

Correlation of corneal epithelial thickness with clinical severity of dry eye



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Background: Spectral-domain optical coherence tomography (OCT) has been used to measure corneal epithelium thickness in dry eye disease, allowing assessment of ocular-surface damage in different disease severity.

Aim: This study aimed to determine the characteristics of corneal epithelial thickness with spectral-domain OCT in patients with dry eye and correlate epithelial thickness with the clinical severity.

Setting: The study was conducted at outpatient clinic in the Department of Ophthalmology, Chulabhorn hospital, Bangkok, Thailand.

Methods: It was a cross-sectional study and 92 dry eye patients were included. All participants were assessed using the Dry Eye Questionnaire-5 (DEQ-5), tear film breakup time and fluorescein staining. Corneal epithelial thickness was measured with spectral-domain OCT. The mean and variance of epithelial thickness were calculated. Correlations of corneal epithelial thickness with other clinical parameters were calculated.

Results: There were no statistical differences in corneal epithelium thickness between the non-severe and severe dry eye groups. The peripheral corneal epithelial thickness variance was significantly higher in the severe dry eye. There was a significant correlation between peripheral epithelial thickness variance and the clinical parameters.

Conclusion: Peripheral corneal epithelial thickness variance was higher in the severe dry eye, suggesting that the peripheral ocular surface is more damaged. This also correlated with the symptoms and signs of dry eye, which can be used to assess the disease severity.

Contribution: This study provided the correlation of corneal epithelial thickness measurement with spectral-domain OCT on the diagnosis of dry eye severities.

Keywords: corneal epithelial thickness; dry eye severity; optical coherence tomography; corneal epithelial thickness variance; Dry Eye Questionnaire-5; tear breakup time; fluorescein staining.

Introduction

Dry eye is a relatively common, multifactorial disease that can markedly affect the quality of life of patients. The pathogenic mechanisms involve cycles of tear film instability and tear hyperosmolarity, which can lead to inflammation and injury to the ocular surface, as well as to various neurosensory eye components.^{1,2} In addition to the patient experiencing sensations of burning, irritation and tearing in their eyes, dry eye also causes inflammation of the eye surface, thus causing abrasion of the cornea and conjunctival surface cells, increasing the risk of corneal infections. Chronic corneal abrasions can induce corneal thinning and can also lead to perforation of the cornea.³ The diagnosis of dry eye disease was defined by the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) and is based on a history taken from the Dry Eye Questionnaire-5 (DEQ-5) score⁴ or the ocular surface disease index score.⁵ Physical examination involves slit lamp biomicroscopy to determine the tear breakup time (TBUT) for tear evaporation and tear film osmolarity and ocular-surface staining.^{6,7} Other methods, including *in vivo* confocal microscopy and impression cytology, and spectral-domain optical coherence tomography (OCT), can also be used for detection of corneal epithelium damage.

Spectral-domain OCT is an imaging technique used to measure the size of components in the eye via laser interferometry. Spectral-domain OCT is non-invasive and has high resolution and good reliability and repeatability. It is widely used in ophthalmology, for example, to measure the optic nerve thickness in glaucoma⁸ and macular thickness in macular oedema.⁹ The OCT has also been used to measure the thickness of corneal epithelial cells in patients with dry eye, providing a

thickness map in each corneal region¹⁰ and allowing assessment of increases, decreases or unevenness in corneal epithelial thickness. Furthermore, the heterogeneity of corneal epithelial thickness is related to the severity of dry eye disease, with increasing severity associated with increasing corneal epithelial thickness unevenness, indicative of ocular-surface damage that changes with disease severity.^{11,12,13,14,15,16,17} Thus, the aim of this study was to determine the characteristics of corneal epithelial thickness maps with spectral-domain OCT in patients with severe dry eye and to correlate epithelial thickness with the clinical severity of dry eye.

