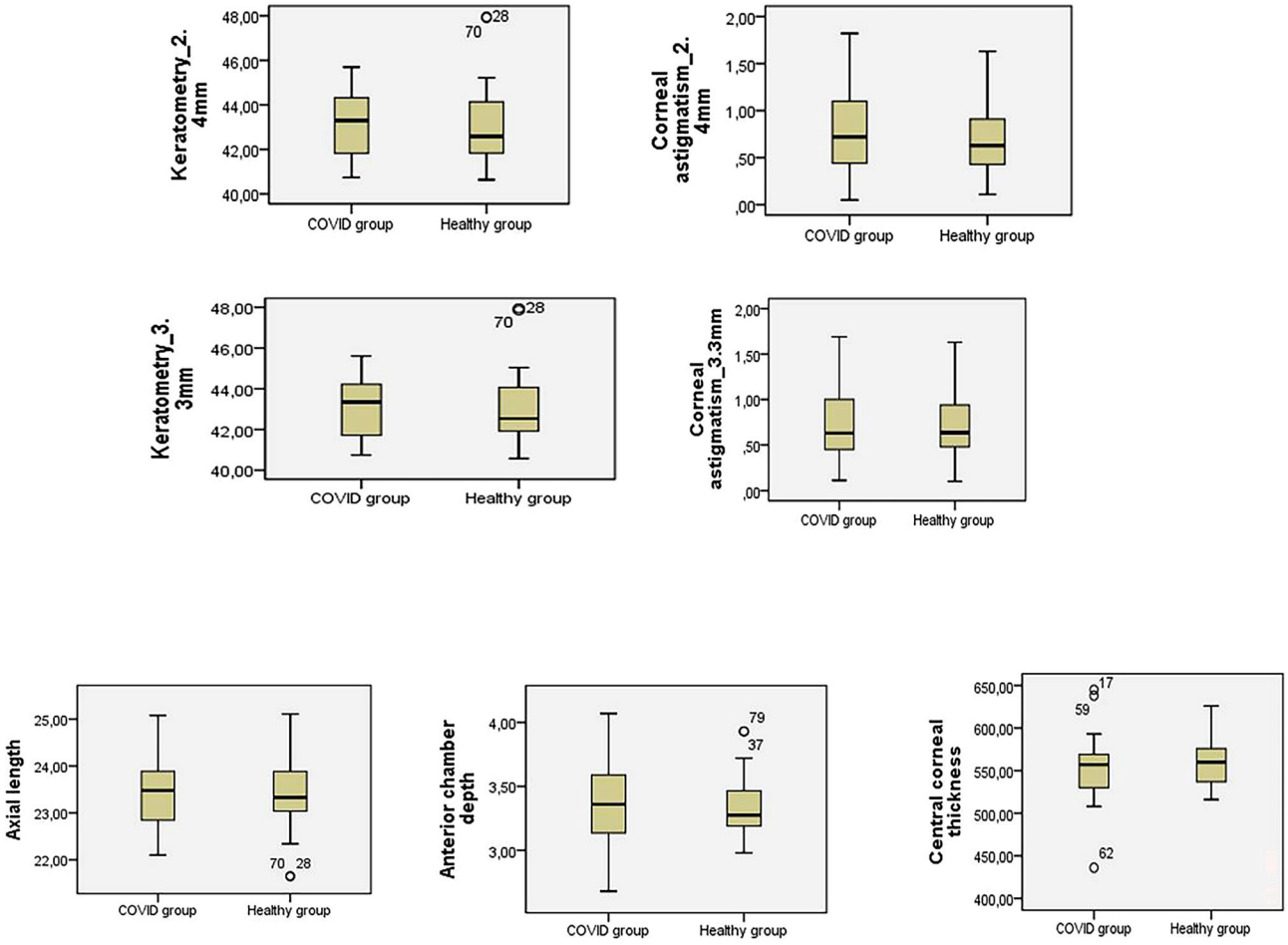

Fig. 1 Distribution of optical biometrical measurements between COVID-19 group and healthy control group

