• Clinical Research •

Layer and zone-specific study of corneal optical density in dry eye disease: links to tear film metrics

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Abstract

● **AIM:** To assess the differences in corneal optical density (COD) between young patients with dry eye and healthy controls, as well as to evaluate the correlations with tear film parameters.

● **METHODS:** This cross-sectional study involved 30 patients with dry eye and 60 age-matched controls (aged 18–35y). All participants underwent a thorough ophthalmic evaluation, including visual acuity testing, refraction, the Ocular Surface Disease Index (OSDI) questionnaire, tear break-up time (TBUT), the Schirmer's test, corneal staining, and Pentacam densitometry.

● **RESULTS:** The groups were matched for age (21.93±2.88y *vs* 20.80±2.27y) and sex (females: 60.0% *vs* 63.3%; *P*>0.05). No statistically significant differences were found in refraction parameters, best-corrected visual acuity, or mean keratometry when comparing the two groups (all *P*>0.05). Patients with dry eye exhibited significantly poorer tear parameters including OSDI (25.5±10.6 *vs* 8.3±6.6, *P*<0.001), TBUT (6.2±2.2s *vs* 12.9±6.4s, *P*<0.001), and Schirmer score (20.9±11.2 *vs* 26.0±11.4 mm, *P*=0.02). Dry eye patients displayed a significantly higher average COD in the midperipheral zone (6–10 mm) for both the anterior (18.81±2.15 *vs* 17.25±1.66, *P*<0.001) and central layers (11.56±1.35 *vs* 10.78±0.90, *P*=0.002) compared to the controls. The anterior COD in the 6–10 mm zone (*β*=0.329, *P*<0.001) and the middle COD in the 6–10 mm zone (*β*=0.267, *P*=0.006) showed a statistically significant direct relationship with OSDI.

● **CONCLUSION:** Young patients with dry eye exhibit increased COD, especially in the anterior and middle corneal layers, which correlates with symptom severity. These results imply that corneal densitometry could act as an objective measure of dry eye severity, supplementing traditional clinical evaluations.

● **KEYWORDS:** dry eye disease; corneal densitometry; Pentacam; tear break-up time; Ocular Surface Disease Index

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INTRODUCTION

Dry eye disease (DED) is a chronic and multifactorial condition affecting the ocular surface, characterized by a loss of tear film homeostasis, leading to symptoms such as discomfort, visual disturbances, and pain[1]. With a prevalence ranging from 5% to 50% globally[2], influenced by various diagnostic criteria and demographic factors, DED poses a significant public health burden[3]. Its rising incidence is associated with contemporary lifestyle factors, such as extended use of digital screens, contact lens wear, environmental factors, and an aging population[4], highlighting the need for enhanced diagnostic and treatment approaches.

Corneal optical density (COD), assessed through corneal densitometry, is an innovative quantitative measure that evaluates light backscatter in the cornea, offering an objective assessment of corneal transparency[5]. Traditionally, densitometry has been utilized to evaluate corneal transparency in conditions like corneal dystrophies, post-refractive surgery changes, and keratoconus[6]. However, advancements in imaging technologies, particularly Scheimpflug-based tomography have significantly enhanced its clinical relevance by allowing detailed, layer and zone-specific analysis of corneal back light scattering[5]. This progress has broadened the scope of its application beyond conventional corneal diseases, enabling researchers to explore subtle microstructural changes in conditions such as DED, where chronic tear film instability may induce subclinical alterations in corneal integrity[7].

Despite the increasing research on DED and corneal densitometry, there remain significant gaps in our understanding of how tear film dysfunction relates to COD. Few studies have investigated the role of corneal densitometry in DED[8-10]. It should be noted that most previous studies have concentrated on assessing changes in COD before and after treatment for DED[9-10], rather than establishing baseline differences between DED patients and healthy individuals. To the best of our knowledge, only one study has directly compared corneal densitometry in DED patients against normal controls[8]. Furthermore, the associations between densitometry values and essential tear film metrics—such as tear break-up time (TBUT), Schirmer's test results, and Ocular Surface Disease Index (OSDI) scores have not been adequately explored. Consequently, the potential of corneal densitometry as an objective biomarker for assessing the severity of DED or the effectiveness of treatments has yet to be comprehensively examined.

