The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 1752-1759

Effect of Topical Combined Beta-Blockers and Carbonic Anhydrase Inhibitors on Corneal Epithelial Thickness by Anterior Segment Optical Coherence Tomography

Fatma Khaled Nasser Ali*, Hamdy Ahmed El-Gazzar,
Ahmed Abdel-shafy Tabl, Mohamed Abdel-Zaher Awwad, Taher Kamel Eleiwa
Department of Ophthalmology, Faculty of Medicine, Benha University, Egypt
***Corresponding author:** Fatma Khaled Nasser Ali, **Mobile:** (+20) 01067271686, **Email:** doctortotti123@gmail.com

ABSTRACT

Background: Prolonged usage of topical antiglaucoma medicines may result in ocular surface disease (OSD) that impairs both life quality and medication adaptation. **Objective:** The aim of the current study is to assess corneal epithelial thickness (CET) changes using anterior segment optical coherence tomography (AS-OCT) in patients using topical combination of beta-blockers and carbonic anhydrase inhibitors (CAIs).

Patients and Methods: A total of 100 eyes of 80 participants were assessed in a randomized controlled clinical trial. *Group A* included 50 eyes of 40 glaucoma patients treated with combined topical Beta-blockers and CAIs with at least 3-month duration, while *Group B* included 50 eyes of 40 healthy participants with completely normal ophthalmological examination. All candidates received AS-OCT imaging with subsequent automated CET and total corneal thickness (CT) mapping.

Results: *Group A* had a mean age of 49.84 (SD 4.83) years, while *Group B* had a mean age of 49.44 (SD 4.81) years (P=0.679). CET was considerably lower in all regions in *Group A* 45.94 (SD 3.96) µm compared to *Group B* 54.54 (SD 3.16) µm; (P-value<0.001). Regarding CT, 8 out of 25 regions were significantly lower in eyes of *Group A* compared to *Group B*. There were significant positive correlations between break up time test (BUT) and CET in *Group A*. **Conclusion:** Topical antiglaucomatous medications seem to affect CET in glaucoma patients as CET was thinner in glaucoma patients, in all regions, than controls, while these medications seem to focally affect CT in some regions. Further studies are required to assess the clinical implications of these findings.

Keywords: Beta-blockers, Carbonic Anhydrase Inhibitors, Glaucoma, Corneal epithelial thickness, Optical coherence tomography.

INTRODUCTION

High intraocular pressure (IOP) and progressive optic neuropathy are frequently linked with glaucoma [(1)]. Using a topical IOP-lowering medication on a daily basis causes ocular discomfort owing to its effects on the ocular surface [(2,3)].

It is probable that both the active ingredient and the preservatives of IOP-lowering eye drops contribute to their negative effects on the ocular surface [(4)]. The most popular preservative in antiglaucoma medications is benzalkonium chloride (BAK), a quaternary ammonium compound that has been found to generate considerable corneal cytotoxicity [(2,3,5)].

Using topical antiglaucoma medications on the long run may cause ocular surface disease (OSD), which decreases life quality and medication adaptation [(4,6)]. Fifteen to 50% of glaucoma patients have serious side effects, such as local allergic responses, chronic conjunctival inflammation, aberrant tear film, and corneal epitheliopathy [(7–9)].

Glaucoma medications have great effects on the cornea including all epithelial layers, stroma, and endothelium [(10)]. The corneal epithelium, exposed to continuous glaucoma therapy, exhibits cellular alterations and inflammatory infiltration that may interfere with its influence in ocular surface homeostasis and corneal trophism [(5)].

Several objective tests, Schirmer, tear film break-up time (TBUT), and in vivo confocal microscopy have been utilized to identify ocular surface disease (OSD) [(11,12)]. Due to the fact that prior methods were invasive and had multiple sources of error, corneal epithelial thickness (CET) is presently used to assess ocular surface damage [(13)].

Measuring corneal epithelial thickness (CET) may provide a novel tool to evaluate corneal epithelial changes (CET). This evaluation has become possible by using the noninvasive imaging tool known as anterior segment optical coherence tomography (ASOCT) [(14)]. CET is an important and unique parameter which provides information about the ocular surface in the early stages of corneal epithelial changes during glaucoma treatment [(13,15)].

In order to have a better knowledge about corneal epithelial abnormalities in glaucoma patients, this study analyzed the corneal epithelial thickness (CET) using ASOCT in patients on topical glaucoma medication (topical combined beta-blockers and CAIs).

