The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 2370-2378

Correlations of Corneal Epithelial Thickness with Dry Eye Symptoms among Egyptian Sample Patients

Sara Abd El meged Nage*, Ahmed Esmail
Ophthalmology Department, Faculty of Medicine, Menoufia University, Menoufia, Egypt
***Corresponding author:** Sara Abd El meged Nage, **Mobile:** (+20) 01009476856,
Email: Sara.attia.12@med.menofia.edu.eg, **ORCID:** 0000-0003-3421-5037

ABSTRACT

Background: The multifactorial condition known as dry eye disease (DED) has the ability to harm the conjunctival and corneal epithelium through its effects on tears and the ocular surface. Instability of the tear film, increased tear osmolarity, abnormalities of the lacrimal gland and meibomian glands, and a multitude of inflammatory processes in the epithelial surface cells are all causes of dry eye disease.

Objective: The aim of the current study was to assess correlations between corneal epithelial thickness and dry eye symptoms among Egyptian sample patients.

Patients and methods: A cross-sectional study was conducted on 80 dry eye patients and 30 healthy people at the Ophthalmology Department, Menoufia University Hospital, from April 2021 to October 2022.

Results: The dry eye group's superior corneal epithelial thickness (50.85 ± 8.35) was considerably lower than that of the normal eye group (52.26 ± 2.98), with a P-value of 0.001. The mean of inferior and central corneal epithelial thicknesses, however, did not differ significantly between dry eyes and normal eyes (P>0.05), measuring 37.08 (SD 12.88) mm, 57.90 (SD 13.85) mm, and 52.67 (SD 2.59) mm, 55.32 (SD 6.84) mm, respectively.

Conclusion: Corneal epithelium of dry eyes has a thinner upper part than that of normal eyes. In individuals with more severe dry eye disease, the superior and minimum epithelium was significantly thinner and had a broader range of map standard deviation.

Keywords: Corneal epithelial thickness, Dry eye, Egyptian patients, Symptoms, Superior region.

INTRODUCTION

The multifactorial ocular disease known as "dry eye disease" (DED) affects people all over the world and is regularly seen in routine ophthalmology practise. Ophthalmologists have discovered that DED is quite prevalent and has a considerable influence on patients' quality of life, making it a prominent topic of research [1]. However, the multifaceted etiology of the disease makes it difficult to accurately and statistically diagnose DED and track therapy response in DED patients, which poses a significant barrier to raising the standard of care for these patients [2].

Depending on which study is cited, how the illness is diagnosed, and which group is questioned, according to research done during the last 20 years, the prevalence of DED ranges from 5% to more than 30% at different ages [3].

According to epidemiological studies on DED, its frequency varies from 5 to 50% depending on the diagnosis of symptoms with or without signs, and it reaches 75% when only signs are taken into account [3]. The damaged corneal epithelium may be what caused the clinical signs of DED in the eyes, such as pain in the eyes, photosensitivity, and shifting vision [4].

Ocular surface staining, tear breakup time (TBUT), the Schirmer's test, and symptom questionnaires are among the diagnostic methods currently used in routine clinical practice. Other methods, such as tear osmolarity measurement, tear film interferometry and examination of tear biomarkers are rapidly being included into patient treatment [5].

Recent studies have used epithelial maps produced by optical coherence tomography to evaluate epithelial thickness, an anatomical parameter, in patients with dry eye [6]. A variety of studies were carried out to map the thickness of corneal epithelium in order to determine epithelium injury's morphological signs [7]. Traditional methods for measuring epithelial thickness include ultrasonography [8]. However, these techniques demand that the instruments make direct or indirect touch with the patient's ocular surface [9].

Furthermore, because the majority of them only pay attention to the central epithelial thickness, none of them can accurately assess the epithelial thickness of the entire cornea (CET) [10].

However, both studies do, concur that the corneas of DED patients have more thickness variation overall than controls do. Regarding the impact of DED on epithelial thickness, two earlier investigations produced contradictory findings, either indicating a thinning in the superior cornea or a thickening in the middle cornea [10]. **Francoz *et al.*** [9] used in vivo spectral-domain Optical coherence tomography (OCT) to measure the thickness of the corneal, limbal, and bulbar conjunctival epithelial layers in healthy eyes.

Li *et al.* [11] employed Fourier-domain OCT to measure the corneal epithelial thickness in keratoconus eyes. Keratoconus is characterized by apical epithelial thinning. The Fourier-domain OCT was shown to be useful in determining the epithelial thickness in post-LASIK eyes by **Ma *et al.*** [12]. Few studies, meanwhile, have discussed about the features of people with dry eyes' corneal epithelial thickness [9].

The aim of the current study was to assess correlations between corneal epithelial thickness and dry eye symptoms among Egyptian sample patients.

Received: 27/09/2022
Accepted: 30/11/2022

PATIENTS AND METHODS

A cross-sectional study was conducted on 80 dry eye patients and 30 healthy people to assess correlations of corneal epithelial thickness with dry eye symptoms at the Ophthalmology Department, Menoufia University Hospital, from April 2021 to October 2022.