This study seeks to investigate the impact of DED on COD by analyzing the correlations between densitometry values and tear film indices. By filling these research gaps, our findings may offer critical insights into the structural implications of chronic tear film instability, thereby improving diagnostic precision and monitoring of DED progression. Clinically, establishing a relationship between corneal densitometry and DED severity could lead to innovative therapeutic approaches aimed at maintaining corneal clarity and enhancing visual quality for patients affected by this condition.

PARTICIPANTS AND METHODS

Ethical Approval This study complied with the guidelines outlined in the Declaration of Helsinki. The Ethics Committee of Iran University of Medical Sciences approved the study protocol (approval number: IR.IUMS.REC.1403.741). All participants gave their written informed consent.

Study Design, Participants, Inclusion and Exclusion Criteria This cross-sectional study was conducted at the Optometry Clinic of the Faculty of Rehabilitation, Iran University of Medical Sciences, between December 2024 and June 2025. Participants were chosen through a convenience sampling method and categorized into two groups: 30 young patients diagnosed with DED and 60 age-matched healthy controls exhibiting normal tear status. The diagnosis of DED was established according to the Dry Eye Workshop 2017 report[11], which required an OSDI score of 13 or higher (indicating subjective symptoms) along with at least one objective sign (TBUT of 10s or less, Schirmer test score of 5 mm or less without anesthesia, and fluorescein corneal staining grade of 1 or higher). Participants needed to be between the ages of 18 and 35y and have a best-corrected visual acuity (BCVA) of 20/25 or better in both eyes. The exclusion criteria included active corneal pathologies (such as keratoconus, corneal dystrophy, or opacity), systemic diseases that could impact the cornea (including diabetes, Sjögren's syndrome, and connective tissue disorders), the use of medications known to compromise corneal integrity or tear film stability, a history of ocular trauma or intraocular surgery, and contact lens usage within the preceding month.

Examinations All participants underwent a thorough ophthalmic evaluation, which included the following assessments. Uncorrected distance visual acuity was measured using a digital chart (HCP-7000; Huvitz, Gyeonggi-do, Korea) at a distance of 6 m under photopic conditions. Objective refraction was carried out with an autorefractometer/keratometer (Huvitz HRK-8000A; Anyang, Korea) under non-cycloplegic conditions, with three consecutive measurements taken and averaged. Subjective refraction was performed to ascertain the BCVA.

To minimize diurnal variations in tear film parameters, all tests were performed at least 2h after waking from nighttime sleep, between 8:00 *a.m.* and 1:00 *p.m.* Symptoms of DED were evaluated using the validated Persian version of the OSDI questionnaire[12], which consists of 12 items that assess the frequency of symptoms, vision-related functionality, and environmental triggers. Scores were computed on a scale ranging from 0 to 100, with elevated scores signifying increased severity of symptoms. The TBUT was measured using a slit-lamp biomicroscope (Haag-Streit AG, 132 Gartenstadtstrasse, Switzerland) equipped with a cobalt blue filter, following the instillation of sodium fluorescein dye (1–2 μL of 1% fluorescein). Participants were instructed to blink naturally and then maintain their eyes in an open position. The duration (in seconds) from the last blink to the initial appearance of a dry spot was recorded. This test was conducted three times, and the mean value was used for analysis. Tear production was assessed through the Schirmer I test without the use of anesthesia. A standardized Schirmer strip was positioned in the lateral one-third of the lower eyelid, with participants advised to keep their eyes gently closed. After a duration of 5min, the length of the wet segment of the strip was measured in mm[13]. Corneal epithelial damage was examined using sodium fluorescein staining under blue light illumination on a slit-lamp biomicroscope. The staining was classified according to the Oxford Grading Scale (0–5), which includes: Grade 0: no staining, Grade 1: minimal scattered staining, Grade 2: mild, partially confluent staining, Grade 3: moderate, confluent staining in less than 50% of the cornea, Grade 4: marked, confluent staining in more than 50% of the cornea, and Grade 5: severe, diffuse staining accompanied by erosions[14].