PATIENTS AND METHODS

A randomized controlled clinical trial was conducted on 80 participants recruited from Ophthalmology Outpatient Clinics Benha University Hospitals. Participants were split into two distinct groups:

- **Group A** (Topical combined Beta-blockers and Carbonic Anhydrase Inhibitors eye drops group**)**: 40 patients treated with topical combined Beta-blockers and Carbonic Anhydrase Inhibitors eye drops (Dorzolamide HCL 2% & Timolol Maleate 0.5%) for more than 3 months.

Received: 23/08/2022
Accepted: 26/10/2022

- **Group B** (Control group): 40 healthy participants with completely normal ophthalmological examination.

Inclusion criteria:

1. Patients with primary open-angle glaucoma.
2. Patients of either sex whose age between 40-60 years.
3. Duration of topical IOP lowering drops ≥ 3 months.
4. Not on other medication affecting the cornea.

Exclusion criteria:

1. Severe dry eye [BUT<5 sec].
2. Past history of corneal surgery.
3. Ocular surface disease: e.g., Ocular cicatricial pemphigoid.
4. Corneal ectasia.
5. Past history of keratitis.
6. Corneal opacities.
7. Corneal dystrophies.
8. Non-compliance with eye drops.

All patients were subjected to a comprehensive history and ophthalmic examination, as well as an AS-OCT system (CET mapping) (Optovue, Inc, Freemont, CA). The Fourier-domain AS-OCT system (Optovue, Fremont, California, USA) with an add-on lens was used to analyze corneal pachymetry and epithelial thickness maps (corneal adaptor module CAM-L mode: 6.0−2.0mm) using a wavelength of 830nm at a rate of 26 000 axial scans per second, of 5µm axial resolution, and of 15µm transverse resolution. After evaluating visual acuity and autorefraction, the RTVue XR OCT equipment with the cornea anterior adapter module was utilised to measure corneal epithelial thickness across a 9-mm diameter zone. To decrease the influence of diurnal variation, All CET measurements were conducted between 10 AM and 2 PM. Any eye drops were forbidden two hours before the examination. According to instrument's datasheet, the "PachymetryWide" scan mode was used for CET zone measurement with a 9-mm diameter. The corneal apex was the focus point of the OCT scan when simultaneously vertical and horizontal reflection stripes developed, suggesting manual alignment. The participant was instructed to blink quickly two seconds before the scan began. The CET of 25 sectors was measured automatically with an axial resolution of 5-µm. This research divided the CET map into four zones: central (0–2 mm diameter), paracentral (2–5 mm diameter), mid-peripheral (5–7 mm diameter), and peripheral (7–9 mm diameter).

All OCT scans were conducted by a technician who has no knowledge of the patient's clinical history. Each eye was examined three times for CET. Average value was utilized for analysis, and CET difference between these scans must be less than 1 µm.

Ethical Consideration:

The Institutional Review Board of the Faculty of Medicine, Banha University approved the study equipment and methodology (19-9-2021). Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis:

The gathered data was analysed using Statistical Package for Social Sciences (IBM Corp. IBM SPSS Statistics Version 25.0 for Windows. Armonk, NY: IBM Corporation). Qualitative data were defined as numbers and percentages. Chi-Square test, 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). Student T-Test was used to assess the statistical significance of the difference between the means of the two groups. Mann-Whitney U-test was used to assess the statistical significance of the difference between two nonparametric variables. Correlations between BUT, CT, and CET was conducted. Age, duration of medication, application of topical beta-blockers and CAIs combination were used as predictors for CT and CET in a linear regression analysis. P value ≤0.05 was considered to be statistically significant.

RESULTS

Table 1 summarizes demographic and clinical features of the studied groups.

Table (1): Comparison of studied groups regarding demographic and clinical data.

