

Evaluation of cornea with specular microscopy in patients with ocular rosacea

Oküler rozasea hastalarında korneanın spekülör mikroskopi ile değerlendirilmesi

Ali Hakim Reyhan¹, Şerife Şule Çınar², Birgul Özkesici Kurt³, Ayşe Sevgi Karadağ²

¹ Department of Ophthalmology, Kilis State Hospital, Kilis, Turkey

² Department of Ophthalmology, Adiyaman University Training and Research Hospital, Adiyaman, Turkey

³ Department of Dermatology, Adiyaman University Training and Research Hospital, Adiyaman, Turkey

Corresponding author: Ali Hakim Reyhan, MD, Department of Ophthalmology, Kilis State Hospital, Kilis, Turkey

E-mail: alihakimreyhan@gmail.com

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SUMMARY





Objective: To investigate changes in corneal endothelial cell density, corneal morphology and central corneal thickness in patients with ocular rosacea.

Method: 60 eyes of 30 ocular rosacea patients and 60 eyes of 30 control group with similar demographic characteristics were included in the study. Detailed ophthalmological examination was performed in all individuals participating in the study. The eyes of all participants were evaluated by specular microscopy, schirmer I test, tear break-up time test (TBUT). Additionally, via specular microscopy the following parameters were assessed: endothelial cell density (ECD), mean cell area (ACA), minimum cell area (CAmin), maximum cell area (CA max), cell area standard deviation (SD), coefficient of variation in the cell area (CV), hexagonal cell ratio (HEX), central corneal thickness (CCT) numerical (NUM).

Results: Although none of the differences are statistically significant, patients with ocular rosacea have lower ACA, CA min, CA max, HEX, CCT and NUM values ($p = 0,169$, $p = 0,897$, $p = 0,694$, $p = 0,649$, $p = 0,164$ and $p = 0,070$, respectively), and higher CD, SD and CV values ($p = 0.509$, $p = 0.437$, $p = 0.165$, respectively). In ocular rosacea patients, there was no significant correlation was found the values of mean Schirmer test between CV, HEX, ECD, CT ($p = 0.394$, $p = 0.906$, $p = 0.222$, $p = 0.208$, respectively). Additionally, no significant correlation was found between tear break-up time and CV, HEX, ECD, CCT ($p = 0.079$, $p = 0.227$, $p = 0.621$, $p = 0.712$, respectively).

Conclusions: Our finding show that, despite the presence of some observable differences, corneal endothelial functions are similar to control group in patients with ocular rosacea.

Keywords: Ocular rosacea, specular microscopy, dry eye syndrome, corneal endothelium.

 Ali Hakim Reyhan
 Şerife Şule Çınar
 Birgul Özkesici Kurt
 Ayşe Sevgi Karadağ

ORCID IDs of the authors:
 A.H.R. 0000-0001-8402-0954
 Ş.Ş.Ç. 0000-0001-8377-0753
 B.Ö.K. 0000-0003-3121-5816
 A.S.K. 0000-0002-7662-6531

ÖZET

Amaç: Oküler rozasea hastalarında korneal endotel hücre yoğunluğundaki, korneal morfolojisindeki ve santral kornea kalınlığındaki değişiklikleri araştırmak.

Yöntem: 30 oküler rozasea hastasının 60 gözü, benzer demografik özelliklere sahip 30 kontrol grubunu bireyin 60 gözü çalışmaya dahil edildi. Çalışmaya katılan tüm bireylerin detaylı oftalmolojik muayene yapıldı. Tüm katılımcıların gözleri speküler mikroskopi, schirmer I testi, gözyaşı kırılma zamanı testi ile değerlendirildi. Ayrıca, speküler mikroskopi ile aşağıdaki parametreler değerlendirildi: endotel hücre yoğunluğu (ECD), ortalama hücre alanı (ACA), minimum hücre alanı (CAmin), maksimum hücre alanı (CA max), hücre alanı standart sapması (SD), hücre alanındaki varyasyon katsayısı (CV), heksagonal hücre oranı (HEX), merkezi kornea kalınlığı (CCT), numerik (NUM).