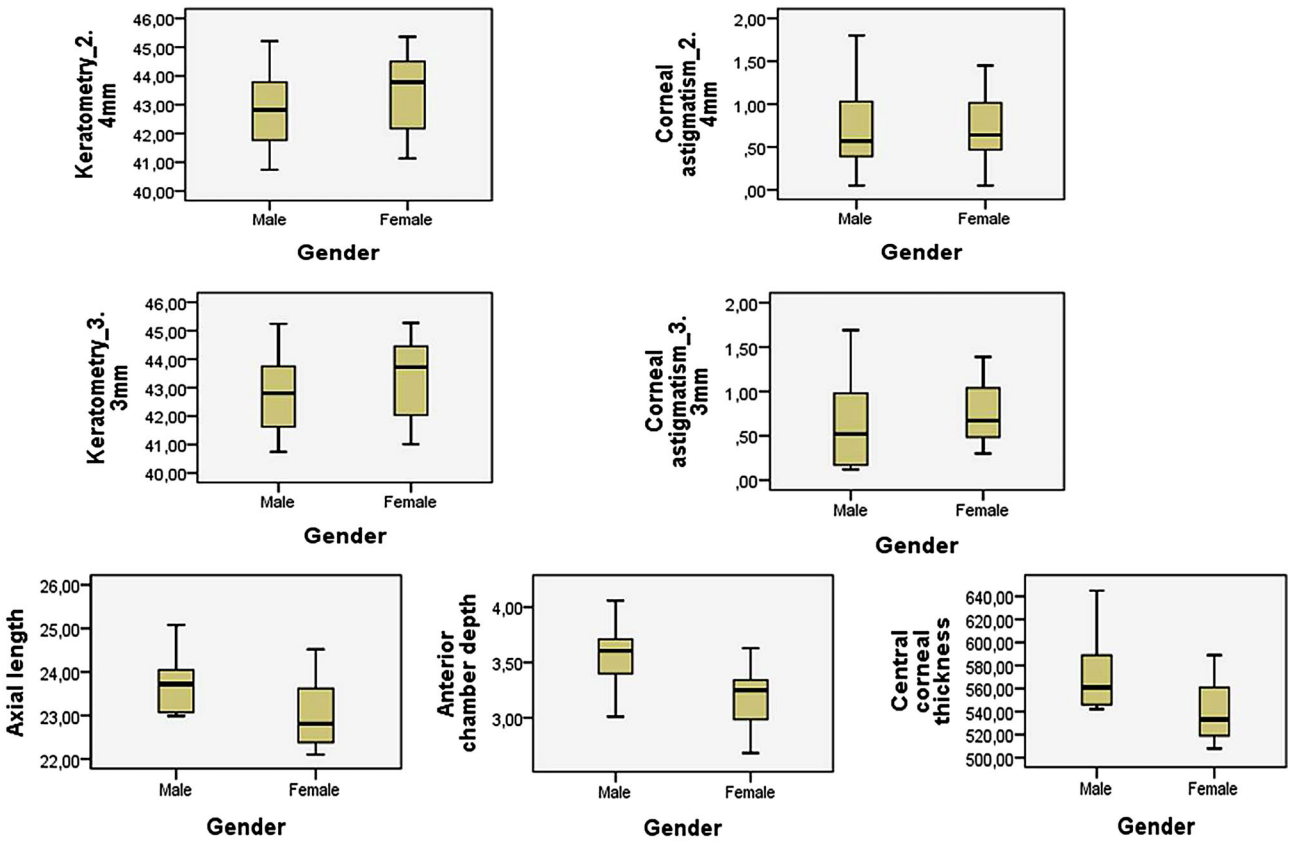

Fig. 2 Distribution of optical biometrical measurements with male and female gender in patients with COVID-19

junctival epithelium, but an association with ACE-2 genes has been demonstrated in some conjunctival cells [18]. Although corneal tissue has a physical barrier against pathogen entrance, ACE-2 and CD147, also expressed in corneal cells, may make it easier for the virus to enter the cell [19].

We conducted this study based on the hypothesis that COVID-19 can lead to changes in optical biometric measurements on the cornea via ACE-2 and CD147. According to the results of the current study, there was no statistically significant difference in the measurements of keratometry, corneal astigmatism, axial length, anterior chamber depth, and central corneal thickness between the COVID-19 group and the healthy control group. The similar results between the COVID-19 group and the healthy control group may be attributed to the number of ACE-2 receptors in the cornea. In previous studies, although the ACE-2 receptor was demonstrated in the cornea and conjunctival epithelium [20, 21], it was reported that the number of receptors in the cornea and conjunctival tissue is 5–20-fold lower than in the heart and lung tissue [12, 21]. Therefore, the statistically insignificant results between the two groups of the current study may be explained by the lack of sufficient numbers of ACE-2 receptors that could lead to significant keratometric changes in the cornea.

On the other hand, the percentage of against-the-rule astigmatism on the central 2.4 mm and 3.3 mm of the cornea was increased in the COVID-19 group with a statistically significant difference between the two groups. While there was no significant difference between the two groups in the measurements of keratometry and corneal astigmatism, the significant difference in the type of astigmatism suggests that COVID-19-related optical biometric measurements may be reversible or may be related to the drug used in the treatment. Therefore, the measurements obtained 1 month after COVID-19 treatment may have been similar for the two groups.