Inclusion criteria: Patients with DED, healthy adults, both sexes, and participants older than 18.

Exclusion criteria: Sjogren syndrome, Stevens-Johnson syndrome, glaucoma, allergic illnesses, ocular trauma, ophthalmic surgery, or any other ocular or systemic ailment that could affect the corneal epithelium participants. Individuals who had recently used eye drops or contact lenses during the three months previous to the study.

The following was DED diagnosis: (1) the presence of dry eye symptoms (OSDI score Q 20) and (2) the existence of qualitative or quantitative disruption of the tear film (TBUT G 5 sec, S1t G 5 mm/5 min, or fluorescein staining Q 3 points) **[13].**

The patients' medical records were used to gather demographic data and medical history. The Ocular Surface Disease Index (OSDI) questionnaire was used to quantify each subject's ocular surface complaints (range: 0–100). After that, the participants underwent ocular surface examinations in the following order: Schirmer test without anesthesia, TBUT measurement, corneal and conjunctival fluorescein staining, tear film lipid layer analysis, and tear film lipid layer analysis. Fluorescein was injected into the inferior cul-de-sac, and the average of three successive break-up times was calculated to estimate the TBUT.

The Oxford scale and fluorescein injection were used to assess corneal and conjunctival stains under a yellow filter. Interferometry (DR-1, Kowa, Tokyo, Japan) was used to analyze the tear film's lipid layer, and scores ranged from 1 to 5 (Grade 5 being the most severe). The Schirmer, I test was carried out on the patient for five minutes while keeping their eyes closed. The SD-OCT system from Optovue Corporation, Fremont, California, USA, was used. After administering fluorescein and using an Oxford scale and yellow filter, corneal and conjunctival stains were assessed. The axial scan rate for this SD-OCT is 26,000 scans per second. Its optical resolution in the axial and transverse directions was 5 μm and 15 μm, respectively.

To assess the thickness of the epithelium and the regional architecture of the cornea and conjunctiva, an addon lens (CAM-L mode: 6.0–2.0 mm) was employed. Since SD-OCT testing is a noncontact procedure, it was done before ophthalmological exams to prevent possible epithelial changes.

Ethical Consideration:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Menoufia University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medica37/4l Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 21 for windows. Qualitative data were defined as numbers and percentages.

Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test and ANOVA (F) test were used for comparison between groups. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

Figure 1 shows a CONSORT flow chart of the study population. Of the 123 patients who attended to Ophthalmology Department, Menoufia University Hospital, Shebin El-Kom. A total 13 patients were excluded from the study (5 patients declined consent and 8 patients did not meet the inclusion criteria, 110 patients were willing to participate in the study and consented for participation. Thus, 80 dry eye patients and 30 healthy.