Bulgular: Çalışmamızda oküler rozasea hastaları, sağlıklı kontrollere göre daha düşük ACA, CAmin, CAmax, HEX, CCT, NUM (sırasıyla p=0,169, p=0,897, p=0,694, p=0,649, p=0,164, p=0,070) değerlerine, daha yüksek CD ve SD, CV (sırasıyla p= 0,509, p=0,437, p=0,165) değerlerine sahip olmasına rağmen istatistiksel olarak anlamlı fark yoktu. Oküler rozasea hastalarında ortalama Schirmer testi değerleri ile CV, HEX, ECD, CT arasında anlamlı bir korelasyon bulunmadı (sırasıyla p = 0,394, p = 0,906, p = 0,222, p = 0,208). Ayrıca, gözyaşı kırılma zamanı ile CV, HEX, ECD, CCT arasında anlamlı bir korelasyon bulunmadı (sırasıyla p = 0,079, p = 0,227, p = 0,621, p = 0,712).

Sonuç: Bulgularımız göre , oküler rozasea hastalarında korneal endotel fonksiyonların kontrol grubuna göre, bazı farklılıkları olmasına rağmen, benzer olduğunu göstermektedir.

Anahtar sözcükler: Oküler rozasea, speküler mikroskopi, kuru göz hastalığı, korneal endotel.

INTRODUCTION

Rosacea is a chronic inflammatory skin disease of unknown origin, characterized by papules, pustule erythema and telangiectasia in the face and neck ¹. It is estimated that up to 58% of patients with rosacea also have ocular rosacea ^{2,3,4}. The degree and characteristics of ocular involvement in rosacea varies greatly, from blepharitis to corneal perforations that may result in vision loss ^{5,6}. Ocular rosacea usually progresses with nonspecific symptoms such as itching, burning, stinging, redness, foreign body sensation, photophobia, pain and blurred vision. The most common findings are blepharitis, telangiectasia at the edge of the eyelid, meibomitis, recurrent chalazion, hordeolum, superficial punctate keratopathy and conjunctival hyperemia. Less frequently, episcleritis, scleritis, keratitis, iritis corneal vascularization, corneal perforation can be seen ⁷. The majority of patients with rosacea also have meibomian gland dysfunction ⁸. Meibomian gland dysfunction can cause blepharitis, dry eye syndrome, abnormalities in tear break-up time and schirmer tests, and recurrent chalazions in patients with rosacea ⁹⁻¹². The etiopathogenesis of the ocular rosacea remains unknown; however, recently, research has focused on matrix metalloproteinase, bacterial lipases and interleukin 1alfa levels in association with blepharitis and corneal epitheliopathy in rosacea patients ¹³.

The corneal endothelium is the posterior layer of the cornea that demonstrates a honeycomb pattern consisting of single-row cells. Corneal endothelial cells are the cells responsible for maintaining the transparency of the cornea by regulating stromal hydration ¹⁴⁻¹⁶. Specular microscopy is a non-invasive imaging method to evaluate the morphology of the corneal endothelium. The

parameters of endothelial cell density (ECD), coefficient of variation (CV) and percent of hexagonal cells or hexagonal cell ratio (HEX) are usually used to evaluate endothelial morphology and stability. ECD is an important biomarker in evaluating corneal health ¹⁷. The value of ECD is expressed as the number of cells per square millimeter. CV is an indicator of the homogeneity of the size of endothelial cells; high values indicate high pleomorphism levels ¹⁸. HEX is the ratio of hexagonal cells to cells with other geometric shapes. Although the ideal rate is around 100%, it has been reported that HEX is in the range of 60-70% in healthy corneas in previous studies ¹⁹. Central corneal thickness (CCT) can be used as a marker that provides information about both the barrier and pump functions of the endothelium and can be measured using specular microscopy ²⁰.

Chronic inflammation occurring in the corneal endothelium and aqueous humor can cause endothelial cell loss. Although the mechanisms involved in endothelial cell loss are not understood, it has been suggested that the breakdown of the blood-ocular barrier due to chronic subclinical inflammation plays a role ²¹. Our hypothesis was that there is a possibility of endothelial damage and endothelial cell dysfunction in a disease such as ocular rosacea that progresses with chronic inflammation. Thus, we aimed to evaluate the corneal endothelial functions and morphology of ocular rosacea in comparison with the eyes of control group.