Materials and methods

From August 2021 to January 2022, we prospectively collected data from 152 patients screened at the outpatient clinic in the Department of Ophthalmology, Chulabhorn hospital. The patients in this study had received treatment for dry eye at Chulabhorn hospital. The inclusion criteria were age ≥ 18 years and symptoms meeting the criteria for diagnosis of dry eye according to the TFOS DEWS II. These criteria include scores from the DEQ-5 questionnaire ≥ 6 , in combination with at least one of the following: non-invasive TBUT < 10 s; and ocular-surface staining > 5 spots on the cornea, > 9 spots on the conjunctiva, or ≥ 2 -mm length on the eyelid and $\geq 25\%$ width⁷. Exclusion criteria included: ocular-surface diseases, such as epithelial basement membrane dystrophy; corneal scar; herpes infection; recurrent corneal erosion; eyelid disease (e.g., lagophthalmos or blinking problems); using other eye drops such as glaucoma medication; wearing contact lens; taking medications that are effective against dry eye (e.g., anti-histamines, oestrogen replacement therapy, anti-depressants, or isotretinoin); a history of eye surgery or trauma; and pregnancy or breastfeeding.

All patients signed an informed consent document before participating in the study. Demographic data were collected, including age, gender, hours of computer use per day and eye drops used. Patients were assessed for dry eye disease using the DEQ-5. The questionnaire was translated into the Thai language to make it easier for patients to complete. Most dry eye clinical assessments are subjective examinations; to reduce inter-assessor variation, all patients received a general eye examination by the same ophthalmologist using the same slit lamp biomicroscope. Fluorescein staining was performed to determine TBUT and fluorescein stain grading (Modified Oxford scale).¹⁸ Fluorescein stain grading was assessed using standard images to reduce intra-assessor variation. The TBUT was measured in seconds using a digital clock. All dry eye data were collected only on the more-affected eye.

All patients also underwent spectral-domain OCT (Cirrus 500; Carl Zeiss Meditec, Dublin, California, United States [US]). The machine offers a high-density 9-mm epithelial thickness map and corneal thickness map, each with over 24000 data points from 24 radial OCT b-scans. The epithelial

thickness values were calculated automatically by the software. The collected images were required to have a signal strength ≥ 8 and cover a total 9-mm area of the corneal epithelial thickness map display.¹⁹ The epithelial thickness map was shown in different zone diameters: central 2 mm, 2 mm to 5 mm, 5 mm to 7 mm, and 7 mm to 9 mm zones, as shown in Figure 1. Corneal epithelial data collected in this study included average thickness and thickness variance. These data were calculated manually in zones of different diameters: 5 mm, 7 mm and 9 mm.

For the clinical severity grading, the criteria for diagnosis of severe dry eye were moderate-to-marked conjunctival or corneal staining and a TBUT ≤ 5 s.²⁰ Data from only the more severely affected eye per participant were used.

Statistical analysis

All data were analysed using statistical software (StataTM software version 15.1; Stata Corporation, College Station, Texas, US). Baseline characteristics are presented using descriptive statistics, categorical data are presented using percentages and frequencies, and continuous data are presented using means and standard deviations or medians and interquartile ranges. Severe and non-severe dry eye population data were compared using an unpaired *t*-test for continuous data or the Chi-square test for categorical data. All analysed variables are presented in the same table. Correlations between corneal epithelial thickness data and the parameters used to assess dry eye severity in the clinical assessment, including DEQ-5, TBUT and fluorescein staining, are presented as Pearson's correlation coefficients. *P*-values < 0.05 were considered statistically significant.