Variable	Group A n= 50	Group B n= 50	P-value
Age (years)	49.84 ± 4.83	49.44 ± 4.81	0.679
Gender			
Male	18 (36%)	18 (36%)	1.000
Female	32 (64%)	32 (64%)	
Visual acuity (Decimal)	0.64 ± 0.10	0.57 ± 0.09	0.565
IOP (mmHg)	17.08 ± 1.56	——	
Duration of therapy (months)	10.94 ± 1.15	——	
TBUT test (seconds)	7.94 ± 0.71	10.26 ± 1.61	<0.001*
PEE	45 (90%)	0 (0%)	<0.001*

IOP: Intraocular pressure *significant, TBUT: Tear breakup time, PEE: Punctate epithelial erosions

Group A: According to Corneal thickness (CT) map, Group A showed significantly regional reduction in lower middle temporal, peripheral temporal, para

central superior, middle superior, para central sup-temporal, middle sup-temporal, peripheral sup-temporal, peripheral inf-temporal regions compared to group B. While no significant difference was found regarding other regions **(Figure 1, Table 2**).

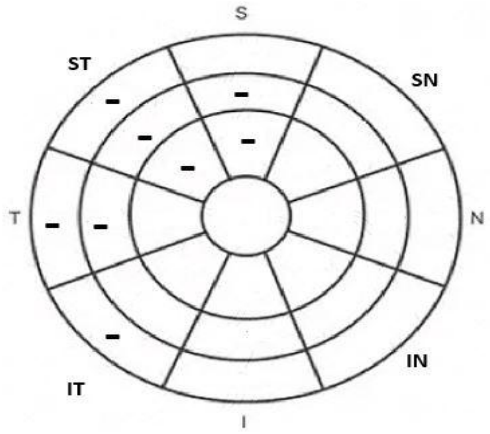


Figure (1): Bullseye map showing a decrease in CT in all the selected locations of Group A compared to Group B.

Table (2): Comparison of studied groups regarding corneal thickness (pachymetry map).

Variable	Group A n= 50	Group B n= 50	P-value
CCT	511.22 ± 37.58 **µm**	520.46 ± 32.97 **µm**	0.194
Nasal Para central	545.20 ± 38.42 **µm**	546.66 ± 34.80 **µm**	0.843
Middle	584.12 ± 42.22 **µm**	582.62 ± 49.75 **µm**	0.871
Peripheral	627.18 ± 47.76 **µm**	633.14 ± 62.06 **µm**	0.592
Temporal Para central	516.28 ± 36.37 **µm**	530.70 ± 36.50 **µm**	0.051
Middle	534.70 ± 35.70 **µm**	555.82 ± 40.70 **µm**	0.007*
Peripheral	554.28 ± 36.10 **µm**	592.66 ± 45.06 **µm**	<0.001*
Superior Para central	541.40 ± 34.23 **µm**	559.56 ± 37.97 **µm**	0.014*
Middle	582.90 ± 36.15 **µm**	605.56 ± 46.14 **µm**	0.007*
Peripheral	632.46 ± 45.88	655.70 ± 69.49 **µm**	0.051
Sup-Nasal Para central	545.44 ± 33.54 **µm**	556.76 ± 39.10 **µm**	0.123
Middle	589.76 ± 38.02 **µm**	595.46 ± 65.91 **µm**	0.598
Peripheral	639.74 ± 48.70 **µm**	655.92 ± 66.16 **µm**	0.167
Sup-Temporal Para central	527.74 ± 34.38 **µm**	546.42 ± 39.74 **µm**	0.014*
Middle	556.72 ± 35.89 **µm**	583.48 ± 43.87 **µm**	0.001*
Peripheral	591.16 ± 41.35 **µm**	628.22 ± 51.57 **µm**	<0.001*
Inferior Para central	531.56 ± 46.30 **µm**	533.70 ± 35.25 **µm**	0.795
Middle	563.12 ± 50.61 **µm**	566.34 ± 37.55 **µm**	0.719
Peripheral	598.70 ± 51.69 **µm**	607.24 ± 43.47 **µm**	0.373
Inf-Nasal Para central	543.84 ± 51.48 **µm**	539.54 ± 34.03 **µm**	0.623
Middle	576.96 ± 47.88 **µm**	575.56 ± 46.47 **µm**	0.882
Peripheral	621.36 ± 54.24 **µm**	623.96 ± 65.28 **µm**	0.829
Inf-Temporal Para central	519.86 ± 42.48 **µm**	529.34 ± 38.64 **µm**	0.246
Middle	547.40 ± 46.68 **µm**	555.74 ± 40.31 **µm**	0.341
Peripheral	568.12 ± 53.66 **µm**	591.60 ± 42.33 **µm**	0.017*

*: significant

Group A: According to epithelium thickness map, *Group A* had statistically lower CET compared to group B with P-value<0.001, on all the studied regions. Also, the minimum and maximum of epithelium map exhibited substantial difference between the two groups investigated, with a significantly higher standard deviation (**Table 3** and **Figure 2**).