MATERIAL AND METHODS

This study was carried out in accordance with the Helsinki declaration. It was carried out after obtaining written informed consent from all participants. Before the study, approval was obtained from the clinical research ethical

committee of Adiyaman University (Date: 21/11/2017 no: 2017/8-2).

Ocular rosacea group comprised 30 patients with a diagnosis rosacea referred to us from the dermatology department of Adiyaman University. 60 eyes of 30 ocular rosacea patients recruited by the ophthalmology department of Adiyaman University and 60 eyes of 30 control group without ocular and systemic diseases were evaluated.

As per report of the expert committee of the American National Rosacea Society, diagnosis of ocular rosacea was made on the findings of anterior blepharitis, meibomitis and/or meibomian gland dysfunction (MGD), recurrent chalazion, eyelid telangiectasia, punctate epitheliopathy, corneal infiltrates or neovascularization, particularly in the peripheral cornea. The subjects were diagnosed MGD by an experienced ophthalmologist based on ocular symptoms, ≥ 1 lid margin abnormality (irregular lid margin, vascular engorgement, plugged meibomian gland orifices, and anterior or posterior replacement of the mucocutaneous junction), and poor meibum expression.

Individuals with systemic diseases, Patients with structural abnormalities of the eyelids, aqueous-deficient dry eye, inflammatory or infectious keratitis, a history of any eye disease or eye trauma, those that had undergone eye surgery, and contact lens users were excluded from the study.

The best corrected visual acuity of each patient was evaluated with Snellen chart. Biomicroscopic examination, fundus examination, intraocular pressure measurements with goldmann applanation tonometer were also performed. Both eyes of all ocular rosacea group were evaluated with the schirmer 1 test (without anesthesia) and tear break-up time test (TBUT). Standard Schirmer filter paper (5x35 mm Clement Clarke International) was used for the Schirmer 1 test. Briefly, the first 5 mm portion was placed in the outer 1/3 conjunctival fornix. After 5 minutes, the amount of wetness was measured. Below 10 mm was considered significant. TBUT was examined using Haag Streit fluorescein paper without using superficial anesthetic. While the patients were looking upward, the fluorescein paper was smoothly touched to the primary temporal inferior fornix conjunctiva and then removed. The patients were directed to blink three times, and then look straight forward without blinking. The tear film was observed under cobalt blue filtered light of the slit-lamp biomicroscope, and the time that elapsed between the last blink and appearance of the first

break in the tear film was recorded with a stopwatch. Measurements were repeated three times and the mean TBUT was calculated.

Patients received topical metronidazole prescribed by the dermatology clinic and our standard ophthalmologic treatment regimen. All patients were treated with hot compresses, eyelash base cleansing, preservative-free artificial tear drops (Tears Naturale Free, Alcon, Fort Worth, Texas, USA or Refresh, topical antibiotic ointment (Ciloxan ophthalmic ointment, Alcon), short-term low-dose topical corticosteroid drops (Lotemax, Bausch&Lomb, Bridgewater, NJ, USA) four times daily, 100 mg oral doxycycline once daily, and topical 0.05% cyclosporine drops (Restasis, Allergan) four times daily.

The eyes of all participants were evaluated by non-contact specular microscopy (Nidek CEM - 530, Japan). Measurements were made at least 3 times by the same technician using the central method. Endothelial cell density (ECD), average cell area (ACA), minimum cell area (CAmin), maximum cell area (CAmax), standart deviation of cell area (SD), coefficient of variation in cell area (CV), hexagonal cell ratio (HEX), central corneal thickness (CCT) and numeric (NUM) parameters were evaluated.

The evaluation of all data was done with the SPSS version 22.0 (SPSS Inc, Chicago, Illinois, USA) software. Comparison of analyzed parameters between groups was performed with the Chi-square test and independent samples t-test depending on data type (continuous, categorical). In the results, a p-value less than 0.05 was considered to demonstrate statistical significance.

