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Investigation of the Effect of Chronic Obstructive Pulmonary Disease on Corneal Transparency and Endothelial Characteristics: Cross-Sectional Study

Kronik Obstrüktif Akciğer Hastalığının Kornea Şeffaflığı ve Endotel Özellikleri Üzerine Etkisinin İncelenmesi: Kesitsel Araştırma

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ABSTRACT Objective: In this study, it was aimed to investigate corneal transparency and endothelial characteristics of patients with chronic obstructive pulmonary disease (COPD) and compare these findings with age- and gender-matched healthy controls. **Material and Methods:** Forty-nine eyes of 49 patients with COPD (24 females, 25 males) and 65 eyes of 65 healthy controls (36 females, 29 males) were included in this study. Participants were evaluated using Scheimpflug corneal topography (Pentacam HR Oculus, Wetzlar, Germany) and specular biomicroscopy (Tomey, Nagoya, Japan) to obtain measurements of corneal pachymetry, keratometry, and densitometry values with corneal endothelial cell characteristics. Spirometry values [forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC ratio], smoking status (pack-years), and disease duration were recorded in the patient group. **Results:** Corneal pachymetry and keratometry measurements were statistically similar in the study groups ($p>0.05$, for all). Although the measurement of endothelial cell count was lower in the patient group, it was not statistically significant ($p=0.130$). Higher corneal densitometry values were observed in the patient group compared to the control group in all depths and diameters ($p<0.05$, for all). Numerous corneal densitometry values in the patient group showed significant negative correlations with FVC measurements and positive correlations with smoking status ($p<0.05$, for all). **Conclusion:** It can be thought that corneal transparency can decrease throughout the entire cornea due to hypoxia in patients with COPD, and this effect is correlated with smoking status and disease severity. Therefore, patients with COPD should be evaluated carefully before ophthalmological procedures which can affect corneal transparency.

Keywords: Chronic obstructive pulmonary disease; corneal densitometry; corneal endothelium; corneal transparency

ÖZET Amaç: Çalışmamızda, kronik obstrüktif akciğer hastalığı (KOAH) olan katılımcılarda kornea şeffaflığının ve endotel özelliklerinin incelenmesi ve bu bulguların yaş ve cinsiyet uyumlu sağlıklı kontroller ile karşılaştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmamıza 49 KOAH hastasının (24 kadın, 25 erkek) 49 gözü ve 65 sağlıklı kontrolün (36 kadın, 29 erkek) 65 gözü dâhil edildi. Katılımcılar Scheimpflug korneal topografi cihazı (Pentacam HR Oculus, Wetzlar, Almanya) ve speküler biyomikroskop (Tomey, Nagoya, Japonya) ile değerlendirilerek korneal pakimetri, keratometri ve dansitometri değerleri ile kornea endotel hücre özellikleri elde edildi. Hasta grubunda spirometri değerleri [zorlu vital kapasite (forced vital capacity "FVC"), birinci sn zorlu ekspirasyon volümleri (forced expiratory volume in 1 second "FEV_1") ve FEV_1/FVC oranı], sigara kullanımı (paket/yıl) ve hastalık süresi kaydedildi. **Bulgular:** Korneal pakimetri ve keratometri ölçümleri çalışma gruplarında istatistiksel olarak benzerdi (tümü için $p>0,05$). Endotel sayısı hasta grubunda daha az olmasına rağmen bu fark istatistiksel olarak anlamlı değildi ($p=0,130$). Hasta grubunda kontrol grubuna göre tüm derinlik ve çaplarda daha yüksek korneal dansitometri değerleri saptandı (tümü için $p<0,05$). Hasta grubundaki çok sayıda korneal dansitometri değeri ile FVC değerleri arasında ters korelasyon izlenirken sigara kullanımı ile pozitif korelasyonlar saptandı (tümü için $p<0,05$). **Sonuç:** KOAH hastalarında hipoksi nedeni ile korneal şeffaflığın tüm kornea boyunca azaldığı ve bu etkinin sigara kullanımı ve hastalık şiddeti ile korele olduğu düşünülmektedir. Bu nedenle KOAH'lı hastaların kornea şeffaflığını etkileyebilecek oftalmik işlemler öncesinde dikkatle değerlendirilmesi gerektiği düşünülmektedir.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı; korneal dansitometri; kornea endoteli; kornea şeffaflığı