Corneal densitometry was evaluated utilizing the Pentacam HR (Oculus Optikgeräte GmbH, Germany) Scheimpflug imaging system. To minimize bias, all Pentacam imaging were performed by a second examiner who was masked to participant group assignments. Participants were directed to focus on a central target while the device automatically captured cross-sectional images of the cornea. The densitometry analysis was conducted using the proprietary software of the device, which quantifies light backscatter in grayscale units (range: 0–100, with higher values signifying increased opacity). Measurements were taken for various corneal layers [anterior layer (0–120 μm), central layer (120–240 μm), and posterior layer (240–500 μm)] and different annular zones [central zone (0–2 mm diameter), paracentral zone (2–6 mm diameter), mid-peripheral zone (6–10 mm diameter), and peripheral zone (10–12 mm diameter)]. Three consecutive scans were executed for each eye, and the average values were considered. Only scans with an "OK" scan quality specification (as indicated by the device's internal quality check) were included in the analysis. If an image did not meet the required quality standards (*e.g.*, due to misalignment, motion artifacts, or incomplete data), the scan was repeated until an acceptable image was obtained.

Statistical Analysis All analyses were conducted using Statistical Package for Social Sciences (version 25; IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean±standard deviation (SD; normal distribution) or median (interquartile range; non-normal distribution). Categorical variables were summarized as frequencies (percentages). The Kolmogorov-Smirnov test was applied to assess data distribution normality. The COD values between the DED and control groups were compared using an independent samples *t*-test or the Mann-Whitney *U* test. For multiple comparisons of COD values across DED and control groups, Bonferroni correction was applied to adjust significance thresholds, with $P<0.003$ ($0.05/n=15$, where n represents the number of comparisons) considered statistically significant. Associations between COD values [gray scale unit (GSU)] and tear film parameters (*e.g.*, TBUT, Schirmer score, OSDI) were evaluated using multiple linear regression analysis after adjusting for age and sex. Given the strong correlation observed between the fellow eyes across all clinical variables and COD indices ($r>0.80$), the entire analysis was conducted using data solely from the right eye.

RESULTS

This study included 30 young patients with DED and 60 age-matched normal controls, all aged between 18 and 35y. The mean age of the DED group was 21.93±2.88y, compared to 20.80±2.27y in the control group. Females comprised 60.0% (18/30) of the DED group and 63.3% (38/60) of the control group. No statistically significant differences were observed in age ($P=0.080$) or sex distribution ($P=0.544$) between the two groups, confirming adequate matching.

Table 1 Comparison of baseline clinical variables between dry eye and control groups mean±SD

Variable	Dry eye group (n=30)	Control group (n=60)	P
BCVA (logMAR)	0.00±0.01	0.00±0.05	0.42
Spherical equivalent (D)	−1.1±1.5	−0.9±1.2	0.31
Cylinder (D)	−0.7±0.5	−0.6±0.4	0.52
Mean keratometry (D)	43.4±1.2	43.2±1.6	0.45
OSDI	25.5±10.6	8.3±6.6	<0.001[a]
TBUT (s)	6.2±2.2	12.9±6.4	<0.001[a]
Schirmer score (mm)	20.9±11.2	26.0±11.4	0.02[a]

[a]Statistically significant. BCVA: Best-corrected visual acuity; logMAR: Logarithm of minimum angle of resolution; OSDI: Ocular Surface Disease Index; TBUT: Tear break-up time; D: Diopter; SD: Standard deviation.

Table 1 summarizes the baseline clinical characteristics of the DED and control groups, including refractive parameters (spherical equivalent, cylinder), BCVA, keratometry, and tear film metrics. As illustrated in Table 1, all tear metrics, including OSDI, TBUT, and Schirmer score, exhibited statistically significant differences between the DED and control groups. However, no statistically significant differences were observed in the other variables when comparing the two groups (all $P>0.05$).