RESULTS

In the patient group, 3 patients were male and 27 patients were female. The age of individuals in the ocular rosacea group ranged between 23 and 63 years, with a mean of 42.1 ± 11.3 years. Similarly, the control group consisted of 3 males and 27 females. Their ages ranged from 26 to 65 years, with a mean of 42.0 ± 10.6 years. The groups were homogeneous in terms of age and gender ($p > 0.05$). The most common ocular symptoms in ocular rosacea patients were itching (65.5%), redness (61%), watery eye (23%), stinging (55%), foreign body sensation (52%). The most common findings in patients were meibomian gland dysfunction (68%), telangiectasia (29%) blepharitis (55%), chalazion (35%), conjunctival hyperemia (55%) and superficial punctate keratopathy (22%). (Table 1)

Table 1: Evaluation of symptoms and signs in ocular rosacea patients

Symptom	n:60	%	Findings	n:60	%
Itching	39	65,5	MGD	41	68
Redness	37	61	Telangiectasia	14	29
Watery Eye	14	23	Blepharitis	33	55
Stinging	33	55	Chalazion	21	35
FBS	31	52	Conjunktival Hyperemia	33	55
			SPK	13	22

FBS: Foreign Body Sensation, SPK: Superficial punctate keratopathy, MGD: Meibomian gland dysfunction

The mean schirmer test result was 11.51 mm in ocular rosacea patients, and the mean tear break-up time result was 7.62 sec. The mean intraocular pressure in patients with ocular rosacea was 17.58 mmHg, whereas it was 16.54 mmHg in the control group ($p=0.227$). Best corrected visual acuity was 0.91 in the ocular rosacea group and 0.97 in the control group.

No statistically significant difference was found in ECD, CAmin, CAmax, SD, CV, HEX, CCT, NUM

values when the rosacea and control groups were compared (Table 2). In ocular rosacea patients, there was no significant correlation was found the values of mean Schirmer test between CV, HEX, ECD, CT ($p = 0.394$, $p = 0.906$, $p = 0.222$, $p = 0.208$, respectively). Additionally, no significant correlation was found between tear break-up time and CV, HEX, ECD, CCT ($p = 0.079$, $p = 0.227$, $p = 0.621$, $p = 0.712$, respectively) (Table 3).

Table 2: Comparison of specular microscopy and corneal endothelial values in ocular rosacea patients and controls

	Ocular Rosacea Group	Control Group	P-values
CD (cells /mm ²)	2577,80±31	2540,72±29	0,509
ACA μm ²	384,38± 66,563	399,68±53,899	0,169
CA min μm ²	141,42±17,90	141,93±17,16	0,897
CA max μm ²	1016,77±305,98	1080,77±214,36	0,694
SD	115,22±27,89	111,80±19,32	0,437
CV	30,93±6,06	29,67± 3,54	0,165
HEX %	66,90±7,25	67,40±4,40	0,649
CCT μm	543,52±31,21	552,13±35,94	0,164
NUM (cell)	155,22±53,28	170,78±38,34	0,070

CD: Endothelial cell density, ACA: mean cell area, CAmin: minimum cell area, CAmax: maximum cell area, SD: standard deviation of the cell area, CV: variation coefficient in the cell area, HEX: hexagonal cell ratio, CCT: central corneal thickness NUM : numerical

Table 3: Evaluation of the correlation between dry eye diagnosis tests and specular microscopy parameters in ocular rosacea patients

	Schirmer	TBUT
CV	r: -0,110 p=0,395	r:-0,225 p=0,079
HEX	r: -0,15 p=0,906	r: 0,140 p=0,277
CD	r: -0,157 p=0,222	r: -0,64 p=0,621
CCT	r: -0,162 p=0,208	r: 0,048 p=0,712

TBUT: tear break-up time, CV: coefficient of variation in the cell area, CD: endothelial cell density, HEX: hexagonal cell ratio, CCT: central corneal thickness

DISCUSSION

Ocular rosacea may cause damage to the cornea due to the presence of chronic inflammation. However, our assessment of corneal endothelial function in patients with ocular rosacea did not show any significant differences from controls, even though some observable differences were determined in patients.

