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Wide Corneal Epithelial Thickness Mapping in Eyes With Topical Antiglaucoma Therapy Using Optical Coherence Tomography

Yiming Ye[1], Yunzhi Xu[1], Yangfan Yang[1], Yanmei Fan[1], Pingping Liu[1], Keming Yu[1], and Minbin Yu[1]

[1] State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China

Purpose: The purpose of this study was to assess the corneal epithelial thickness (CET) of the 9-mm diameter zone in patients treated using topical antiglaucoma medications and to evaluate the factors associated with CET changes.

Methods: Seventy-five patients treated using topical antiglaucoma medications and 65 healthy subjects were included in this cross-sectional study. Each patient completed the Ocular Surface Disease Index (OSDI) questionnaire and underwent examinations including the Schirmer I test, tear breakup time (TBUT), and fluorescein staining. CET mapping of the 9-mm diameter zone was performed using RTVue XR. The CET of the different analyzed zones was compared between groups. The relationship between CET and confounding factors was investigated.

Results: The patient group had a significantly shorter TBUT, shorter Schirmer I test, and greater fluorescein staining than those of the control group (all $P < 0.05$). The mean CET of patients with glaucoma was significantly lower than that of controls in the central, paracentral, mid-peripheral, and peripheral zones (all $P < 0.001$). Age affected the CET in the paracentral, mid-peripheral, and peripheral zones (all $P < 0.01$). The number of medications affected the CET in the central, paracentral, and mid-peripheral zones (all $P < 0.05$). The duration of treatment affected the CET in the central and peripheral zones (all $P < 0.05$).

Conclusions: Use of topical IOP-lowering medications leads to epithelial thinning in the 9-mm diameter zone in glaucomatous eyes. Epithelial protection should be considered in older patients and patients treated with multiple medications from the early stages of long-term topical antiglaucoma therapy.

Translational Relevance: The 9-mm diameter CET mapping by using widefield optical coherence tomography (OCT) can be a valuable and convenient method to assess the ocular surface damage in patients with topical antiglaucoma therapy.

Introduction

Topical intraocular pressure (IOP)-lowering medications are the first-line therapy for glaucoma, which is the second leading cause of blindness worldwide.[1] However, long-term use of topical antiglaucoma eye drops leads to ocular surface changes, such as conjunctival inflammation, abnormal tear film, and corneal epitheliopathy.[2–4] Recently, corneal epithelial thickness (CET) was suggested to be an indicator of corneal epithelial damage.[5,6] Various studies have used confocal microscopy and high-frequency scanning ultrasound biomicroscopy to measure CET.[2,7,8] However, these devices use contact-based techniques and require topical anesthesia, which increases the risk of ocular surface damage and infection. Therefore, spectral-domain optical coherence tomography (OCT) has been developed for corneal thickness measurement, which has the advantages of non-contact, faster performance, and high reliability and repeatability.[9–11] Moreover, the OCT automatically generates a CET

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and corneal stroma thickness map, by which clinicians can obtain a wide-field evaluation of corneal thickness.

The few studies that investigated CET changes in glaucomatous eyes using OCT found significant corneal epithelial thinning in eyes that underwent chronic topical antiglaucoma therapy.[12–15] Nonetheless, in these studies, the area analyzed using previous generation OCT was the 6-mm diameter zone. The change in epithelial thickness (ET) in the peripheral cornea in glaucomatous eye remains unknown. Furthermore, the relationship between treatment factors and CET is unclear.

The aim of the current study was to map the 9-mm diameter zone CET in eyes treated with topical antiglaucoma medications using the novel RTVue XR widefield OCT and assess the influences of confounding factors on the CET of different analyzed areas.

Patients and Methods

Subjects

This cross-sectional observational study was conducted at the Department of Glaucoma in Zhongshan Ophthalmic Center (ZOC) and performed in accordance with the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of ZOC. Written informed consent was obtained from each participant before the examination.

All participants were examined between February and July 2019. For all participants, one eye was randomly selected for analysis. The inclusion criteria included: age ≥18 years, ability to read and complete the Ocular Surface Disease Index (OSDI) questionnaire, and refractive error <2 diopters. The additional inclusion criteria for the glaucoma group were as follows: patients with open angle glaucoma and ocular hypertension treated with at least one topical antiglaucoma medication for at least 3 months. The exclusion criteria for both groups included any history of ocular and/or systemic disease affecting the ocular surface, contact lens use, ocular trauma or surgery, use of any non-antiglaucoma eye drops. For the glaucoma group, the additional exclusion criteria were as follows: change in antiglaucoma medication within the last 3 months.