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A progressive lung disorder called chronic obstructive pulmonary disease (COPD), which influences a huge number of individuals globally, is primarily induced by smoking, exposure to air pollution, and respiratory infections.[1] COPD is characterized by hypoxemia and systemic inflammation, with oxidative stress playing a major role in its pathogenesis.[2] The illness is a prominent factor contributing to sickness and death rates in developed nations and is increasingly emerging as a significant public health concern in developing nations.[3]

The cornea is a transparent structure that covers the front surface of the eye, and its transparency is essential for normal vision. Corneal opacity, caused by various factors such as inflammation, infection, or metabolic disorders, can lead to vision impairment or blindness.[4] Corneal densitometry is a non-invasive method used to evaluate the transparency of the cornea by measuring the amount of light scattered from the cornea.[5] Studies have shown that corneal densitometry measurements can be used as a valuable tool to evaluate corneal health and detect early signs of corneal pathology.[6,7]

The objective of this research was to examine the corneal densitometry measurements and endothelium characteristics obtained from individuals with COPD and compare them with those of individuals without any health issues. The research strives to enhance our comprehension of how chronic hypoxemia in COPD impacts corneal densitometry and endothelial morphology, ultimately paving the way for novel diagnostic and therapeutic strategies for COPD patients experiencing eye-related disorders.

MATERIAL AND METHODS

The study was cross-sectionally planned and designed in accordance with the Helsinki Declaration with approval from the Ankara Training and Research Hospital Ethics Committee (date: March 23, 2022, no: E-20-563). The study included 49 individuals diagnosed with COPD who visited the Department of Chest Diseases, along with 65 healthy subjects who participated for control purposes. Prior to inclusion, all individuals were informed, and written informed consent was taken from all participants.

According to Global Intelligence for Chronic Obstructive Lung Disease (GOLD) criteria, individuals who reported symptoms of pulmonary distress, such as persistent coughing, shortness of breath, and production of sputum; were defined as patients with COPD.[8] Subsequently, patients were investigated with spirometry (Pneumotrac, Vitalograph, Buckingham, UK) to assess their respiratory function. A chest specialist, who possessed extensive expertise in the field, confirmed the diagnosis by assessing the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) ratio, which was found to be less than 70% after administration of a bronchodilator, as well as FEV_1, which was less than 80%. The duration of the disease and smoking history were also documented. Smoking status was determined according to the duration of smoking in years and daily cigarette consumption.

All participants underwent a detailed ophthalmological investigation including the measurement of refractive error and intraocular pressure (IOP), best-corrected visual acuity (BCVA) using the Snellen chart, anterior segment, and dilated fundus examination. Participants who had the following criteria were excluded from the study: the presence of systemic vascular diseases such as hypertension or diabetes, history of any ocular disease or surgery, previous ocular trauma or laser treatment, BCVA<20/25, spherical equivalent exceeding ±3.0D, IOP measurement >21 mmHg, or non-cooperative behavior during the ophthalmic examination. Individuals with known corneal disease, corneal disease detected during the examination, and a history of medication other than medication for COPD were not included in the study. COPD patients were only receiving systemical beta-blocker treatment. It was ensured that the patients had never worn contact lenses. The control group consisted of individuals without any ocular or systemic diseases and no history of smoking.

The Pentacam HR device (Oculus, Wetzlar, Germany) was used, which is a Scheimpflug corneal topography system capable of measuring corneal thickness, curvature, and densitometry. This system employs a rotating Scheimpflug camera, enabling accurate assessment of corneal densitometry. Corneal densitometry is a non-invasive method used to eval-

uate corneal transparency by measuring the amount of light scattered from the cornea. Advanced software divided the cornea into four concentric zones and three depth layers for corneal density assessment. The first zone, located at the corneal center, had a diameter of two millimeters, while the other zones were annular areas situated 2-6 mm, 6-10 mm, and 10-12 mm away from the first zone. The three depth layers included the anterior 120 µm (outermost), posterior 60 µm (innermost), and central regions. Corneal density values, ranging from 0 (transparent) to 100 (opaque), were automatically calculated and expressed in grayscale units (Figure 1). In addition to densitometry measurements, parameters such as corneal curvature, thickness, white-to-white diameter, anterior chamber depth, volume, and angle were analyzed.