Results

Of the 152 eyes screened from August 2021 to January 2022, 92 were enrolled in this study. The baseline characteristics are shown in Table 1, in which eyes were categorised into two

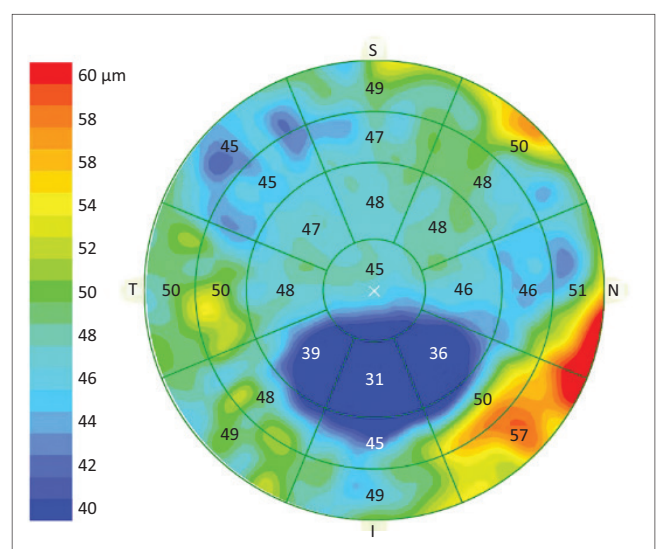


FIGURE 1: The epithelial thickness maps were shown in zones with different diameters.

TABLE 1: Clinical characteristics of the 92 eyes with severe or non-severe dry eye.

Clinical characteristics	Total (N = 92)				Non-severe (n = 60)				Severe (n = 32)				p
	Mean	s.d.	n	%	Mean	s.d.	n	%	Mean	s.d.	n	%	
Age (years)	57.4	13.4	-	-	58.75	13.3	-	-	55.0	13.6	-	-	0.21
Gender	-	-	-	-	-	-	-	-	-	-	-	-	0.43
Women	-	-	72	78.3	-	-	45	75.0	-	-	27	84.4	-
Men	-	-	20	21.7	-	-	15	25.0	-	-	5	15.6	-
Computer-use time per day	-	-	-	-	-	-	-	-	-	-	-	-	0.12
4–6 h	-	-	61	66.3	-	-	41	68.3	-	-	20	62.5	-
6–8 h	-	-	24	26.1	-	-	17	28.3	-	-	7	21.9	-
> 8 h	-	-	7	7.6	-	-	2	3.3	-	-	5	15.6	-
Eye drop use	-	-	-	-	-	-	-	-	-	-	-	-	0.49
None	-	-	31	33.7	-	-	22	36.7	-	-	9	28.1	-
artificial tears	-	-	61	66.3	-	-	38	63.3	-	-	23	71.9	-
Other eye drop	-	-	-	-	-	-	-	-	-	-	-	-	-
DEQ-5 score	-	-	7.19	1.3	-	-	6.91	1.0	-	-	7.71	1.7	0.005
TBUT	-	-	6.00	1.5	-	-	6.87	1.0	-	-	4.37	0.9	< 0.001
Cornea fluorescein grade	-	-	-	-	-	-	-	-	-	-	-	-	0.054
0	-	-	19	20.7	-	-	16	26.7	-	-	3	9.4	-
1	-	-	72	78.3	-	-	44	73.3	-	-	28	87.5	-
2	-	-	1	1.1	-	-	0	0.0	-	-	1	3.1	-
3	-	-	-	-	-	-	-	-	-	-	-	-	-

s.d., standard deviation; DEQ-5, Dry Eye Questionnaire-5; TBUT, tear break-up time.