Table (3): Comparison of studied groups regarding epithelium map (Thickness).

Variable	Group A n= 50	Group B n= 50	P-value
CCT	45.94 ± 3.96 µm	54.54 ± 3.16 µm	<0.001*
Nasal Para central	45.16 ± 3.78 µm	54.18 ± 2.86 µm	<0.001*
Middle	45.62 ± 4.51 µm	54.10 ± 3.28 µm	<0.001*
Peripheral	47.26 ± 5.78 µm	55.58 ± 4.30 µm	<0.001*
Temporal Para central	44.42 ± 3.73 µm	53.92 ± 2.83 µm	<0.001*
Middle	43.28 ± 4.15 µm	53.14 ± 2.82 µm	<0.001*
Peripheral	43.00 ± 6.25 µm	52.04 ± 2.92 µm	<0.001*
Superior Para central	41.60 ± 4.72 µm	53.52 ± 3.42 µm	<0.001*
Middle	38.94 ± 5.64 µm	51.52 ± 4.21 µm	<0.001*
Peripheral	37.44 ± 8.16 µm	48.28 ± 3.95 µm	<0.001*
Sup-Nasal Para central	42.70 ± 3.74 µm	53.90 ± 2.82 µm	<0.001*
Middle	41.40 ± 5.03 µm	53.14 ± 3.08 µm	<0.001*
Peripheral	40.18 ± 7.04 µm	51.42 ± 3.83 µm	<0.001*
Sup-Temporal Para central	42.68 ± 4.16 µm	53.74 ± 3.05 µm	<0.001*
Middle	40.48 ± 4.74 µm	52.40 ± 3.60 µm	<0.001*
Peripheral	39.38 ± 5.71 µm	49.72 ± 3.60 µm	<0.001*
Inferior Para central	47.60 ± 3.48 µm	55.88 ± 2.97 µm	<0.001*
Middle	47.08 ± 3.58 µm	55.08 ± 2.69 µm	<0.001*
Peripheral	46.04 ± 4.36 µm	53.12 ± 3.46 µm	<0.001*
Inf-Nasal Para central	47.02 ± 3.36 µm	54.98 ± 3.05 µm	<0.001*
Middle	46.88 ± 4.86 µm	54.22 ± 2.58 µm	<0.001*
Peripheral	46.48 ± 6.70 µm	54.64 ± 4.23 µm	<0.001*
Inf-Temporal Para central	46.54 ± 3.32 µm	55.08 ± 2.91 µm	<0.001*
Middle	45.70 ± 2.91 µm	54.88 ± 2.69 µm	<0.001*
Peripheral	45.60 ± 3.22 µm	53.56 ± 2.62 µm	<0.001*

*: significant.

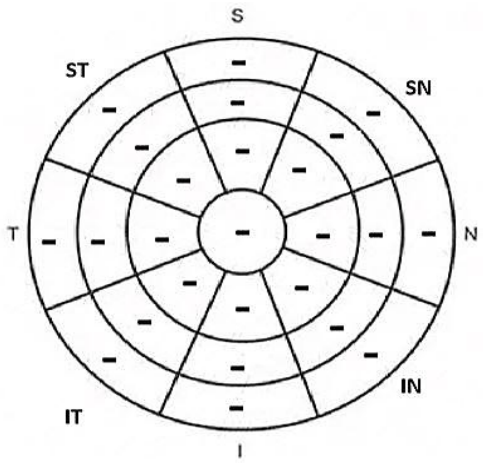


Figure (2): Bullseye map showing reduction in CET on all regions in Group A compared to group B.

There were significant positive correlations between BUT, CT and CET (**Table 4**). According to linear regression analysis, CET was 8 times significantly thinner with using topical combined Beta-blockers and CAIs drops (***β***= -8.600, P<0.001*). CT values were predicted to decrease with increasing age (**Table 5**).