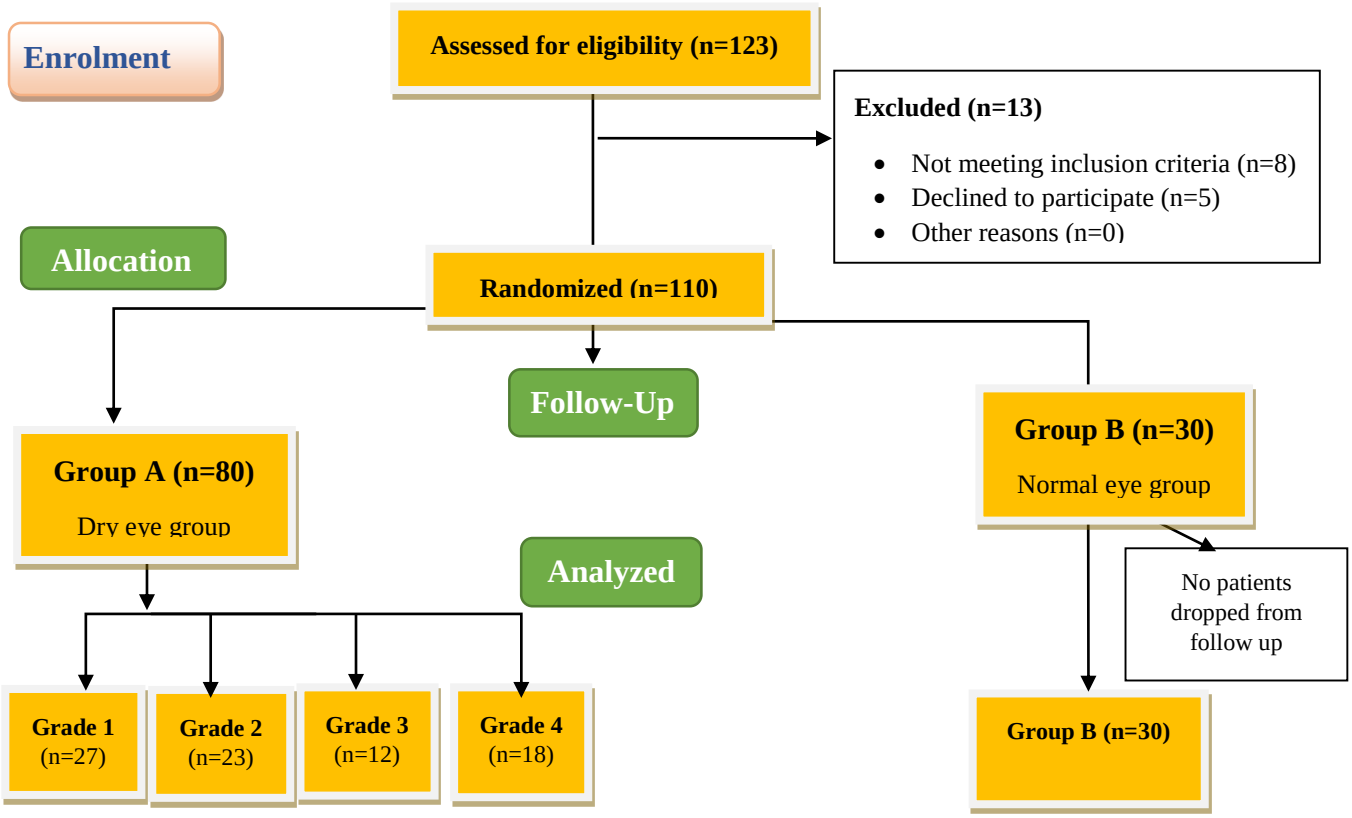

Figure (1): Flowchart of the studied patients.

Table 1 summarizes and compares the sociodemographic data of the studied group.

Table (1): Socio-demographic data among dry eye and normal eye studied groups (N=110).

Variables	Dry eye (n=80)		Normal eye (n=30)		Total (n=110)		t-test	P-value
Age								
Mean ± SD	27.16 ± 5.53		30.57 ± 5.99		28.87 ± 5.76		2.711	0.059
Range	20 - 39		21 - 37		20 - 39			
Median (IQR)	27 (7)		34 (9)		29.12 (8)			
Sex	**No.**	**%**	**No.**	**%**	**No.**	**%**		
Male	53	66.25	15	50	68	61.81	X^2 2.441	0.118
Female	27	33.75	15	50	42	38.18		

t: independent t-test. X^2: Chi-square test. *: Significant.

Results in **Table 2** indicated that, inferior corneal epithelial thickness was significantly thinner among dry eye group than normal eye group (P<0.001). While, the mean of superior and central corneal epithelial thickness was 37.08 µm, 57.90 µm in dry eyes and 52.67 µm, 55.32 µm in normal eyes, respectively, with no significant differences (P>0.05).

Table (2): Corneal epithelial thickness among dry eye and normal eye studied groups (N=110).

Variables	Dry eye (n=80)	Normal eye (n=30)	t-test	P-value	95% CI	
					Lower	Upper
Inferior corneal epithelial thickness (µm), Mean ± SD	50.85 ± 8.35	52.26 ± 2.98	10.289	**<0.001***	-18.60	-12.58
Superior corneal epithelial thickness (µm), Mean ± SD	37.08 ± 9.10	52.67 ± 2.59	1.297	0.198	-1.36	6.52
Central corneal epithelial thickness (µm), Mean ± SD	57.90 ± 13.85	55.32 ± 6.84	1.302	0.196	-3.54	0.73

t: independent t-test. **X^2:** Chi-square test. ***:** Significant. **CI:** Confidence interval for Mean.

Regarding, visual acuity (6/6) was the most common among dry eye group (40%) while, visual acuity (6/9) was the most common among normal eye group (40%), with a significant difference (P=0.002), (**Table 3**). Also, Grade 1 of DED was the most common among dry eye group (33.75%) followed by grade 2 (28.75%) followed by grade 4 (22.5%) then grade 3 (15%) (**Figure 1**).

Table (3): Visual acuity and grades of DED among dry eye and normal eye studied groups (N=110).

Variables	Dry eye (n=80)		Normal eye (n=30)		Total (n=110)		X^2	P-value
	No.	%	No.	%	No.	%		
VA								
6/9	7	8.75	12	40	19	17.27	16.8	**0.002***
6/12	23	28.75	5	16.66	28	25.45		
6/36	7	8.75	0	0.0	7	6.36		
6/18	11	13.75	4	13.33	15	13.63		
6/6	32	40	9	30	41	37.27		

VA: Visual acuity. **X^2:** Chi-square test. ***:** Significant.