The endothelial structure of the cornea was evaluated using a specular biomicroscope (Tomey, Nagoya, Japan). This type of microscope allows for non-invasive visualization and measurement of the corneal endothelium. Specular biomicroscopy provides detailed information about the number, size, and shape of endothelial cells. Corneal endothelial parameters were evaluated solely based on high-quality images acquired using the central method, which ensured the presence of ≥110 distinguishable endothelial cells. The recorded parameters included central corneal thickness (CCT), minimum (MIN) cell area values, average (AVG), coefficient of variation (CV), standard deviation (SD), cell density (CD), maximum (MAX) cell area values, and percentage of hexagonal cells (HEX). The CD is a crucial measurement of corneal transparency and represents the number of endothelial cells. HEX measures the degree of variation in corneal endothelial cell shape or pleomorphism, while CV (calculated by dividing SD by the mean cell area) measures the degree of variation in corneal endothelial cell size or polymegathism.

STATISTICAL ANALYSIS

All statistical analyses were conducted using the SPSS (SPSS version 24.0; IBM Corp., Armonk, NY, USA). The variables that do not show a normal distribution are presented as the median with the minimum and maximum values (min-max), while normally distributed variables are presented as mean±standard deviation. The distribution pattern of variables was assessed through both the Kolmogorov-Smirnov and Shapiro-Wilk tests. To exam-

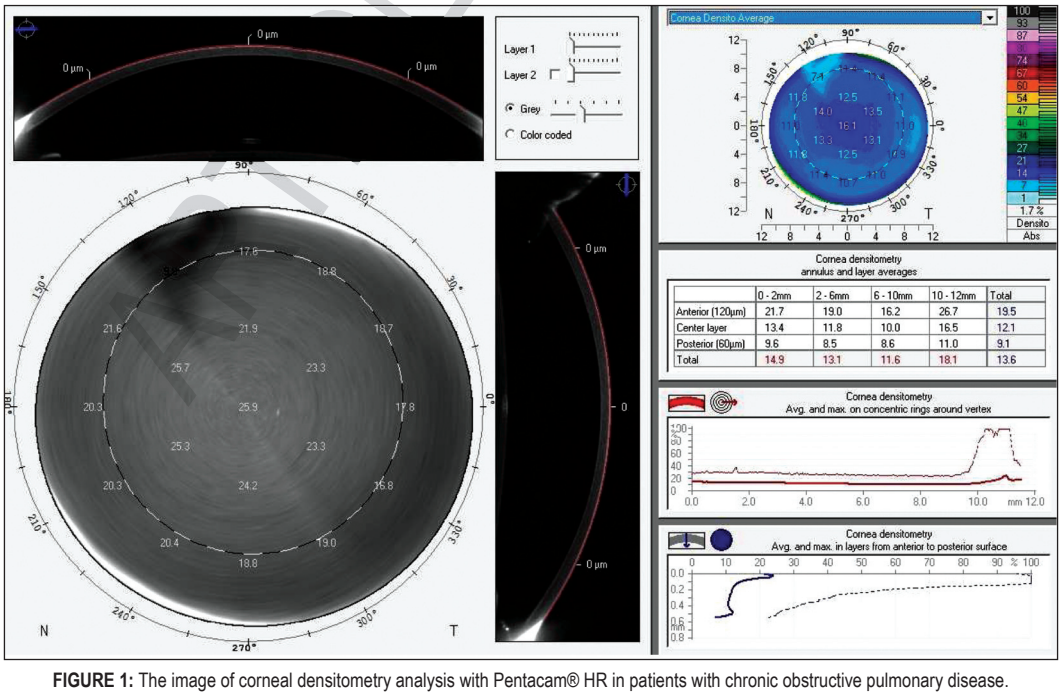

FIGURE 1: The image of corneal densitometry analysis with Pentacam® HR in patients with chronic obstructive pulmonary disease.