Ophthalmologic Examination

Demographic information and medical history were obtained from the patients' medical records. The detailed history of antiglaucoma medication, including the duration of therapy (number of months), active agent, preservative and number of antiglau-

coma medications (Supplementary Table SA), and total number of applied eye drops, was collected. Before the examination, patients who met the inclusion criteria were given the OSDI questionnaire to complete. Total OSDI scores were calculated as previously reported, which ranged from 0 to 100.[16] The participants then underwent comprehensive ophthalmologic examination including visual acuity using a Snellen chart, IOP measurement using the Goldmann applanation tonometry, autorefraction, and corneal epithelial measurement using RTVue XR widefield OCT, slit lamp biomicroscopy, and fundus examination using a 90-D lens. The examinations of the ocular surface were performed in the following fixed order: tear breakup time (TBUT) measurement, corneal and conjunctival fluorescein staining, and the Schirmer I test.

TBUT was measured by applying a drop of 2% fluorescein solution onto the lower conjunctival cul de sac. The patients were then asked to blink two times. The tear film was assessed using a slit lamp at 10 × magnification with cobalt blue illumination. The time between the last blink and appearance of a first dry spot or black gap was recorded as the TBUT. The test was repeated two times, and the mean value was used for analysis.

Corneal fluorescein staining was conducted following the TBUT test; each cornea was stained with one drop of 2% fluorescein solution and scored using the Oxford scale (0 = no staining, I = minimum, II = mild, III = moderate, IV = marked, and V = severe).[17] The Schirmer test was performed after a drop of 0.5% proparacaine was instilled. A sterile Schirmer strip was hooked between the lower eyelid margin and lower fornix. The subjects were asked to gently close their eyes for 5 minutes. The strip was then removed, and the result was recorded.

CET Measurement

After the examining visual acuity and autorefraction, the RTVue XR OCT system with a cornea anterior adaptor module was used to obtain the corneal epithelial thickness across the 9-mm diameter zone. All ET measurements were performed between 2:00 PM and 5:00 PM to minimize the influence of diurnal variation. The use of any eye drops was prohibited from 2 hours before the examination.

The "PachymetryWide" scan mode was selected to measure the 9-mm diameter zone ET according to the device manual. The OCT scan was aligned manually when both vertical and horizontal reflection stripes appeared simultaneously, which means the scan was centered on the corneal apex. The subject was asked

to blink quickly, and the scan was triggered within 2 seconds. The ET of 25 sectors was automatically measured with 5-µm axial resolution. In this study, the ET map was further redefined into a central zone (0–2 mm diameter), paracentral zone (2–5 mm diameter), mid-peripheral zone (5–7 mm diameter), and peripheral zone (7–9 mm diameter). All OCT scans were performed by the same experienced operator who was masked to the participants' clinical data. The ET measurement was repeated three times for each eye. The difference in central ET should be within 1 µm between these scans, and the average value was used for analysis.

Statistical Analysis

The statistical analysis was performed using SPSS version 24.0. The data were presented as mean ± standard deviation (SD). The Kolmogorov–Smirnov test was used to assess the normality of numeric variables. Demographic data, OSDI scores, TBUT, Schirmer I test, Oxford scores, and each sector of the ET map were compared between the glaucomatous and control groups. For normally distributed variables, independent *t*-test was applied. For nonparametric variables, the Mann-Whitney *U* test and the Kruskal-Wallis test and was used. A 1-way analysis of variance (ANOVA) followed by Bonferroni post hoc analysis was used to analyze the differences in ET in each analyzed zone between the subgroups of patients with glaucoma treated with different antiglaucoma medications and treatment duration. The paired *t*-test was used to compared the ET of different analyzed sections in each eye. Correlations among the ET of each sector, age, Oxford scores, number of benzalkonium chloride (BAK) applied, number of total drops applied, duration of treatment (months), and number of antiglaucoma medications were evaluated using Spearman's coefficient. Multivariate linear regression analysis was used to investigate the influence of confounding factors on the mean ET of the whole 9-mm diameter zone are and the ET in the different analyzed zones. The *P* values < 0.05 were considered statistically significant.