Table (4): Correlations of CT and CET BUT

Variable	*CT*		*CET*	
	R	***P-value***	***r***	***P-value***
BUT	0.324	0.001	0.570	<0.001*

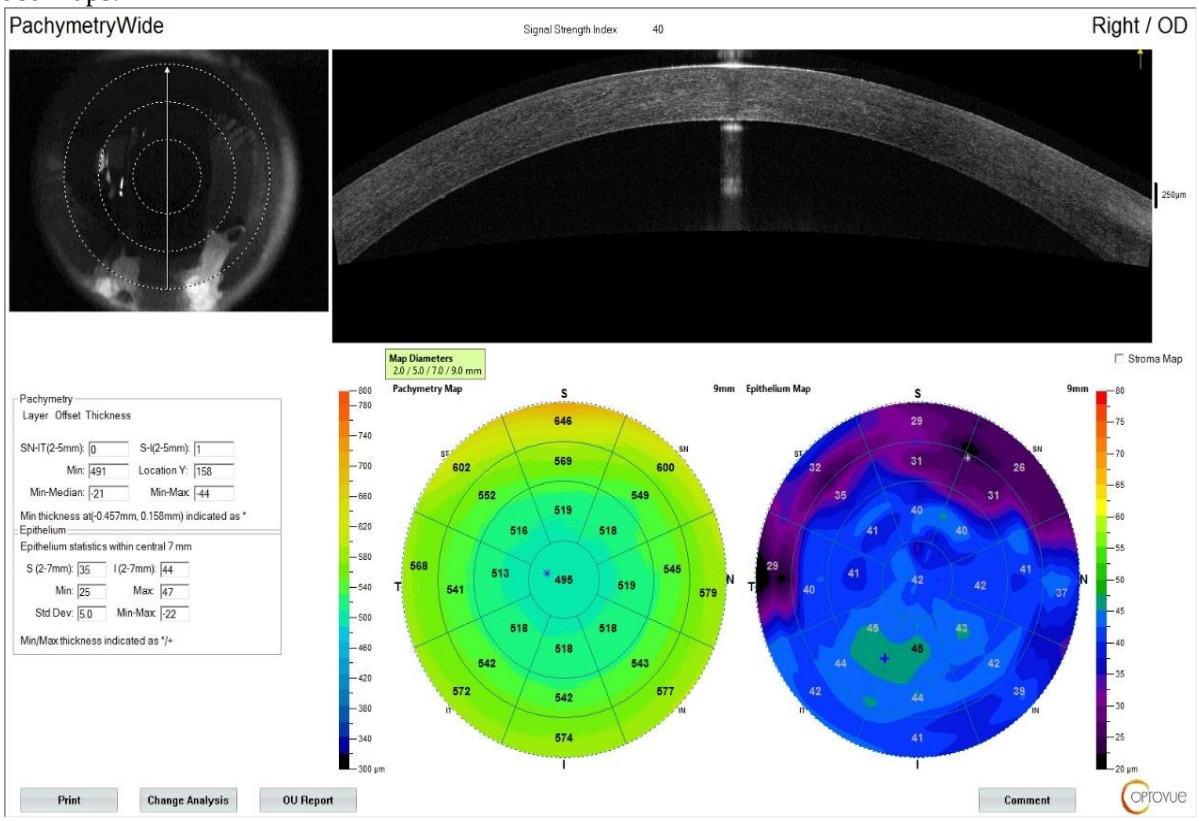
*: significant, BUT: break up time test, CT: corneal thickness, CET: corneal epithelial thickness

Table (5): Regression analysis for prediction of CT and CET among patients using topical combined Beta-blockers and Carbonic Anhydrase Inhibitors