ine gender differences, we utilized the χ^2 test, which is ideal for categorical data. For normally distributed data, a Student's t-test was employed to compare means between the two groups. When dealing with non-normally distributed data, we opted for the Mann-Whitney U test, which compares medians for two groups. To measure the strength and direction of the linear relationship between continuous variables, the Pearson correlation coefficient was used. Our predetermined threshold for statistical significance was set at $p<0.05$, meaning that results with p-values below this level were considered statistically significant. Initially, we only included data from the right eye of each participant in the analysis. However, if the right eye did not meet the inclusion criteria, measurements from the left eye were included for statistical analysis.

RESULTS

This study included a total of 114 participants. Demographic and disease characteristics of individuals are shown in Table 1. The COPD group (n=49) consisted of 24 females (49%) and 25 males (51%). In the control group (n=65), there were 36 females (55%) and 29 males (45%). The mean age was 49.7±9.4 years in the COPD group and 49.2±5.5 years for healthy subjects. Study groups had statistically similar age and gender features (p=0.714 and p=0.498, respectively) (Table 1). Median smoking status was 10.2 (0.0-70.0) pack-years and median disease duration was 5.0 (1.0-30.0) years in the COPD group. Mean FEV_1, FVC, and FEV_1/FVC values were 41.7±12.9%, 75.7±16.6%, and 63.0±7.0%, respectively.

Analysis of Scheimpflug corneal measurements indicated statistically similar values in anterior and posterior keratometry values, thinnest corneal thickness, anterior chamber depth, anterior chamber volume, anterior chamber angle, and white-to-white corneal diameter. ($p>0.05$, for all) (Table 2). Endothelial cell characteristics (CD, AVG, SD, MAX, MIN, CV and HEX) and CCT obtained through specular biomicroscopy were not statistically significant between the study groups ($p>0.05$, for all) (Table 3). However, corneal densitometry measurements demonstrated statistically significant higher values in all areas in the COPD group compared to the healthy group ($p<0.05$, for all) (Table 4).

Correlation analysis revealed negative associations between corneal densitometry values and FVC measurements in the patient group. Additionally, positive correlations were observed between corneal densitometry values and smoking status of patients. Table 5 shows correlations between the corneal den-

TABLE 1: The table shows the demographic characteristics of the study groups and the spirometric impairments of the COPD group.

	COPD group (n=49)	Control group (n=65)	p value
Age, years	49.7±9.4	49.2±5.5	0.714*
Gender, n			
Male	25	29	0.498†
Female	24	36	
Smoking, pack-years	10.2 (0.0-70.0)	-	
Disease duration, years	5.0 (1.0-30.0)	-	
FEV_1, %	41.7±12.9	-	
FEV_1/FVC, %	63.0±7.0	-	
FVC, %	75.7±16.6		

*Student t- test; †χ^2 test; The variables that do not show a normal distribution are presented as the median with the minimum and maximum values (min-max), while normally distributed variables are presented as mean±standard deviation; COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC; Forced vital capacity.

TABLE 2: Comparison of Scheimpflug corneal parameters between the study groups.

	COPD group (n=49)	Control group (n=65)	p value*
Anterior cornea			
Kmin, D	43.6±1.8	43.1±1.4	0.199
Kmax, D	44.6±2.0	44.1±1.4	0.144
Kmean, D	44.1±1.9	43.6±1.4	0.159
Posterior cornea			
Kmin, D	-6.2±0.3	-6.1±0.2	0.056
Kmax, D	-6.5±0.3	-6.4±0.2	0.077
Kmean, D	-6.4±0.3	-6.2±0.2	0.090
Thinnest pachymeter, µm	544.9±29.0	531.8±38.2	0.057
Anterior chamber depth, mm	2.9±0.5	2.9±0.3	0.742
Anterior chamber volume, mm^3	159.8±34.4	163.2±34.4	0.617
Anterior chamber angle, degree	31.2±8.2	29.2±7.9	0.270
White to white diameter, mm	11.5±0.4	11.6±0.4	0.671

*Student t test; Normally distributed variables are presented as mean±standard deviation; COPD: Chronic obstructive pulmonary disease.