Results

Seventy-five eyes in 75 patients undergoing topical antiglaucoma therapy and 65 eyes in 65 untreated healthy subjects were included in this study. The participants' demographics and OSDI indicators are presented in Table 1. The mean age of patients and controls was 46.88 ± 16.61 years and 45.94 ± 15.74 years, respectively. There was no significant difference in age or sex between the two groups. The TBUT and Schirmer I test results of the patient group were significantly lower than those of the control group (TBUT: $P = 0.001$ and the Schirmer I test: $P = 0.021$). The OSDI scores and Oxford scores for fluorescein corneal staining were significantly higher in the patient group (OSDI: $P = 0.024$ and Oxford scores: $P < 0.001$). The duration of antiglaucoma treatment was 22.2 ± 10.5 months. The mean number of eye drops was 1.61 ± 0.74, and the mean number of drops applied was 1205.9 ± 988.8.

Table 1. Demographics, OSD Data, and Treatment of Eyes with Antiglaucoma Therapy and Controls

Parameter	Patients (*n* = 75)	Controls (*n* = 65)	*P* Value
Age, y	46.88 ± 16.61 (23–82)	45.94 ± 15.74 (21–83)	0.732[a]
Sex, F:M	44:31	37:28	0.865[b]
OSDI	9.47 ± 10.20 (0–45.40)	6.04 ± 6.97 (0–24.97)	0.024[c]
TBUT, s	6.37 ± 2.34 (2–10)	7.88 ± 2.52 (3–13)	0.001[c]
Schirmer I test, mm	10.45 ± 4.93 (2–21)	12.49 ± 5.40 (4–24)	0.021[c]
Corneal staining, grade	0.75 ± 0.82 (0–3)	0.26 ± 0.52 (0–2)	<0.001[c]
0: No epitheliopathy, % (*n*)	44.00 (33)	73.85 (48)	0.001[b]
MD, dB	−4.73 ± 3.87 (−19.04 to −0.05)		
Duration of treatment, mo	22.2 ± 10.5 (3.6–42)		
No. of topical glaucoma medications	1.61 ± 0.74 (1–4)		
No. of drops applied	1205.9 ± 988.8 (108–3960)		

[a]Independent *t*-test.
[b]Chi-square test.
[c]Mann-Whitney *U* test.
MD, mean deviation; OSDI, ocular surface disease index; TBUT, tear film breakup time.

Table 2. Corneal Epithelial Thickness (μm) in Different Analyzed Zones

	Central	Paracentral					Mid-Peripheral					Peripheral				
	Average	Average	S-I	ST-IT	T-N	SN-IN	Average	S-I	ST-IT	T-N	SN-IN	Average	S-I	ST-IT	T-N	SN-IN
Controls	53.15 ± 3.65	52.55 ± 3.29	−2.09 ± 2.80	−1.03 ± 2.18	−0.78 ± 1.73	−1.47 ± 2.44	51.67 ± 3.22	−3.37 ± 3.06	−1.69 ± 2.73	−1.31 ± 2.40	−1.54 ± 2.85	50.31 ± 3.61	−4.87 ± 4.37	−3.02 ± 3.89	−2.02 ± 2.73	−1.68 ± 4.29
Patients	50.56 ± 3.26	49.66 ± 3.27	−2.18 ± 2.58	−0.91 ± 2.45	−0.67 ± 2.04	−1.24 ± 2.24	48.98 ± 3.28	−3.52 ± 2.98	−1.48 ± 2.91	−0.85 ± 1.91	−1.36 ± 3.02	48.20 ± 2.95	−5.81 ± 4.94	−3.63 ± 4.00	−1.53 ± 3.34	−2.47 ± 4.03
P value	<0.001	<0.001	0.847	0.766	0.748	0.575	<0.001	0.768	0.658	0.208	0.721	<0.001	0.240	0.363	0.349	0.265

S, superior; I, inferior; T, temporal; N, nasal; S-T, superior temporal; I-T, inferior temporal; S-N, superior nasal; I-N, inferior nasal.