According to the normality testing, the middle COD within the zones of 0–2 mm, 2–6 mm, and 10–12 mm, as well as the posterior COD within the 10–12 mm zone, exhibited a non-normal distribution, whereas the remaining densitometric variables displayed a normal distribution. Table 2 presents a comparison of COD values across different corneal layers and zones between the DED group and the control group. As seen in Table 2, the average COD in the anterior cornea within the 6–10 mm zone was significantly higher in the DED group compared to the control group ($P<0.001$). Additionally, the DED group exhibited a significantly higher average COD in the middle cornea within the 6–10 mm zone when compared to the control group ($P=0.002$). No statistically significant differences were observed in the average COD across other corneal layers and zones between the DED and control groups.

Table 3 displays the results from the multiple regression analysis conducted between the anterior and middle COD within the 6–10 mm zone and the tear film parameters, after controlling for the effects of age and sex. As shown in Table 3, the anterior COD within the 6–10 mm zone exhibited a statistically significant direct association with OSDI ($\beta=0.329$, $P<0.001$); however, no significant relationship was identified between the anterior COD and TBUT ($\beta=-0.166$, $P=0.117$) or the Schirmer score ($\beta=-0.150$, $P=0.159$). Additionally, the middle

Table 2 Comparison of COD across different corneal layers and zones between the dry eye and control groups mean±SD/median (IQR) (95%CI)

COD	Dry eye group (*n*=30)	Control group (*n*=60)	*P*	Effect size (Cohen's *d)*
Anterior 120 μm (GSU)				
0–2 mm	22.66±1.42 (22.12–23.20)	22.33±1.08 (22.05–22.61)	0.228	0.26
2–6 mm	20.05±1.18 (19.61–20.50)	19.76±1.02 (19.49–20.02)	0.226	0.26
6–10 mm	18.81±2.15 (17.54–19.06)	17.25±1.66 (16.83–17.69)	<0.001[a]	0.81
10–12 mm	27.50±8.00 (24.46–30.54)	25.80±7.62 (23.83–27.77)	0.334	0.22
Total	21.18±2.02 (20.41–21.95)	20.36±1.90 (19.88–20.86)	0.067	0.42
Middle (GSU)				
0–2 mm	13.50 (12.55, 13.90) (12.99–13.84)	13.00 (12.52, 13.37) (12.85–13.22)	0.061	0.40
2–6 mm	11.80 (11.35, 12.35) (11.62–12.27)	11.60 (11.30, 11.90) (11.42–11.74)	0.023	0.48
6–10 mm	11.56±1.35 (11.05–12.07)	10.78±0.90 (10.55–11.02)	0.002[a]	0.68
10–12 mm	16.00 (14.95, 19.70) (15.61–18.22)	16.55 (13.80, 19.65) (15.96–18.01)	0.933	0.02
Total	12.90±1.19 (12.45–13.35)	12.46±0.92 (12.22–12.70)	0.058	0.41
Posterior 60 μm (GSU)				
0–2 mm	12.06±0.87 (11.73–12.39)	11.75±0.79 (11.55–11.96)	0.103	0.37
2–6 mm	10.87±0.83 (10.55–11.19)	10.68±0.65 (10.51–10.85)	0.236	0.25
6–10 mm	11.08±1.03 (10.69–11.47)	10.68±0.91 (10.44–10.92)	0.067	0.41
10–12 mm	13.00 (12.35, 15.55) (12.82–14.84)	13.80 (12.20, 16.05) (13.44–14.76)	0.648	0.10
Total	11.64±0.98 (11.27–12.02)	11.43±0.88 (11.20–11.66)	0.298	0.22

[a]Statistically significant adjusted by Bonferroni correction (*P*<0.003 is statistically significant). Median (IQR) is reported for variables with non-normal distribution and mean±SD for normally distributed variables. COD: Corneal optical density; GSU: Gray scale unit; SD: Standard deviation; IQR: Interquartile range; CI: Confidence interval.