TABLE 3: Comparison of endothelial cell characteristics and central corneal thickness between the study groups.

	COPD group (n=49)	Control group (n=65)	p value
CD, cell/mm^2	2446.8±386.5	2542.2±231.8	0.130†
AVG, µm^2	423.2±99.2	397.1±23.4	0.160†
SD, µm^2	149.0 (112.0-477.0)	158.5 (127.0-241.0)	0.381*
MAX, µm^2	979.5 (659.0-2554.0)	1048.0 (724.0-2499.0)	0.132*
MIN, µm^2	97.0 (73.0-268.0)	103.0 (63.0-135.0)	0.861*
CV, (%)	37.5 (31.0-58.0)	40.5 (32.0-56.0)	0.069*
HEX, (%)	45.5 (29.0-59.0)	43.5 (28.0-53.0)	0.108*
CCT, µm	532.5 (461.0-599.0)	517.0 (435.0-634.0)	0.870*

*Mann-Whitney U test; †Student t-test; The variables that do not show a normal distribution are presented as the median with the minimum and maximum values (min-max), while normally distributed variables are presented as mean±standard deviation; CD: Cell density; AVG: Average cell area; SD: Standard deviation of cell area; MAX: Maximum cell area; MIN: Minimum cell area; CV: Coefficient of variation; HEX: Variability in hexagonal shape; CCT: Central corneal thickness.

TABLE 4: Comparison of corneal densitometry measurements between the COPD and control groups.

	COPD group (n=49)	Control group (n=65)	p value*
Anterior 120 µ			
0-2 mm	20.8±2.7	16.3±1.2	**<0.001**
2-6 mm	19.2±3.1	14.9±1.2	**<0.001**
6-10 mm	24.2±9.7	17.0±3.1	**<0.001**
10-12 mm	30.8±10.9	27.6±8.5	**0.049**
Total	23.0±5.7	17.9±2.2	**<0.001**
Central			
0-2 mm	13.5±1.5	11.2±0.8	**<0.001**
2-6 mm	12.6±1.9	10.3±0.9	**<0.001**
6-10 mm	16.7±6.2	12.2±2.3	**<0.001**
10-12 mm	20.0±6.7	17.2±3.7	**0.007**
Total	15.3±3.5	12.2±1.4	**<0.001**
Posterior 60 µ			
0-2 mm	9.1±0.8	8.7±1.0	**0.020**
2-6 mm	8.9±1.1	8.3±1.0	**0.003**
6-10 mm	13.0±3.7	10.3±1.8	**<0.001**
10-12 mm	16.2±4.9	13.4±2.1	**<0.001**
Total	11.5±2.1	9.9±1.3	**<0.001**
Total thickness			
0-2 mm	14.5±1.6	12.1±1.0	**<0.001**
2-6 mm	13.6±2.0	11.1±1.0	**<0.001**
6-10 mm	18.0±6.4	13.2±2.3	**<0.001**
10-12 mm	22.4±7.9	19.4±4.4	**0.015**
Total	16.6±3.7	13.3±1.6	**<0.001**

*Student t-test; Bold values in a table indicate that the p-value is statistically significant; Normally distributed variables are presented as mean±standard deviation; COPD: Chronic obstructive pulmonary disease.

TABLE 5: Correlations between corneal densitometry measurements with forced vital capacity and smoking status in the COPD group.

r	FVC, %	Smoking status, pack-years
Anterior 120 µ		
0-2 mm	-0.208	0.282*
2-6 mm	**-0.304***	**0.439****
6-10 mm	**-0.415****	0.293*
10-12 mm	0.032	0.048
Total diameter	**-0.431****	**0.347***
Central		
0-2 mm	-0.219	**0.339***
2-6 mm	**-0.317***	**0.439****
6-10 mm	**-0.410****	**0.302***
10-12 mm	-0.165	0.204
Total diameter	**-0.424****	**0.340***
Posterior 60 µ		
0-2 mm	**-0.314***	0.345
2-6 mm	**-0.319***	**0.348***
6-10 mm	**-0.381***	0.232
10-12 mm	-0.054	0.077
Total diameter	**-0.400****	0.248
Total thickness		
0-2 mm	-0.247	**0.307***
2-6 mm	**-0.321***	**0.437****
6-10 mm	**-0.414****	**0.289***
10-12 mm	-0.126	0.196
Total diameter	-0.245	**0.333***