groups according to the severity of dry eye based on clinical assessment. This study included 32 eyes with severe dry eye (34.8%) and 60 eyes without severe dry eye ('non-severe' dry eye) (65.2%). The mean age was 57.4 ± 13.4 years (age range: 24–87 years). Most patients were women (78.3%) and most spent 4–6 h per day using a computer (66.3%). Most patients had used artificial tears prior to this study (66.3%). Overall, there were no differences in age, gender, computer-use time per day or eye drops used between the non-severe dry eye and severe dry eye groups. The mean DEQ-5 score was 7.2 ± 1.3 overall, with scores of 6.9 ± 1.0 in the non-severe dry eye group and 7.7 ± 1.7 in the severe dry eye group ($p = 0.005$). The mean TBUT was 6.0 ± 1.5 s, with times of 6.9 ± 1.0 s in the non-severe dry eye group and 4.4 ± 0.9 s in the severe dry eye group ($p < 0.001$). Corneal fluorescein staining was grade 0 in 19 eyes (20.6%), grade 1 in 72 eyes (78.3%), and grade 2 in 1 eye (1.1%). In the non-severe dry eye group, corneal fluorescein was grade 0 in 16 eyes (26.7%) and grade 1 in 44 eyes (73.3%). In the severe dry eye group, corneal fluorescein grading was grade 0 in 3 eyes (9.4%), grade 1 in 28 eyes (87.5%), and grade 2 in 1 eye (3.1%). There were no significant differences in corneal fluorescein grades between the two groups ($p = 0.054$).

The corneal epithelial thicknesses are listed in Table 2, in which the data are divided into three subgroups depending on the zone of measurement. The average thickness of the corneal epithelium was $45.9 \mu\text{m} \pm 3.5 \mu\text{m}$, $47.5 \mu\text{m} \pm 2.9 \mu\text{m}$ and $49.0 \mu\text{m} \pm 3.0 \mu\text{m}$ in the zones of 5 mm, 7 mm and 9 mm, respectively. There were no statistical differences between the non-severe dry eye and severe dry eye groups. The corneal epithelial thickness variances were $4.1 \mu\text{m}^2 \pm 3.4 \mu\text{m}^2$, $4.2 \mu\text{m}^2 \pm 2.2 \mu\text{m}^2$ and $4.4 \mu\text{m}^2 \pm 2.3 \mu\text{m}^2$ in the zones of 5 mm, 7 mm and 9 mm, respectively. There were no statistical differences between the two groups in the 5-mm and 7-mm zones, but the variance of epithelial thickness in the 9-mm zone was significantly higher in the severe dry eye group than in the

TABLE 2: Corneal epithelial thickness values in patients with severe and non-severe dry eye.

Corneal epithelial thickness	Total (N = 92)		Non-severe (n = 60)		Severe (n = 32)		p
	Mean	s.d.	Mean	s.d.	Mean	s.d.	
Average epithelial thicknesses (μm)							
5-mm zone	45.9	3.5	46.0	3.6	45.6	3.3	0.59
7-mm zone	47.5	2.9	47.4	3.0	47.74	2.77	0.62
9-mm zone	49.0	3.0	49.2	3.1	48.52	2.64	0.25
Epithelial thickness variances (μm^2)							
5-mm zone	4.1	3.4	4.0	3.3	4.3	3.7	0.66
7-mm zone	4.2	2.2	3.9	1.7	4.6	2.8	0.19
9-mm zone	4.4	2.3	3.9	2.0	5.2	2.7	0.01

s.d., standard deviation.

TABLE 3: Correlation coefficients for corneal epithelial thickness and clinical dry eye parameters.

Variable	DEQ-5 score		TBUT		Cornea fluorescein staining	
	r	p	r	p	r	p
Average epithelial thicknesses						
5-mm zone	0.01	0.95	0.06	0.55	0.08	0.45
7-mm zone	0.09	0.36	0.01	0.92	0.09	0.38
9-mm zone	0.04	0.74	0.06	0.59	-0.09	0.41
Epithelial thickness variances						
5-mm zone	0.18	0.09	0.03	0.75	0.10	0.36
7-mm zone	-0.04	0.69	-0.29	0.006	0.15	0.15
9-mm zone	0.29	0.005	-0.31	0.003	0.03	0.79

DEQ-5, Dry Eye Questionnaire-5; TBUT, tear break-up time.

group without severe dry eye ($5.2 \mu\text{m}^2 \pm 2.7 \mu\text{m}^2$ vs $3.9 \mu\text{m}^2 \pm 1.9 \mu\text{m}^2$, $p = 0.01$).