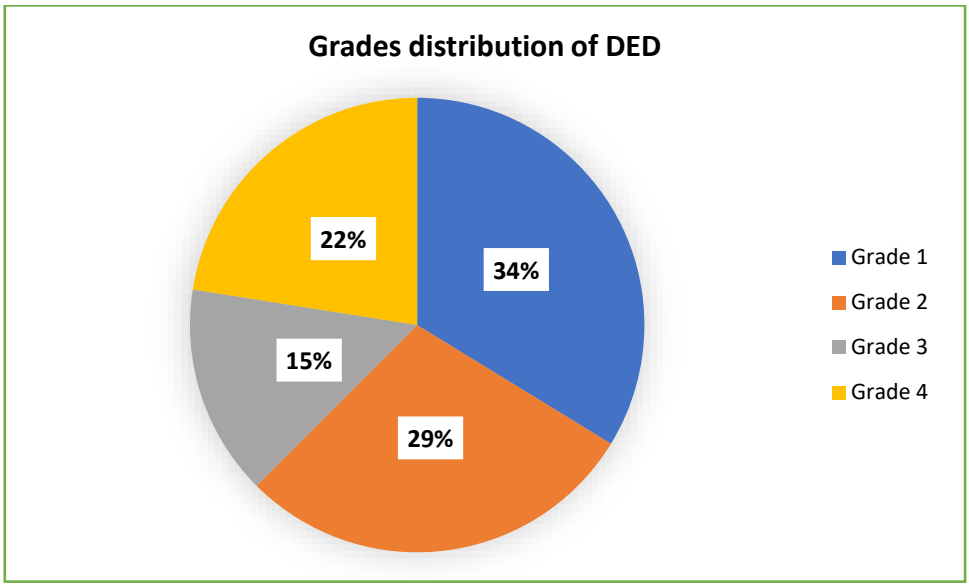

Figure (2): Grades distribution of DED among dry eye and normal eye studied groups (N=110).

In our study, dry eye patients were divided into four subgroups according to the severity of DED: In grade 1 (24 men and 3 women; mean age, 25.78 years; range, 20 to 39 years, In grade 2 (17 men and 6 women; mean age, 29.30 years; range, 20 to 39 years), In grade 3 (4 men and 8 women; mean age, 26.42 years; range, 24 to 30 years) and In grade 4 (8 men and 10 women; mean age, 27.00 years; range, 24 to 30 years), with no statistical difference in age (F = 1.851, P = 0.145) and statistical difference in sex (X^2= 16.436, P<0.001) among these subgroups (Table 4).

Table (4): Relation between socio demographic data and grades of DED (N=80).

Variables	Grade 1 (n=27)		Grade 2 (n=23)		Grade 3 (n=12)		Grade 4 (n=18)		Total (n=80)		F	P-value
Age/year												
Mean ± SD	25.78±5.45		29.3 ± 6.96		26.42 ± 5.04		27 ± 2.79		27.13 ± 5.06		1.851	0.145
Range	20.00-39.00		20 - 39		20 - 39		24 - 30		20 - 39			
Sex	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**X^2**	**<0.001***
Male	24	88.88	17	73.91	4	33.33	8	44.44	53	66.25	16.436	
Female	3	11.11	6	26.08	8	66.67	10	55.55	27	33.75		

DED: Dry eye disease. **F:** ANOVA F test. **X^2:** Chi-square test. ***:** Significant.

Also, in dry eye patients, a significant relation found between corneal epithelial thickness and grades of DED. Mean of superior, central and inferior corneal epithelial thickness was 40.44, 71.56 and 59.30 among grade 1. In grade 2, mean of superior, central, and inferior corneal epithelial thickness was 40, 62.78 and 53.48**.** In grade 3, mean of superior, central, and inferior corneal epithelial thickness was 33.33, 44.33 and 42.75**.** In grade 4, mean of superior, central, and inferior corneal epithelial thickness was 30.78, 40.22 and 40.22, with significant association (**Table 5**).

Table (5): Relation between corneal epithelial thickness and grades of DED (N=80).

Variables	Grade 1 (n=27)	Grade 2 (n=23)	Grade 3 (n=12)	Grade 4 (n=18)	F	P-value	95% CI	
							Lower	Upper
Superior corneal epithelial thickness (µm) Mean ± SD	40.44 ± 9.70	40.00 ± 7.92	33.33 ± 4.68	30.78 ± 0.81	2.99	**0.036***	34.21	39.94
Central corneal epithelial thickness (µm) Mean ± SD	71.56 ± 5.42	62.78 ± 2.70	44.33 ± 8.56	40.22 ± 0.43	195.98	**<0.001***	54.82	60.98
Inferior corneal epithelial thickness(µm) Mean ± SD	59.30 ± 2.88	53.48 ± 2.33	42.75 ± 4.88	40.22 ± 0.43	206.87	**<0.001***	48.99	52.71

DED: Dry eye disease. **F:** ANOVA F test***:** Significant. **CI:** Confidence interval for Mean.

Additionally, each visual acuity (6/12) and (6/6) were 37.03% among grade 1. Visual acuity (6/6) was the most common among grade 2 (47.82%). Visual acuity (6/18) was the most common among grade 3 (58.00%). Visual acuity (6/6) was the most common among grade 4 (44.44%), with a significant relation (P<0.001) (**Table 6**).

Table (6): Relation between visual acuity and grades of DED (N=80).