Differences in ET Between Groups

The mean ET of the central (2 mm), paracentral (2–5 mm), mid-peripheral (5–7 mm), and peripheral zones (7–9 mm) are summarized in Table 2. The mean central ET was 53.15 ± 3.65 μm and 50.56 ± 3.26 μm in the control and patient groups, respectively ($P < 0.001$). The mean ET of annular analyzed zones decreased from the center toward the periphery. In the paracentral, mid-peripheral, and peripheral zones of both groups, the ET was significantly lower in the three superior sections (superior, superior-nasal, and superior-temporal) than in the corresponding three inferior sections (inferior, inferior-nasal, and inferior-temporal, all $P < 0.001$, except for the superior-inferior (S-I) in the patient group: $P < 0.05$; the ET was significantly greater nasally than temporally ($P < 0.001$). The average ET of four analyzed annular zones was significantly lower in the patients than in controls (all $P < 0.001$).

The mean and SD of the ET in 25 sections in the control and patient groups are shown in the Figure. Compared to those in the control group, the average ET of all sections were significantly lower in the patient group (all $P < 0.05$). The greatest ET attenuation, which was >3 μm, was observed in the inferior-nasal section of the paracentral zone, and in the superior sections of the peripheral zones.

Differences in OSD Data and ET Between Different Antiglaucoma Medications and Different Treatment Durations

As shown in Table 3, 29 eyes were treated with prostaglandin analogs (PGAs), 6 eyes were treated with beta blockers, one eye was treated with alpha-2 agonists, and one eye was treated with carbonic anhydrase inhibitor (CAI) as monotherapy. Thirty-two eyes were treated with a combination of medications, including PGAs and six eyes were treated with a combination of medications without PGAs. To assess the influences of PGAs and combination therapy on the ET, these eyes were divided into the PGAs monotherapy group, the combined therapy with PGAs group, and the non-PGA medications group. No significant difference in baseline or OSD data was found among the three groups. The average ET of all four analyzed zones was significantly lower in the combined therapy with PGAs group than in the non-PGA medication group (central, paracentral, and mid-peripheral: $P < 0.001$ and peripheral: $P = 0.016$). The average ET of the central, paracentral, and mid-peripheral zones was significantly lower in the combined therapy with PGAs
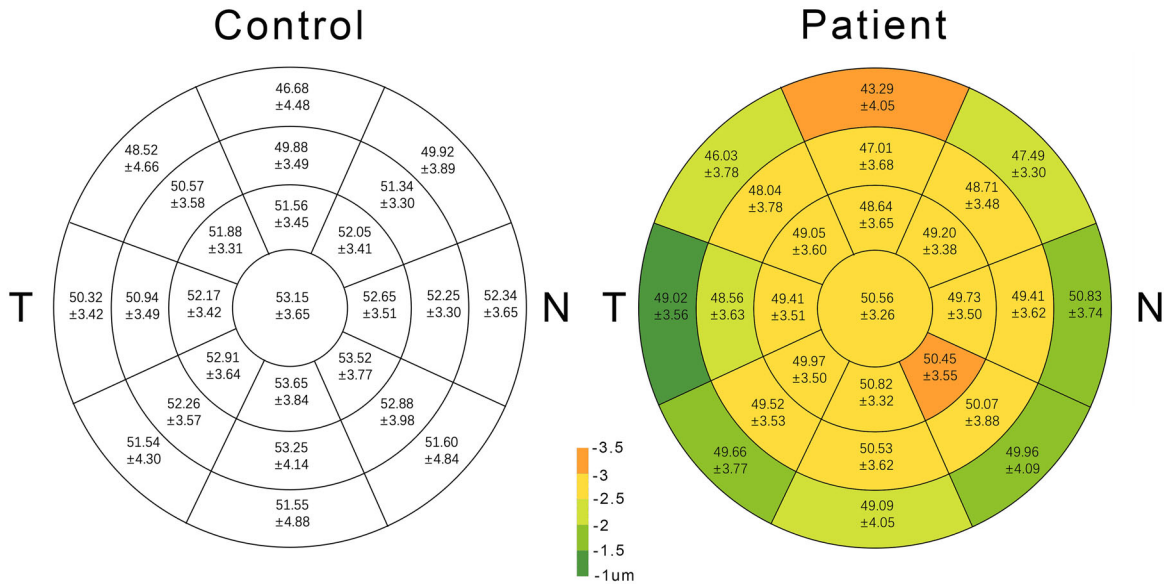
Figure. Comparison of corneal epithelial thickness (mean values ± SDs) between eyes with topical antiglaucoma therapy and controls in all 25 sections. Color coding represents the ET change compare with the controls.

group than in the PGAs monotherapy group (central, paracentral: $P < 0.001$ and mid-peripheral: $P = 0.001$). However, there was no significant difference between the PGAs monotherapy and non-PGA medications groups.