Bold values indicate statistically significant correlations. *p<0.05; **p<0.01; r: Pearson correlation coefficient; COPD: Chronic obstructive pulmonary disease; FVC: Forced vital capacity.

sitometry measurements with FVC and smoking status in the COPD group. There were no significant correlations between the corneal densitometry measurements and other patient parameters including FEV_1, FEV_1/FVC, disease duration, and age.

DISCUSSION

The current study aimed to investigate the impact of COPD on corneal densitometry measurements and endothelial characteristics. The corneal densitometry values and corneal endothelial characteristics of COPD patients were compared with those of healthy individuals. The findings indicated a notable elevation in corneal densitometry values among individuals with COPD, whereas no significant distinction was observed in terms of endothelial characteristics between the study groups.

COPD leads to a decrease in pulmonary capacity due to inflammation in the lungs and airways, obstruction of the airway, destruction of the pulmonary parenchyma, and pulmonary vascular abnormalities.[9] The decrease in gas exchange capacity leads to hypoxemia and hypercapnia.[9] Vascular endothelial damage in COPD leads to the secretion of endothelin-1, an inflammatory cytokine that can contribute to the regulation of blood flow and can cause vasoconstriction and a decrease in blood flow.[10] Previous studies have shown that patients with COPD may have increased ocular blood flow resistance and decreased blood flow.[11] Autoregulation of ocular blood flow can be disrupted in all stages of COPD. The decrease in oxygen saturation and increase in oxidative stress in COPD can affect retina cells that are highly susceptible to ischemia.[12] Previous research have found that patients with COPD may have thinner retinal and choroid thickness and decreased retinal vascular density, indicating that systemic effects of COPD may affect ocular function.[13,14] Additionally, a previous study found a direct correlation between oxygen saturation and retinal nerve fiber layer thickness.[15] The results of this study were parallel to other research that has demonstrated a correlation between hypoxia in patients with obstructive sleep apnea and a reduction in ganglion cell layer thickness.[16] Therefore, it can be suggested that vascular changes in COPD patients may affect avascular cornea like the hypoxia-sensitive retina.

The avascular structure and parallel organization of corneal collagens provide corneal transparency. The flow of fluid from the corneal stroma to the aqueous humor is facilitated by the pump function of the endothelium. A decrease in oxygen saturation can cause impairment in the corneal endothelium, which is responsible for maintaining corneal transparency.[17] Corneal opacity, which can cause deterioration in normal vision, can be measured by evaluating the amount of light backscattering from the cornea, and it can be quantified using corneal densitometry. Therefore, it can be suggested that corneal densitometry measurements indirectly provide information about the health of the cornea.

Previous research have primarily concentrated on examining the impact of COPD on the corneal endothelium. Soler et al. examined COPD patients after cataract surgery and found increased corneal edema, HEX and CV values, and decreased CD values compared to the control group.[18] It is important that CV and hexagonality are the two most important parameters that show the early changes in the corneal endothelial layer. The number of corneal endothelial cells is affected in the late stages. The parameters in the early stages, indicating that the endothelial layer is under stress, are CV and HEX values. The authors stated that COPD may be a risk factor for post-surgical endothelial damage.[18] Furthermore, Margo et al. and Ishikawa have identified COPD as a risk factor for reduced endothelial CD.[19,20]