Variables	Grade 1 (n=27)		Grade 2 (n=23)		Grade 3 (12)		Grade 4 (n=18)		Total (n=80)		X^2	P-value
	No.	%	No.	%	No.	%	No.	%	No.	%		
VA												
6/9	1	3.7	5	21.73	1	8.3	0	0.0	7	8.75		
6/12	10	37.03	6	26.08	1	8.3	6	33.33	23	28.75	44.44	**<0.001***
6/36	6	22.22	1	4.34	0	0.0	0	0.0	7	8.7		
6/18	0	0.0	0	0.0	7	58.33	4	22.22	11	13.75		
6/6	10	37.03	11	47.82	3	25	8	44.44	32	40		

VA: Visual acuity. **DED:** Dry eye disease. **X^2:** Chi-square test. ***:** Significant.

Regarding correlation coefficient, there were significant positive correlations between superior with central and inferior corneal epithelial thickness (P<0.001) and negative correlation with grades of DED (P<0.001). Also, central corneal epithelial thickness was significant positive correlation with superior and inferior corneal epithelial thickness (P<0.001) and negative correlation with grads of DED (P<0.001). Also, grads of DED were significant negative correlation with superior, central, and inferior corneal epithelial thickness (P<0.001) (**Table 7**).

Table (7): Correlation between superior, Central, inferior corneal epithelial thickness and grads of DED.

Variables	Corneal epithelial thickness (um)					
	Superior		Central		Inferior	
	r	P value	r	P value	r	P value
Superior corneal epithelial thickness (um)	1.000	---	0.575**	**<0.001***	0.485**	**<0.001***
Central corneal epithelial thickness (um)	0.575**	**<0.001***	1.000	---	0.983**	**<0.001***
Inferior corneal epithelial thickness(um)	0.485**	**<0.001***	0.983**	**<0.001***	1.000	---
Grads of DED	-0.577**	**<0.001***	-0.905**	**<0.001***	-0.903**	**<0.001***

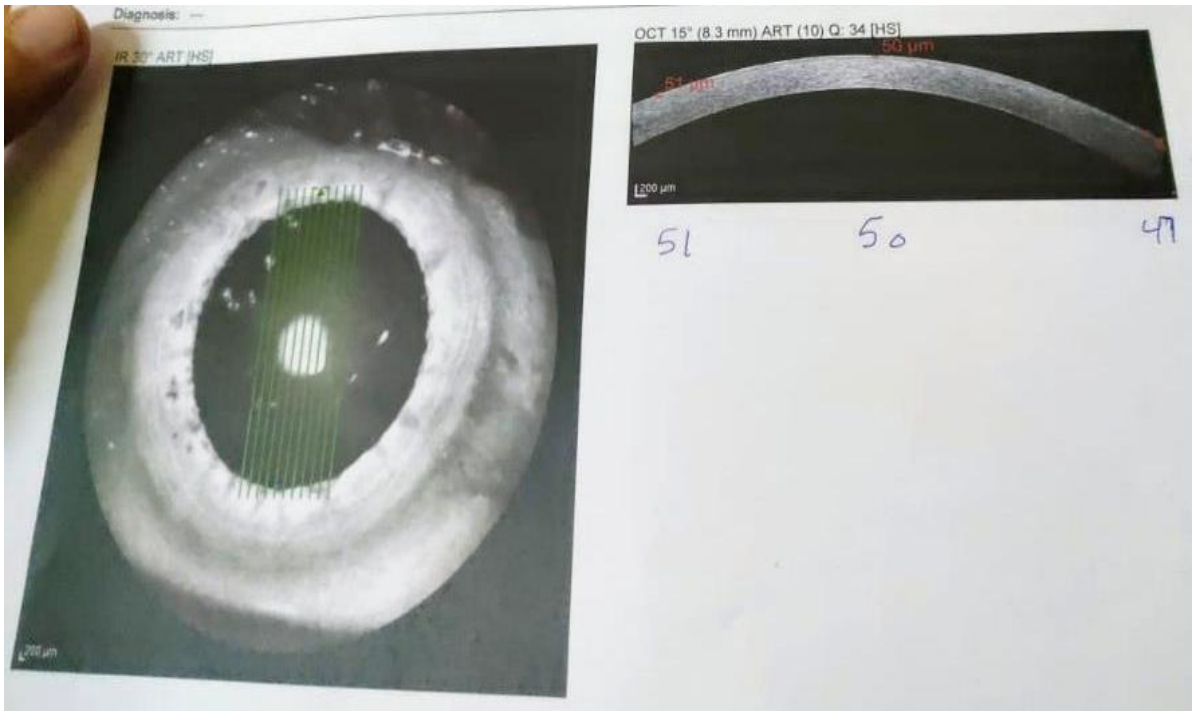

Figure (3): A control eye patient, superior epithelial thickness of 51 micrometres, middle epithelial thickness of 50 micrometres, and inferior epithelial thickness of 47 micrometres.