The correlations between corneal epithelial thickness and dry eye clinical parameters (Pearson's correlation coefficients) are shown in Table 3. There were no significant correlations between average epithelial thickness and clinical parameters of dry eye in any zone of measurement. In contrast, a significant positive correlation was found between the epithelial thickness variance in the 9-mm zone and the DEQ-5 score ($r = 0.29$,

$p = 0.005$). There were also significant negative correlations between the variances of the 7-mm and 9-mm zones and TBUT ($r = -0.29, p = 0.006$ and $r = -0.31, p = 0.003$, respectively).

Discussion

In dry eye disease, a loss of both the quantity and quality of the tear film leads to damage of the ocular surface, resulting in dry eye symptoms. Diagnosis of dry eye using the TFOS DEWS II involves taking a history of dry eye symptoms, as a symptom score, and using clinical examinations of tear film (TBUT) and ocular-surface abnormalities (i.e. fluorescein staining). Newer, less invasive, and easily measurable testing methods such as OCT have been developed to help assess dry eye severity and corneal epithelial thickness measurement with OCT has a high reproducibility in both the normal and diseased cornea, so can be used for assessment of dry eye disease.^{21,22,23}

The aim of this study was to determine the characteristics of corneal epithelial thickness maps from spectral-domain OCT in patients with severe dry eye and to correlate epithelial thickness with the clinical severity of dry eye.

Several studies have been performed to measure corneal epithelial thickness using OCT, to understand the epithelial changes in dry eye disease and find correlations between epithelial thickness and dry eye symptoms. Cui et al.¹² found that the thickness of the corneal epithelium in the superior region was thinner in dry eye than in normal eyes. In more-severe cases, the superior epithelium was much thinner, with a wider range of standard deviation in the map. The average thickness of the superior epithelium also correlated positively with the Schirmer 1 test. Francoz et al.¹¹ reported thinner limbal epithelium and thicker conjunctival epithelium in patients with dry eye. They also found a correlation between dry eye symptoms (Ocular Surface Disease Index [OSDI], TBUT) and epithelial thickness.

While evaluating the epithelium of patients with dry eye, some authors reported a decrease in thickness, whereas others found no change or even an increase, compared with the control group. Comparison between studies is complicated by the different durations and severity of the disease, the characteristics of the patients, and the different techniques used to measure epithelial thickness.^{11,12,24} The other reason for the contradictory findings could be that the damage to the ocular surface in dry eye does not affect the entire ocular surface homogeneously. Some areas of the epithelium may have tear film instability leading to tear breakage and epithelial erosion that decreased thickness measurement. Epithelial hyperplasia because of epithelial regeneration or an inflammatory process may lead to an increase in epithelial thickness. Thus, mean epithelial thickness may not directly reflect epithelial damage because of dry eye disease. Corneal epithelial surface-irregularity studies may be more appropriate in this case.

Using ultrahigh-resolution OCT to assess corneal epithelium thickness in dry eye disease, Abou Shousha et al.¹⁷ reported

that the eyes of patients with dry eye disease had a highly irregular corneal epithelial surface, compared with the corneas of control subjects. In that study, the variance of the epithelial thickness profile could be used to differentiate the severity of dry eye disease by determining the epithelium irregularity factor or EIF (i.e., the epithelial thickness variance measured in the central 3-mm zone); an EIF cut-off point of ≥ 3.949 could diagnose severe dry eye with a sensitivity of 81.8% and specificity of 77.7%. Furthermore, there was a decrease in epithelial thickness variance after dry eye treatment, suggesting that a greater epithelial thickness variance may reflect a damaging effect of dry eye disease on the ocular surface.