According to the treatment duration, the glaucomatous eyes were divided into three groups: ≤1 year (16 eyes), 1–2 years (25 eyes), and ≥2 years (34 eyes). As shown in Table 4, there were no significant differences in age, OSDI scores, Oxford scores, Schirmer I test results, or TBUT value among these three groups. The average ET in the central, paracentral, and peripheral zones was significantly different among the three groups (all $P < 0.05$); post hoc Bonferroni analysis revealed that the average ET in the central, paracentral, and peripheral zones were higher in those with antiglaucoma therapy for ≤1 year than in those with

antiglaucoma therapy for ≥2 years (central: $P = 0.021$; paracentral: $P = 0.040$; and peripheral: $P = 0.026$).

Correlation Between Influencing Factors and ET of Different Sections

The relationship between the influencing factors and average ET of different analyzed zones are summarized in Table 5. The average ET of the 9-mm diameter zone negatively correlated with the age of the patient ($P < 0.001$), duration of treatment ($P = 0.022$), numbers of medications ($P = 0.017$), and total number of eye drops applied ($P = 0.038$). A negative correlation was observed between the age and average ET in the paracentral ($P = 0.004$), mid-peripheral ($P < 0.001$), and peripheral zones ($P < 0.001$). The grade of fluorescein staining was significantly corre-

Table 3. The OSD Data and Corneal Epithelial Thickness of Eyes with Different Antiglaucoma Medications

	Total	PGAs (1)	Combination With PGAs (2)	Non-PGA Medications (3)	Combination Without PGAs	Beta Blockers	Alpha-2 Agonists	CAI	P Value 1 vs. 2 vs. 3
Eye, *n*	75	29	32	14	6	6	1	1	
Age, y	46.88 ± 16.61	45.17 ± 14.8	48.28 ± 17.6	47.21 ± 18.6	47.83 ± 20.0	44.67 ± 17.4	74.00	32	0.768[a]
OSDI	9.47 ± 10.20	8.61 ± 10.27	9.65 ± 11.11	10.86 ± 8.17	11.73 ± 7.65	10.97 ± 10.29	11.35	4.54	0.382[b]
Fluorescein staining, grade	0.75 ± 0.82	0.55 ± 0.74	1.00 ± 0.92	0.57 ± 0.65	0.67 ± 0.82	0.50 ± 0.548	1.00	0	0.088[b]
Schirmer I test, mm	10.45 ± 4.93	10.90 ± 4.94	11.00 ± 5.05	8.29 ± 4.32	9.00 ± 4.73	6.50 ± 2.35	6.00	17.00	0.180[b]
TBUT, s	6.37 ± 2.34	6.55 ± 2.32	6.28 ± 2.35	6.19 ± 2.50	6.33 ± 2.50	6.83 ± 2.64	4.65	3	0.808[b]
Duration of treatment, mo	22.2 ± 10.5	21.10 ± 11.5	22.88 ± 10.7	23.06 ± 12.1	34.2 ± 4.2	14.0 ± 9.8	19.2	14.4	0.792[b]
Central, µm	50.56 ± 3.26	51.71 ± 2.99	48.50 ± 2.61	52.89 ± 2.38	51.83 ± 2.18	53.42 ± 2.48	55.00	56.00	<0.001[a]
Paracentral, µm	49.66 ± 3.27	50.99 ± 2.64	47.35 ± 2.73	52.16 ± 2.15	51.24 ± 2.01	52.64 ± 2.15	51.63	55.31	<0.001[a]
Mid-peripheral, µm	48.98 ± 3.28	49.92 ± 2.60	47.17 ± 3.22	51.17 ± 2.61	50.65 ± 2.08	52.18 ± 1.84	45.08	54.13	<0.001[a]
Peripheral, µm	48.20 ± 2.95	48.45 ± 2.59	47.25 ± 3.36	49.85 ± 1.67	49.42 ± 2.06	50.64 ± 1.46	45.85	50.31	0.017[a]

[a]One-way ANOVA.
[b]Kruskal-Wallis test.
OSDI, ocular surface disease index; TBUT, tear film breakup time; PGA, prostaglandin analog; CAI, carbonic anhydrase inhibitor.