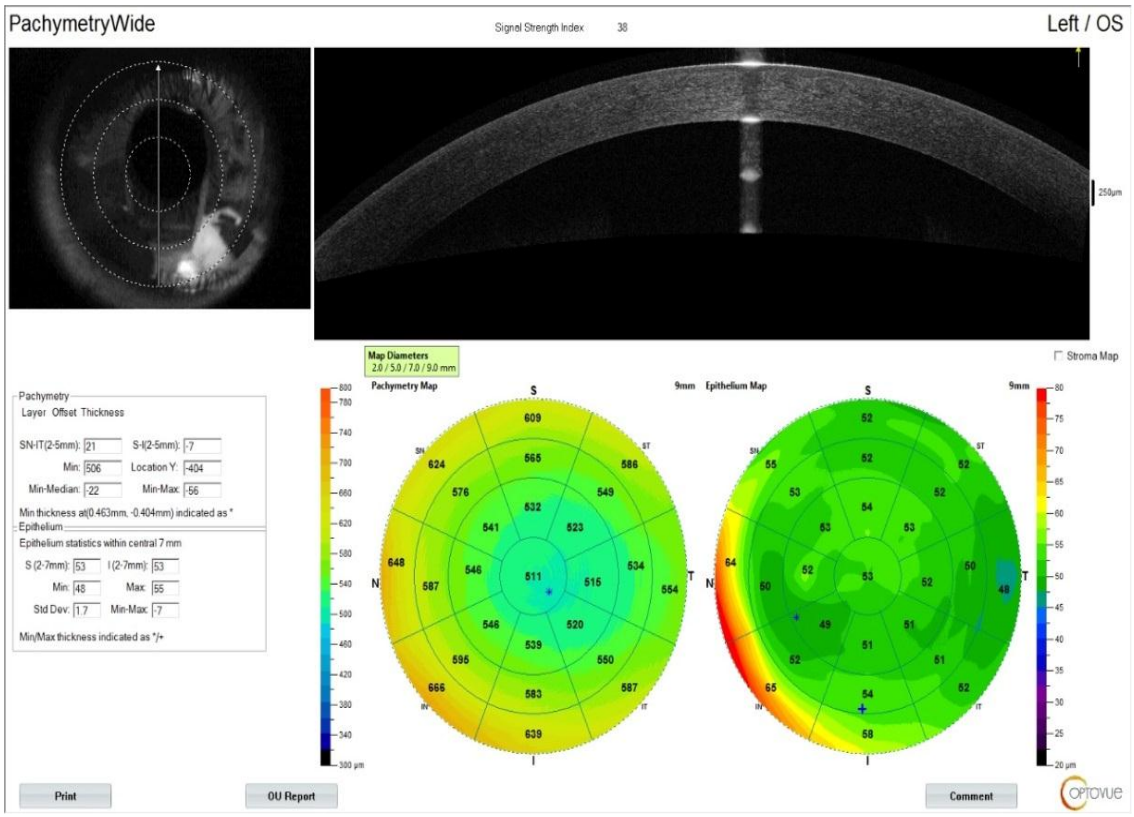
Variable	*CT*		*CET*	
	β	***P-value***	***β***	***P-value***
Age	-2.704	0.004*	-0.154	0.190
Duration of therapy	-1.753	0.673	0.722	0.143
topical combined Beta-blockers and Carbonic Anhydrase Inhibitors	9.240	0.194	-8.600	<0.001*

B, regression coefficient, CT: corneal thickness, CET: corneal epithelial thickness.

Figure 3 visualizes the striking difference in the CET map in *Group A* compared to *Group B* as highlighted in the color-coded maps.



Group A



Group A

Figure (3): Anterior segment OCT pictures showing difference between group A and group B regarding corneal epithelial thickness and total corneal thickness, Group A showing diffuse thinning in the CET map.

DISCUSSION

In our study, according to epithelium thickness, we reported generalized thinning of CET in glaucoma patients using topical combined Beta-blockers and CAI eye drops for more than 3 months. This thinning was significantly and positively correlated with BUT test.

Our results were parallel to **Doğan *et al.*** [15], who reported reduced CET in glaucoma patients compared to healthy individuals. However, **Doğan *et al.*** [15], reported that central CET was unaffected by treatment duration, number of drugs, and daily drug instillations number.

In the study made by **Halkiadakis *et al.*** [16] 62 glaucoma patients were compared to the same number of healthy controls, and the glaucoma patients were found to have consistently thinner corneal epithelial thicknesses than controls. However, **Halkiadakis *et al.*** [16], said that CET parameter was not significantly linked with drug numbers, number of instillations, and years of therapy.

Our results also agreed with **Nam and Kim** [17]. As in their study, compared to the control group, CET declined in all 25 sectors of a 9.0 mm diameter region in the glaucoma group, corroborating their prior work comparing cohorts of 250 individuals. In both the superior and inferior corneas, Comparable differences in CET were seen between control and glaucoma groups. The overall number of drugs and severity of glaucoma were shown to be correlated with epithelial layer thickness. In simple regression analysis, there was a correlation between the severity of glaucoma and CET.