COD within the 6–10 mm zone demonstrated a statistically significant direct association with OSDI (β=0.267, *P*=0.006). The middle COD did not show a statistically significant relationship with TBUT (β=-0.098, *P*=0.374) or the Schirmer score (*r*=-0.029, *P*=0.789).

DISCUSSION

Research on COD in patients with DED remains limited. Koh *et al*[8] found that individuals with DED exhibit increased anterior corneal backward light scattering when compared to healthy individuals, aligning with our own results. Koh *et al*'s[8] study also showed a moderate positive correlation between superficial punctate keratopathy in the central 6-mm corneal zone and corneal backward light scattering from the anterior cornea. In the study conducted by Asena *et al*[10], the average corneal densitometry values showed no statistically significant difference before and after DED treatment. In the research conducted by Wegener *et al*[9], DED patients who received treatment with lubricants, specifically those containing carbomer as the viscous agent, exhibited a significant decrease in COD within the anterior layers of the cornea when compared to the control group. Our study further adds to the existing literature by revealing a significant direct relationship between anterior and middle COD (within 6–10 mm zone) and OSDI scores. These findings indicate that corneal densitometry could serve as an objective biomarker for assessing the severity of DED, thereby enhancing the evaluation provided by subjective symptom assessments and conventional clinical tests.

Table 3 Association between the anterior and middle COD within the 6–10 mm zone and tear film parameters after adjusting for age and sex

Parameters	Standardized coefficient (β)	*r*	*P*
Anterior COD			
OSDI	0.329	0.340	<0.001[a]
TBUT	-0.166	0.277	0.117
Schirmer score	-0.150	0.229	0.159
Middle COD			
OSDI	0.267	0.250	0.006[a]
TBUT	-0.098	0.211	0.374
Schirmer score	-0.029	0.172	0.789

[a]Statistically significant (*P*<0.05). COD: Corneal optical density; OSDI: Ocular Surface Disease Index; TBUT: Tear break-up time.

The increased COD in DED can be attributed to various pathophysiological mechanisms. Chronic DED results in epithelial damage characterized by superficial punctate keratopathy, erosions, and heightened cell desquamation[15], which disrupt the cornea's smooth optical surface and lead to increased light scattering[16]. This process is driven by tear film instability and hyperosmolarity, which cause epithelial cell shrinkage, apoptosis, and the release of pro-inflammatory cytokines such as matrix metalloproteinase-9 (MMP-9) and interleukin 6 (IL-6)[17-18]. The resulting inflammation activates keratocytes, promotes extracellular matrix remodeling, and can lead to leukocyte infiltration and stromal edema, further

contributing to stromal backscatter[19]. Furthermore, oxidative damage from reduced antioxidant defenses in the tear film leads to the accumulation of reactive oxygen species, causing protein cross-linking and corneal opacification[20].

The varying impact of DED on different corneal layers can be explained by both anatomical and physiological factors. The anterior cornea, being directly exposed to factors such as tear film instability, mechanical irritation from blinking, and environmental elements, is particularly vulnerable to microtrauma and inflammation[21]. In contrast, the posterior cornea, which relies on nourishment from the aqueous humor rather than the tear film, remains largely unaffected unless DED is severe or accompanied by endothelial dysfunction[22]. Additionally, this finding may be attributed to inherent differences in collagen fiber organization and biochemical composition between these regions. The anterior stroma is characterized by a more tightly packed and irregular arrangement of collagen fibrils, which are also smaller in diameter compared to those in the posterior stroma[23]. This structural heterogeneity could render the anterior cornea more susceptible to biomechanical and metabolic alterations induced by DED. In contrast, the posterior stroma exhibits a more uniform and lamellar collagen arrangement[24], potentially conferring greater resistance to COD changes despite similar disease exposure.