Additionally, in the literature, favipiravir-related blurred vision and bluish discoloration of the cornea that may be associated with favipiravir or its metabolites have been reported [22–25], and this effect has been shown to be reversible. It has been demonstrated that favipiravir has a high absorption rate of 97.6% and plasma protein binding of 54% [23–25]. Since aqueous humor is an ultrafiltrate of plasma, high concentrations of favipiravir in plasma can also be detected in aqueous humor, which may cause keratometric changes in the cornea [23–25]. As the patients were assessed 1 month after completion of their treatment that included favipiravir, the statisti-

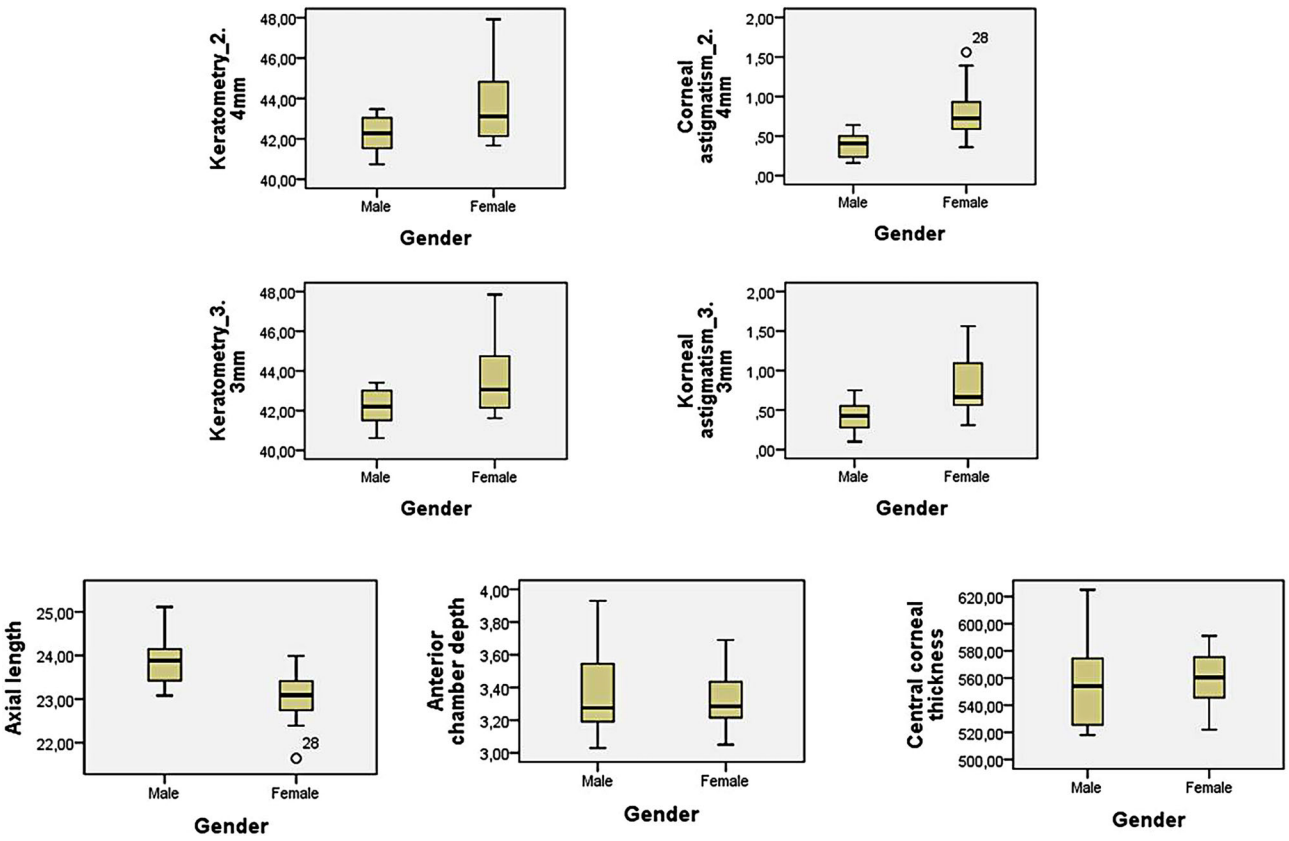

Fig. 3 Distribution of optical biometrical measurements with male and female gender in the healthy control group

cally insignificant results may also have been due to favipiravir-related reversible corneal changes.

Previous studies have shown that severe morbidity and mortality related to COVID-19 are more common in the male sex [26, 27]. In the current study, the results of the subgroup analysis may be attributed to the greater severity of the disease in males. The increased viral load and more severe disease may explain the higher AL, ACD, and CCT measurements in men.

Consequently, COVID-19 disease and its treatment may affect the keratometry values.

Limitations

The limitation of our study is that due to the fact that the pre-COVID optical biometric values of the patients could not be obtained we could not compare the measurements before and after the disease.

Conclusion

To our knowledge, there is no previous report on optical biometric results in COVID-19 patients. Conducting other studies to investigate corneal involvement by SARS-CoV-2 and the effects of the drugs used in COVID-19 treatment will shed more light on this subject.

Conflict of interest T. Çetinkaya and M.M. Kurt declare that they have no competing interests.

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