The causes of chronic corneal endothelial cell damage have not been clearly identified²². Intraocular operations, glaucoma, chronic inflammation and aging can cause corneal endothelial cell damage²³⁻²⁶. Especially endothelial cell disruptions associated with anterior uveitis have been known and studied for a long time²⁷. In another study, various disorders and functional losses (that were thought to be due to chronic inflammation) were observed in endothelial cells around keratic precipitates after anterior uveitis²⁸. Even though no corneal decompensation was shown in this study, losses in cell morphology were detected. Compared to the fellow eye with no uveitis attack, the eye that developed chronic uveitis-induced keratic precipitate showed significant differences in cell size and cell density, especially around keratic precipitates²⁸. However, as stated in the study, these differences disappeared after treatment [28]. It was known that some inflammatory cytokines have endothelial cell loss even in *in vitro* conditions and may have a toxic effect on endothelial cells²⁹. In addition, it has been shown that inflammatory cytokines may be related to endothelial cell loss²².

Therefore, it is feasible to suggest that ocular rosacea may lead to significant inflammation that could, in turn, lead to endothelial damage. However, the results of our study demonstrated an absence of meaningful differences between patients and controls. However, we did not assess

the uvea and retina, which could have been disproportionately affected by ocular rosacea. For instance, Kheirkhah et al showed corneal endothelial cell loss in patients with dry eye syndrome and their study was guiding for us in this context³⁰. Kheirkhah et al showed that patients with dry eye syndrome had a lower level of endothelial cells compared to the normal population, and observed faster cell loss (in excess of age-related loss) in their follow-up³⁰. Although the cause of this loss was not explicitly found in this study, the authors emphasized that chronic inflammation could explain their findings³⁰. As such, we hypothesized that a disease such as ocular rosacea which often causes dry eye syndrome and is associated with chronic inflammation in the entire body and eyes, could have a comparatively greater effect on endothelial cells. We can explain the lack of meaningful alterations in our study with the treatments received by our patients. Pillai et al stated that the changes they showed in the corneal endothelium due to chronic anterior uveitis decreased with the regression of inflammation; furthermore, they reported that the damage suffered by the epithelium was not permanent after treatment [28]. Therefore, we may associate the absence of significant levels of endothelial cell loss in our study with the administration of anti-inflammatory treatments in the patient group. Also, the small sample size of our study may have affected the results. More accurate results may be obtained by increasing the study sample and evaluating the effects of treatments in patients with ocular rosacea.

When we evaluated the relationship between dry eye syndrome and corneal endothelium, we found that there was no correlation between any of the corneal endothelial parameters and results from the Shirmer test and TBUT. There are contradictory studies on this subject in the literature. In some

studies, it has been reported that patients with dry eye syndrome suffer from damages to the corneal endothelium –with regard to the severity of disease³¹. Additionally, in the same study, they graded dry eye patients according to TBUT and tear meniscus heights, which demonstrated a significant worsening in specular microscopy findings that correlated with the severity of dry eye syndrome³¹. In another study, Kreikah et al found ECD reduction in dry eye patients in line with the degree of the disease³². It is known that dry eye syndrome initiates an inflammatory process³³. In these studies, although the mechanism of dry eye syndrome causing endothelial damage cannot be clearly explained, it is said that the inflammatory process in the eye may be effective in this condition^{31,32}. There are also publications where these results could not be repeated; for instance, one study reported no significant change in the corneal endothelium in patients with dry eye³⁴. Sopapornamorn et al also reported that corneal endothelium density or corneal endothelial morphology were not associated with the parameters of dry eye syndrome³⁴. In another interesting study, significant morphological changes were detected in the endothelium only in patients with dystyroid ophthalmopathy; whereas no significant change was determined in other patients with dry eye syndrome³⁵. However, the authors could not provide any explanation regarding their findings³⁵.

Study Limitations

The limitations of this study are its retrospective design, the need for a larger patient population and the administration of anti-inflammatory treatments in the patient group

CONCLUSION

Our results demonstrate that there were no differences between patients with ocular rosacea and control group in terms of corneal endothelial functions. Although all parameters assessed in this study were similar in these two groups, some comparisons were only marginally insignificant; therefore, we believe that future studies that include a higher number of patients that were stratified according to treatments could be instrumental for the accurate assessment of the effects of ocular rosacea on the corneal endothelium.

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