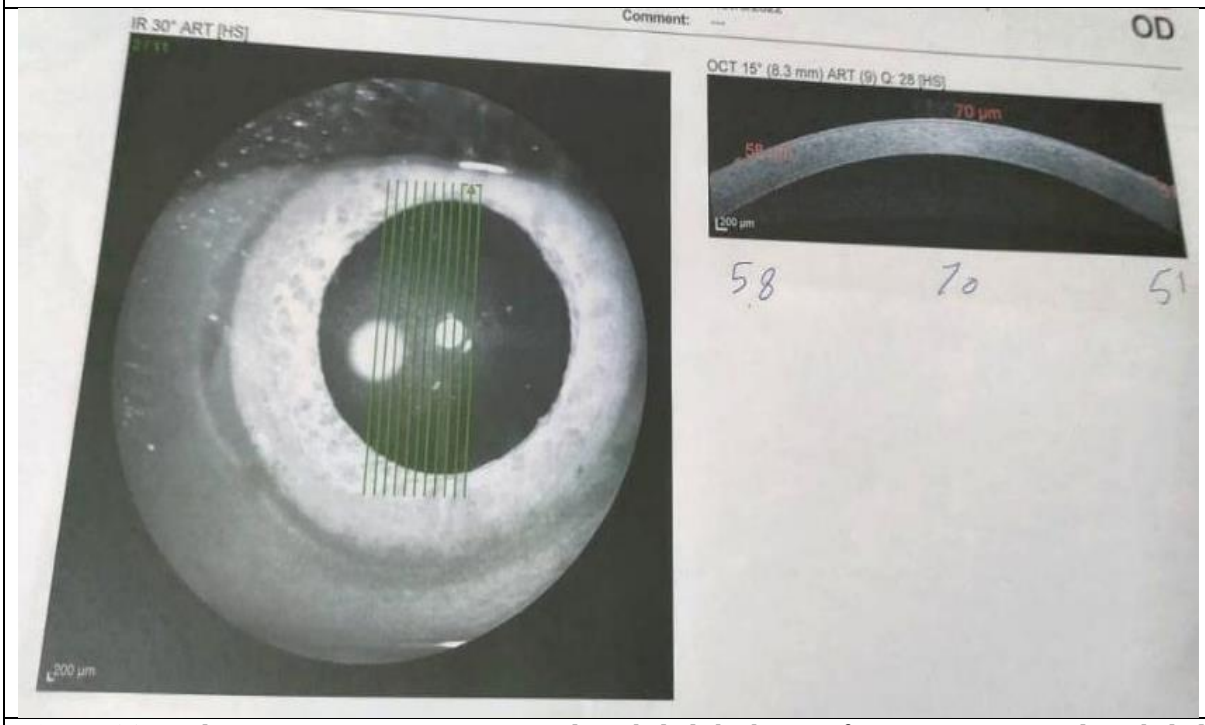

Figure (4): A dry eye patient, superior corneal epithelial thickness of 58 microns, central epithelial thickness of 70, and inferior epithelial thickness of 51.

DISCUSSION

DED, a multifactorial condition, has the ability to impair the conjunctival and corneal epithelium through influencing tears and the ocular surface. Some of the reasons of DED include the instability of the tear film, increased tear osmolarity, abnormalities in the meibomian and lacrimal glands, and a string of inflammatory processes in the epithelial surface cells. Clinically noticeable ocular symptoms of DED, such as eye pain, photosensitivity, and fluctuating vision, may have been brought on by the damaged corneal epithelium [14].

Several studies were carried out to map CET in order to determine the morphological evidence of epithelial damage. Traditional methods for measuring epithelial thickness include brush cytology, impression cytology, ultrasonography, and in vivo confocal microscopy. However, the techniques used in these procedures must come into direct or indirect touch with the patient's ocular surface. Furthermore, because the majority of them only pay attention to CET, none of them can accurately assess the epithelial thickness of the entire cornea [15]. So, evaluation of the relationships between CET and dry eye symptoms among Egyptian sample patients was the main goal of this study.

According to the current study, the normal eye group included 15 (50%) patients who were males and 15 (50%) patients who were females, with no discernible difference in age or sex between the two groups. The dry eye group included 53 (66.25%) patients who were males and 27 (33.75%) patients who were females. On the other hand, studies on the relationship between dry eye and age consistently demonstrates that older people are more likely to experience dry eye [16-18].

This discrepancy between our findings and those of other research could be attributed to the limited sample size, the demographic differences between our Egyptian patients and those in other studies, as well as the retrospective nature of the earlier investigations. Future long-term studies will be necessary to confirm this debate.

The present study showed that, inferior corneal epithelial thickness was substantially lower in the dry eye group than in the normal eye group ($P<0.001$). However, the mean of superior and central corneal epithelial thicknesses did not differ significantly between dry eyes and normal eyes.

Similar to this, **Cui *et al.*** [10] found that DED patients' superior corneal epithelium was thinner than that of normal participants', with a difference of less than 2 m, even less than the standard deviation of epithelial thickness assessments. OCT has a rough resolution of 5 μm, and corneal epithelium is thinner than normal (typical thickness is 50 μm around), thus it makes sense that the difference was as little as 2 μm, as **Li *et al.*** [11] discovered in their study.