The literature contains only a few studies that have examined corneal transparency in patients with COPD. Coskun investigated 25 patients with COPD and determined a significant decrease in lens transparency in COPD patients but did not find a significant change in corneal densitometry values.[21] The author suggested that this may be due to the corneal oxygen uptake from atmospheric oxygen rather than aqueous humor.[21] In contrast, our study identified statistically significant elevations in corneal densitometry values across all depths and diameters in the COPD group. The disparities between these findings may stem from differences in patient characteristics and the sample sizes among the studies. According to our results, it was thought that chronic hypoxia in COPD could affect corneal densitometry measurements by disrupting the normal function and structure of the cornea. The numerous significant correlations found between disease severity and smoking status with corneal densitometry values in

our study support this hypothesis. Therefore, we suggest that COPD and smoking, which can decrease ocular blood flow and increase vascular resistance, may be factors for the impairment of corneal health and transparency. This hypothesis may be supported by other studies which detected abnormal corneal function in smokers.[22] Additionally, COPD patients should be warned against using contact lenses, which can increase corneal hypoxemia.[23]

In patients who remain on mechanical ventilation for more than 7 days, cell number and transplant suitability decrease due to chronic hypoxia.[24] ECD decreases by 100 cells/mm^2 in patients exposed to mechanical ventilation for more than 30 days.[24] It was thought that it might be unsuitable for corneal transplant because the number of cells decreased. The fact that we showed in our study that COPD patients have decreased corneal transparency suggests that COPD patients may not be suitable donors for corneal transplantation.

One of the strengths of our study was the investigation of both corneal endothelium characteristics and corneal densitometry in the same participants. Moreover, the inclusion of a larger number of COPD patients in this study compared to previous studies investigating corneal transparency in COPD patients may increase the value and generalizability of our findings. There were some limitations to our study, such as the lack of SpO_2 values in statistical analysis. Because of the close relationship between SpO_2 and smoking and the dynamic changes in SpO_2 values, spirometry measurements may be more accurate in determining disease severity.[25] Additionally, including a group of smokers without COPD could provide more comprehensive information about the effects of smoking on corneal health. The inadequacy of our sample size is another limitation of our study. Further studies with an increased number of patients are necessary. Due to the low number of cases, patients with COPD were not classified into groups according to the GOLD classification. All patients diagnosed with COPD were included in a single group for the study. This creates a limitation in terms of examining the effects of COPD severity on the cornea. Subgroup analyses based on the medications used by patients with COPD were not conducted. COPD patients were only receiving beta-blocker treatment. However, there is no study examining the effect of beta-blocker usage on corneal transparency.

To summarize, the findings of this study indicate higher corneal densitometry values, which suggest reduced corneal transparency, among individuals with COPD in comparison to healthy individuals. Consequently, it is recommended that patients with COPD undergo thorough evaluation prior to ophthalmic procedures that can affect the function of the cornea, and surgeons should be mindful of potential corneal impairments following these procedures.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Tuğçe Horozoğlu Ceran, Ali Mert Koçer, Gülden Bilgin;* ***Design:*** *Tuğçe Horozoğlu Ceran, Ali Mert Koçer;* ***Control/Supervision:*** *Tuğçe Horozoğlu Ceran, Ali Mert Koçer, Pınar Kösekahya;* ***Data Collection and/or Processing:*** *Tuğçe Horozoğlu Ceran, Ali Mert Koçer, Halil İbrahim Ateşoğlu, Gülden Bilgin, Mine Turkay, Pınar Kösekahya;* ***Analysis and/or Interpretation:*** *Tuğçe Horozoğlu Ceran, Ali Mert Koçer, Pınar Kösekahya;* ***Literature Review:*** *Tuğçe Horozoğlu Ceran, Ali Mert Koçer, Halil İbrahim Ateşoğlu, Gülden Bilgin, Mine Turkay, Pınar Kösekahya;* ***Writing the Article:*** *Tuğçe Horozoğlu Ceran, Ali Mert Koçer;* ***Critical Review:*** *Gülden Bilgin, Pınar Kösekahya;* ***References and Fundings:*** *Tuğçe Horozoğlu Ceran, Ali Mert Koçer, Halil İbrahim Ateşoğlu, Gülden Bilgin, Mine Turkay, Pınar Kösekahya;* ***Materials:*** *Halil İbrahim Ateşoğlu, Mine Turkay, Gülden Bilgin, Pınar Kösekahya.*

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