In the same way, **Ye *et al.*** [18]**,** reported that glaucoma patients had a lower mean central CET as compared to healthy controls. Additionally, his findings indicated that the average CET of annular-analyzed zones dropped from the centre to the periphery. In the paracentral, midperipheral, and peripheral zones of both groups, the CET in the superior sections (superior, superior-nasal, and superior-temporal) was significantly lower than in the inferior sections; however, in the superior-inferior section of the patient group, the CET was significantly higher nasally than temporally. In comparison to controls, the average CET of four annular zones was considerably lower in patients.

In the study made by **Batawi *et al.*** [19], caliper-based assessments of central CET were performed On OCT images of 58 male glaucoma patients and revealed reduction in corneal stromal thicknesses and lower central CETs, and established a negative relationship between CET and CCT and the quantity of anti-glaucoma medications.

In our study, the higher SD of CET in group A could be a tomographic representation of subclinical punctate epithelial erosions (PEE). **Abou Shousha *et al.*** [20], using ASOCT, reported a link between thickness variability and patient complaints, as well as increased thickness variation in dry eyes. In addition, they discovered a substantial decrease in epithelial thickness variability after therapy and indicated that profiles of epithelial thickness may be used to assess a response of the patient to treatment during follow-up.

Our results didn't agree with **Kanellopoulos and Asimellis** [21] who observed increased thickness variability and epithelium thickening in patients suffering from dryness, and recommended OCT-based epithelial thickness evaluation in these patients. In this study, the Fourier-domain AS-OCT system RTVue-100 with software version A6 (Optovue Inc, Fresno, California, USA) was utilized. All pair tests of the respective epithelium thickness metrics between the control and dry eye groups show statistically significant differences.

In the current study, according to linear regression analysis, CET was 8 times significantly thinner with using topical combined Beta-blockers and Carbonic Anhydrase Inhibitors eye drops. Older age was associated with prediction of lowering CT. In the same way **Ye *et al.*** [18]**,** reported that there was a high association between the average CET and the total amount of topical medications and eye drops used in the central, paracentral, and midperipheral regions. No link was found between the total quantity of BAK applied and the average ET of any zone analysed. Multivariate linear regression analysis indicated that the patient's age and the number of drugs had a significant influence on the average CET of the 9-mm diameter zone. Age altered the average CET of the paracentral, midperipheral, and periphery zones. The number of topical drugs had a significant impact on the mean CET in paracentral and central zones, but only central and peripheral zones were influenced by duration of treatment.

Similar to our results, **Montorio *et al.*** [22] found no link between treatment duration and CET thinning. The authors hypothesised that epithelial thinning may occur early in the therapy course.

Cennamo *et al.* [13] reported that CET thinning was only found in glaucomatous eyes with early and moderate epithelial microvilli alterations using scanning electron microscopy and OCT

Our results showed that CET had no relation with age of the patient. This result is consistent with the findings of **Batawi *et al.*** [19]**,** using Cirrus HD-OCT, who analyzed central ET in eyes which suffer from POAG. In opposite side, **Montorio *et al.*** [22] age-related increases in the CET have been recorded. The authors hypothesized continuous usage of antiglaucoma drugs and age-associated changes might reduce microvilli number, leading to mild epithelial edema and a rise in CET.

Recent researches have connected a thin central corneal thickness (CCT) to the development of glaucoma [17]. Intraocular pressure (IOP) measurements have long been recognized to be affected by CT, with thinner corneas resulting in an underestimating of IOP.

The link between CT and glaucoma may be due to structural and biomechanical alterations at the optic nerve head [18].

This discrepancy between our findings and those of earlier researches may be due to changes in treatment duration, patient demographics, and measuring techniques.

Finally, this study was constrained by its single-center design and small sample size which hindered a more thorough analysis. Our results imply that topical antiglaucoma medications affect the CET, since the CET was thinner in glaucoma patients than in controls. This thinning was associated with reduced BUT in the affected eyes. Hence, these findings demonstrated the need for protecting the corneal epithelium prior to the initiation of antiglaucoma topical therapy, especially in eyes treated with several IOP-lowering drops. OCT of the anterior segment may be beneficial for evaluating the effect of antiglaucoma medications on CET during treatment. There is a need for more extensive prospective researches with bigger sample sizes to study this problem and identify different measures of prevention.

CONCLUSION

Our results showed that the use of topical antiglaucomatous drugs appears to influence the CET in glaucoma patients associated with significantly reduced tear film BUT.

Funding: None.
Conflict of Interest: None declared.