Some authors discovered a decrease in the CET of DED patients, while others showed no change or even a rise in comparison to the control group [9,10,19]. The diverse illness onset times and severity levels, the wide age range of DED patients, and the various CET measurement methods make it challenging to compare research. After 7 days, **Fabiani *et al.*** [7] constructed a mouse model of dry eye and discovered that the average CET in dry eye mice thickened substantially more than in control mice. These findings showed that the average CET in the early stages of DED was significantly impacted by inflammatory processes and epithelial growth.

It is possible to use increased epithelial thickness as a clinically reliable indicator of dry eye, according to researches by **Chen *et al.*** [20] and **Kanellopoulos and Asimellis** [6].

On the other hand, as a result of the death near the limbus of stem cells, **Erdélyi *et al.*** [21] and **Villani *et al.*** [22] also proved that DED patients' CET tends to be thinner. According to the study of **Liang *et al.*** [23], DED patients' CET did not differ significantly from that of the control groupm, which was in line with their earlier findings [15], and the findings of **Tuominen *et al.*** [24].

To understand why the superior epithelium was thinner in dry eyes, it is important to first look at the spatial variation of epithelial thickness in normal eyes. It has been demonstrated that in healthy eyes, the superior and inferior areas of the corneal epithelium are significantly thinner [11, 25]. Although not systematically researched, it was proposed that the friction caused by mechanical dynamics in blinking was what caused the inhomogeneous thickness profile [26]. More of the ocular surface is rubbed by the upper lid's wider-ranging movement and vertical traversal. The superior epithelium thins as a result of the mechanical damage caused by friction to epithelial cells.

Also, the mechanical hypothesis is supported by **Cui *et al.*** [10] discovery that there is a relationship between a thinner superior corneal epithelium and a lower S1t. Patients with dry eyes often do not produce enough tears to serve as lubrication; they claim that the increased mechanical friction weakened the superior epithelium and hastened epithelial degradation. Blinking typically happens more frequently in dry eyes to make up for the lack of tears [27]. They hypothesized that because blinking occurs more frequently, the mechanical friction would be accentuated, leading to even thinner superior epithelium. Numerous studies have shown that the inflammatory process that is triggered by DED's hyperosmolar tears and unstable tear films could be the cause of the epithelial thickness change [28,29].

In the current study, Grade 1 of DED was found to be the most prevalent among dry eye patients (33.75%), followed by Grade 2 (28.75%), Grade 4 (22.5%), and Grade 3 (15.00%).

Despite the fact that normal visual acuity has been demonstrated using accepted testing procedures, dry eye has a detrimental impact on a number of elements of visual function [30]. In a trial by **Szczotka-Flynn *et al.* [31],** their findings support the finding that decreased visual acuity is associated with worse scores on the OSDI vision-related complaints subscale in dry eye patients, even among those with reasonably excellent visual acuity (20/50 or better). But, none of the dry eye signs we looked at in the study had a detrimental impact on visual acuity. Tiny changes in visual acuity could be detected based on differences in tear film debris and tear break-up time; however, the mean changes were minimal (2 letters), and not in the way one might expect [32].

It's important to mention that multiple studies have shown that dry eye disturbances in the tear film increase higher-order aberrations compared to normal eyes, impairing optical quality and vision [32-35].