In this study, the average thickness of the cornea did not differ significantly between the group with non-severe dry eye and the group with severe dry eye, in any measurement range. In addition, the variances of the epithelial thickness in the 5-mm and 7-mm zones showed no statistical difference between the two groups, but the variance of the epithelial thickness in the 9-mm zone was significantly higher in the severe dry eye group than in the other group. Our results support the previous findings that the ≥ 3.949 cut-off for epithelial thickness variance can be used to diagnose severe dry eye, but the difference is that the previous study measured epithelial thickness variance in the central 3-mm zone, whereas in our study, the significant zone was 9 mm. These data may indicate that in severe dry eye, the peripheral ocular surface is more damaged than the central, resulting in greater irregularity of epithelial thickness in the periphery than in non-severe dry eye. However, there were no significant differences in central and paracentral ocular-surface damage between the two groups. This may be explained by the fact that the peripheral corneal epithelium is more susceptible to dry eye damage, such as the area of eyelid exposure, inflammatory cytokines and toxicity of preservatives, which prolong exposure through the inferior tear meniscus.¹¹

Of note, there were no correlations between the average thickness of the corneal epithelium and the parameters used to assess the severity of dry eye in clinical evaluation, such as DEQ-5, TBUT and fluorescein staining, in any zone of measurement. However, the correlations between the variance of corneal epithelial thickness and these parameters were interesting, even if they were low correlations. The significant positive correlation was found between the 9-mm-zone epithelial thickness variance and the DEQ-5 score. There were also significant negative correlations between the 7-mm and 9-mm epithelial thickness variances and TBUT. These data suggest that peripheral epithelial thickness variance correlates with dry eye symptoms and signs. This can be explained by the fact that the irregularity of the corneal epithelium can cause instability of the tear film, resulting in rapid evaporation of tears and a short TBUT.

A strength of this study was the use of a commercially available spectral-domain OCT device to measure corneal epithelial thickness. This diagnostic method can be widely and repeatedly performed, so it can be used to monitor the changes of the ocular surface epithelium and to follow up on dry eye treatment. Our data measurement in this study was

also performed in multiple zones, so it can demonstrate the relationship between epithelial thickness and the corneal zone. Conversely, limitations of this study were the small number of enrolled subjects and limited statistical significance. Changes in epithelial thickness are not specific to dry eye disease and may occur in other ocular-surface diseases. Discrepancies in dry eye symptoms and signs also make it difficult to diagnose patients with severe dry eye but only mild clinical manifestations.^{25,26,27}

It is suggested that future studies evaluate diagnostic performance and determine the cut-off value for corneal epithelial thickness deviation in different measurement ranges for the diagnosis of severe dry eye. Another suggestion is to monitor the change(s) in corneal epithelial thickness deviation after dry eye treatment.

Conclusion

This study describes the characteristics of the corneal epithelial thickness map with spectral-domain OCT in patients with dry eye of varying severity. The average thickness of the corneal epithelium did not differ between the group of patients with non-severe dry eye and the group with severe dry eye. In contrast, the variance of the peripheral corneal epithelial thickness showed a difference between the two groups, suggesting that the peripheral ocular surface is more damaged in severe dry eye. The variance in peripheral epithelial thickness also correlated with the symptoms and signs of dry eye and, so, may be used to assess the severity of dry eye. In conclusion, examination of the corneal epithelial thickness with OCT can be useful for assessing clinical severity of dry eye disease and monitoring treatment success.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

P.P. and T.S. designed and performed the experiments, derived the models and analysed the data. P.S. assisted with statistic measurements and helped to supervise the project. P.P. and T.S. wrote the manuscript in consultation with P.S.

Ethical considerations

An application for full ethical approval was made to the Chulabhorn Research Institute Ethics Committee and ethics consent was received on 25 June 2021. The ethics approval number is 040/2564. Written informed consent was obtained from all individual participants involved in the study. All

procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Data availability

Data supporting the findings of this study are available from the corresponding author, T.S., on request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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