REFERENCES

1. **Tham Y, Li X, Wong T *et al.* (2014):** Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology, 121(11):2081-90.
2. **Pisella P, Pouliquen P, Baudouin C (2002):** Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol., 86(4):418-23.
3. **Baudouin C, Pisella P, Fillacier K *et al.* (1999):** Ocular surface inflammatory changes induced by topical antiglaucoma drugs: human and animal studies. Ophthalmology, 106(3):556-63.
4. **Fechtner R, Godfrey D, Budenz D *et al.* (2010):** Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea, 29(6):618-21.
5. **Martone G, Frezzotti P, Tosi G *et al.* (2009):** An in vivo confocal microscopy analysis of effects of topical antiglaucoma therapy with preservative on corneal innervation and morphology. Am J Ophthalmol., 147(4):725-35.
6. **Skalicky S, Goldberg I, McCluskey P (2012):** Ocular surface disease and quality of life in patients with glaucoma. Am J Ophthalmol., 153(1):1-9.
7. **Baudouin C, Renard J, Nordmann J *et al.* (2013):** Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension. Eur J Ophthalmol., 23(1):47-54.
8. **Leung E, Medeiros F, Weinreb R (2008):** Prevalence of ocular surface disease in glaucoma patients. J Glaucoma, 17(5):350-5.
9. **Garcia-Feijoo J, Sampaolesi J (2012):** A multicenter evaluation of ocular surface disease prevalence in patients with glaucoma. Clin Ophthalmol (Auckland, NZ), 6:441-6.
10. **Mastropasqua L, Agnifili L, Mastropasqua R *et al.* (2014):** In vivo laser scanning confocal microscopy of the ocular surface in glaucoma. Microsc Microanal, 20(3):879-94.
11. **Schrems W, Schrems-Hoesl L, Mardin C *et al.* (2016):** The effect of long-term antiglaucomatous drug administration on central corneal thickness. J Glaucoma, 25(3):274-80.
12. **Villani E, Sacchi M, Magnani F *et al.* (2016):** The ocular surface in medically controlled glaucoma: an in vivo confocal study. Invest Ophthalmol Vis Sci., 57(3):1003-10.
13. **Cennamo G, Montorio D, Del Prete S *et al.* (2018):** Anterior-segment optical coherence tomography and scanning electron microscopy to evaluate corneal epithelial changes in patients undergoing glaucoma therapy. Cornea, 37(12):1522-6.
14. **Liang Q, Le Q, Cordova D *et al.* (2020):** Corneal epithelial thickness measured using anterior segment optical coherence tomography as a diagnostic parameter for limbal stem cell deficiency. Am J Ophthalmol., 216:132-9.
15. **Doğan E, Çakır B, Aksoy N *et al.* (2020):** Effects of topical antiglaucomatous medications on central corneal epithelial thickness by anterior segment optical coherence tomography. Eur J Ophthalmol., 30(6):1519-24.
16. **Halkiadakis I, Vernikou A, Tzimis V *et al.* (2021):** Assessment of Corneal Epithelium Thickness in Glaucomatous Patients Undergoing Medical Treatment. J Glaucoma, 30(1):44-9.
17. **Nam M, Kim S (2021):** Changes in corneal epithelial thickness induced by topical antiglaucoma medications. J Clin Med., 10(16):3464. doi: 10.3390/jcm10163464
18. **Ye Y, Xu Y, Yang Y *et al.* (2022):** Wide Corneal Epithelial Thickness Mapping in Eyes With Topical Antiglaucoma Therapy Using Optical Coherence Tomography. Transl Vis Sci Technol., 11(1):4. doi: 10.1167/tvst.11.1.4
19. **Batawi H, Lollett I, Maliakal C *et al.* (2018):** A comparative study of central corneal epithelial, stromal and total thickness in males with and without primary open angle glaucoma. Cornea, 37(6):712-19.
20. **Abou Shousha M, Wang J, Kontadakis G *et al.* (2020):** Corneal epithelial thickness profile in dry-eye disease. Eye, 34(5):915-22.
21. **Kanellopoulos A, Asimellis G (2016):** In pursuit of objective dry eye screening clinical techniques. Eye Vis., 3(1):1-7.
22. **Montorio D, Cennamo G, Breve M *et al.* (2020):** Evaluation of corneal epithelial thickness in glaucomatous patients using anterior- segment optical coherence tomography. J Biophotonics, 13(1):e201900095. doi: 10.1002/jbio.201900095.