CONCLUSION

Dry eyes' superior CET map was thinner than that of normal eyes. Patients with more severe cases of DED had superiors that were considerably thinner and had a wider range of map standard deviation.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Nichols K, Nichols J, Mitchell G (2004):** The lack of association between signs and symptoms in patients with dry eye disease. Cornea, 23:762-70.
2. **Abou Shousha M, Wang J, Kontadakis G *et al.* (2020):** Corneal epithelial thickness profile in dry-eye disease. Eye, 34:915-22.
3. **Stapleton F, Alves M, Bunya V *et al.* (2017):** TFOS DEWS II epidemiology report. Ocul Surf., 15:334-65.
4. **Pflugfelder S (2011):** Tear dysfunction and the cornea: LXVIII Edward Jackson Memorial Lecture. Am J Ophthalmol., 152:900-9.
5. **Zeev M, Miller D, Latkany R (2014):** Diagnosis of dry eye disease and emerging technologies. Clin Ophthalmol., 8:581-90.
6. **Kanellopoulos A, Asimellis G (2014):** In vivo 3-dimensional corneal epithelial thickness mapping as an indicator of dry eye: preliminary clinical assessment. American Journal of Ophthalmology, 157(1):63-8.
7. **Fabiani C, Barabino S, Rashid S *et al.* (2009):** Corneal epithelial proliferation and thickness in a mouse model of dry eye. Experimental Eye Research, 89(2):166-71.
8. **Karon M, Klyce S (2003):** Effect of inhibition of inflammatory mediators on trauma-induced stromal edema. Invest Ophthalmol Vis Sci., 44:2507-11.
9. **Francoz M, Karamoko I, Baudouin C *et al.* (2011):** Ocular surface epithelial thickness evaluation with spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci., 52:9116-23
10. **Cui X, Hong J, Wang F *et al.* (2017):** Assessment of corneal epithelial thickness in dry eye patients. Optom Vis Sci., 91:1446-54.
11. **Li Y, Tan O, Brass R *et al.* (2012):** Corneal epithelial thickness mapping by Fourier-domain optical coherence tomography in normal and keratoconic eyes. Ophthalmology, 119:2425-33.
12. **Ma X, Wang L, Koch D (2013):** Repeatability of corneal epithelial thickness measurements using Fourier-domain optical coherence tomography in normal and post-LASIK eyes. Cornea, 32:1544-8.
13. **Ibrahim O, Dogru M, Kojima T *et al.* (2017):** OCT assessment of tear meniscus after punctal occlusion in dry eye disease. Optom Vis Sci., 89:770-6.
14. **Baudouin C, Aragona P, Messmer E *et al.* (2013):** Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. The Ocular Surface, 11(4):246-58.
15. **Lin P, Tsai S, Cheng C *et al.* (2003):** Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology, 110(6):1096-101.
16. **McCarty C, Bansal A, Livingston P *et al.* (1998):** The epidemiology of dry eye in Melbourne, Australia. Ophthalmology, 105(6):1114-9.
17. **Moss S, Klein R, Klein B (2000):** Prevalence of and risk factors for dry eye syndrome. Archives of Ophthalmology, 118(9):1264-8.
18. **Schaumberg D, Sullivan D, Buring J *et al.* (2003):** Prevalence of dry eye syndrome among US women. American Journal of Ophthalmology, 136(2):318-26.
19. **Reinstein D, Yap T, Archer T *et al.* (2015):** Comparison of corneal epithelial thickness measurement between Fourier-domain OCT and very high-frequency digital ultrasound. Journal of Refractive Surgery, 31(7):438-45.
20. **Chen W, Li Z, Hu J *et al.* (2011):** Corneal alternations induced by topical application of benzalkonium chloride in rabbit. PloS One, 6(10):e26103. doi: 10.1371/journal.pone.0026103.
21. **Erdélyi B, Kraak R, Zhivov A *et al.* (2007):** In vivo confocal laser scanning microscopy of the cornea in dry eye. Graefe's Archive for Clinical and Experimental Ophthalmology, 245(1):39-44.
22. **Villani E, Galimberti D, Viola F *et al.* (2007):** The cornea in Sjogren's syndrome: an in vivo confocal study. Investigative Ophthalmology & Visual Science, 48(5):2017-22.
23. **Liang Q, Liang H, Liu H *et al.* (2016):** Ocular surface epithelial thickness evaluation in dry eye patients: clinical correlations. Journal of Ophthalmology, 16:1628469. doi: 10.1155/2016/1628469
24. **Tuominen I, Konttinen Y, Vesaluoma M *et al.* (2003):** Corneal innervation and morphology in primary Sjogren's syndrome. Investigative Ophthalmology & Visual Science, 44(6):2545-9.
25. **Reinstein D, Archer T, Coleman D (2008):** Epithelial thickness in the normal cornea: three-dimensional display with Artemis very high-frequency digital ultrasound. Journal of Refractive Surgery, 24(6):571-81.

26. **Reinstein D, Silverman R, Trokel S *et al.* (1994):** Corneal pachymetric topography. Ophthalmology, 101(3):432-8.
27. **Evinger C, Bao J, Powers A *et al.* (2002):** Dry eye, blinking, and blepharospasm. Movement Disorders, 17(2):75-8.
28. **Lemp M, Foulks G (2007):** The definition and classification of dry eye disease. Ocul Surf., 5(2):75-92.
29. **Zhang J, Yan X, Li H (2013):** Analysis of the correlations of mucins, inflammatory markers, and clinical tests in dry eye. Cornea, 32(7):928-32.
30. **Uchino M, Schaumberg D (2013):** Dry eye disease: impact on quality of life and vision. Current Ophthalmology Reports, 1(2):51-7.
31. **Szczotka-Flynn L, Maguire M, Ying G *et al.* (2013):** Impact of dry eye on visual acuity and contrast sensitivity: dry eye assessment and management study. Optometry and Vision Science, 96(6):387-96.
32. **Montés-Micó R, Cáliz A, Alió J (2004):** Wavefront analysis of higher order aberrations in dry eye patients. Journal of Refractive Surgery, 20(3):243-7.
33. **Goto E, Yagi Y, Matsumoto Y *et al.* (2002):** Impaired functional visual acuity of dry eye patients. American Journal of Ophthalmology, 133(2):181-6.
34. **Kaido M, Matsumoto Y, Shigeno Y *et al.* (2011):** Corneal fluorescein staining correlates with visual function in dry eye patients. Investigative Ophthalmology & Visual Science, 52(13):9516-22.
35. **Zhang Y, Potvin R, Gong L (2013):** A study of the short-term effect of artificial tears on contrast sensitivity in patients with Sjögren's syndrome. Investigative Ophthalmology & Visual Science, 54(13):7977-82.