The observation that the 6–10 mm zone shows the most pronounced changes in COD can also be attributed to various anatomical, physiological, and environmental factors specific to DED. This mid-peripheral region experiences greater mechanical friction during blinking than both the central and far peripheral areas[25]. The central cornea benefits from protection by the tear meniscus, which mitigates the impact of eyelid shear forces, while the far periphery is shielded by the conjunctiva near the limbus, providing additional lubrication[26]. The mid-peripheral zone is particularly vulnerable as it is the primary contact area for the eyelid margin, where tear film break-up is most pronounced in DED[27]. In contrast, the central cornea often retains residual tears and is refreshed by reflex tearing, and the far periphery receives some compensatory lubrication and nutrients from the limbal vasculature[28]. Furthermore, inflammatory cytokines associated with DED are predominantly found in the mid-peripheral cornea, likely due to inflammation from mechanical stress during blinking and the slower clearance of inflammatory mediators in this area[19]. The collagen structure in the mid-peripheral stroma is transitional, being less densely packed than in the central cornea but more organized than in the far periphery[29], rendering it more susceptible to light scatter when affected by microstructural changes induced by DED.

A notable point of the present study was the investigation into the relationship between COD and tear film parameters. The results revealed that the anterior and middle COD within the 6–10 mm zone showed a significant positive association with the OSDI. However, no significant correlation was found with the TBUT or the Schirmer score. The association of elevated COD in the anterior/mid layers (6–10 mm zone) with poorer OSDI scores implies that microstructural alterations (increased light scatter due to epithelial/stromal changes)[30] may directly lead to visual symptoms induced by light scattering (such as glare and halo) reported in the OSDI, or may indicate chronic epithelial stress resulting from hyperosmolarity/inflammation[31], which intensifies symptom perception.

The results of this study have significant implications for clinical practice. Corneal densitometry can be utilized as a quantitative tool for evaluating disease progression and the effectiveness of treatments, thereby minimizing dependence on subjective symptom assessments. Patients exhibiting high COD in the anterior and middle layers, despite showing few symptoms, may benefit from proactive interventions to avert permanent corneal alterations. Additionally, those with increased anterior and middle COD may necessitate more intensive anti-inflammatory treatments, such as cyclosporine or corticosteroids, instead of relying solely on lubricants. The impact of DED on COD is primarily evident in the anterior and middle layers of the mid-peripheral region of the cornea. Therefore, corneal densitometry analysis should focus on this specific area when evaluating the severity of DED. Therapeutic interventions should also ensure adequate coverage of the mid-peripheral cornea, where damage is most pronounced.

Despite its contributions, this study has some limitations. While a 1:2 case-control ratio was employed, the overall sample size (30 patients with DED and 60 controls) remained relatively limited. This limitation may have reduced the statistical power of the analyses, particularly the regression models, and should therefore be considered when interpreting the findings. In particular, the lack of a statistically significant association between COD and certain tear film parameters, such as TBUT and Schirmer scores, may be attributable to the limited sample size as well as the absence of severity-based stratification. Stratifying DED into mild, moderate, and severe subgroups might potentially reveal more nuanced and clinically relevant relationships. Accordingly, future studies with larger sample sizes and severity-based classification are warranted to better clarify these associations. In addition, the cross-sectional design, the absence of advanced imaging correlations, and the inclusion of various DED subtypes should be considered as additional limitations of this study. To ascertain whether changes in corneal densitometry are reversible with treatment, longitudinal studies are essential. Future research could enhance understanding by integrating

densitometry with confocal microscopy to examine cellular-level alterations in DED. Additionally, investigating the distinctions between aqueous-deficient and evaporative DED may yield deeper mechanistic insights.

This research indicates that DED significantly elevates COD in the anterior and middle layers, which correlates with the severity of symptoms. The posterior cornea appears to be unaffected, likely due to its different exposure levels and structural resilience. These results underscore the potential of corneal densitometry as a valuable objective tool for diagnosing and monitoring DED. Future studies should prioritize longitudinal evaluations and mechanistic investigations to enhance therapeutic approaches aimed at maintaining corneal transparency in patients with DED.

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