Table 4. The OSD Data and Corneal Epithelial Thickness of Eyes with Different Treatment Duration

	≤1 y (n = 16)	1–2 y (n = 25)	≥2 y (n = 34)	P Value
Age, y	43.44 ± 14.42	47.40 ± 17.82	48.12 ± 16.89	0.643[a]
OSDI	6.67 ± 10.47	9.81 ± 9.35	10.55 ± 10.70	0.237[b]
Fluorescein staining, grade	0.69 ± 0.95	0.68 ± 0.75	0.82 ± 0.83	0.683[b]
Schirmer I test, mm	9.19 ± 4.07	11.56 ± 5.72	10.24 ± 4.62	0.480[b]
TBUT, s	6.69 ± 2.47	6.95 ± 2.42	5.79 ± 2.14	0.149[b]
Central, μm	52.25 ± 3.71	50.76 ± 3.22	49.61 ± 2.77	0.024[a]
Paracentral, μm	51.29 ± 3.45	49.73 ± 3.45	48.84 ± 2.84	0.046[a]
Mid-peripheral, μm	50.55 ± 2.75	48.87 ± 3.88	48.32 ± 2.86	0.080[a]
Peripheral, μm	49.89 ± 2.18	47.99 ± 3.40	47.56 ± 2.66	0.028[a]

[a]One-way ANOVA.
[b]Kruskal-Wallis test.
OSDI, ocular surface disease index; TBUT, tear film breakup time.

Table 5. The Correlation Between the Influencing Factors and Corneal Epithelial Thickness of Different Sections

	Average		Central		Paracentral		Midperipheral		Peripheral	
	r	P Value	r	P Value	r	P Value	r	P Value	r	P Value
Age, y	−0.435	<0.001	−0.100	0.392	−0.328	0.004	−0.510	<0.001	−0.429	<0.001
Fluorescein staining, grade	−0.207	0.074	−0.234	0.044	−0.261	0.024	−0.204	0.080	−0.106	0.367
No. of medications	−0.274	0.017	−0.341	0.003	−0.395	<0.001	−0.262	0.023	−0.086	0.461
Duration of treatment, mo	−0.264	0.022	−0.303	0.008	−0.249	0.032	−0.223	0.054	−0.276	0.017
No. of drops applied	−0.240	0.038	−0.251	0.030	−0.276	0.016	−0.239	0.039	−0.156	0.183

lated with the average ET in the central ($P = 0.044$) and paracentral zones ($P = 0.024$). The average ET decreased with increasing duration of treatment in the central, paracentral, and peripheral zones (central: $P = 0.008$, paracentral: $P = 0.032$, and periphery: $P = 0.017$). The average ET was significantly related to the number of topical medications (1) and total number of eye drops applied (2) in the central (1: $P = 0.003$ and 2: $P = 0.030$), paracentral (1: $P < 0.001$ and 2: $P = 0.016$), and mid-peripheral zones (1: $P = 0.023$ and 2: $P = 0.039$). However, no significant correlation was observed between the total number of BAK applied and average ET of any analyzed zone.

Effects of Confounding Factors on the ET of Different Analyzed Zones

The multivariate linear regression analysis showed that the average ET of the 9-mm diameter zone was significantly influenced by age ($P < 0.001$) and number of medications ($P = 0.012$). Age had an effect on the mean ET of the paracentral ($P = 0.003$), mid-peripheral ($P < 0.001$), and peripheral zones ($P < 0.001$). The number of topical medications significantly influenced the mean ET in the central ($P = 0.007$), paracentral ($P < 0.001$), and mid-peripheral zones ($P = 0.013$), whereas the duration of treatment only affected the ET of the central ($P = 0.020$) and peripheral zones ($P = 0.031$; Table 6).

Table 6. Influencing Factors on Corneal Epithelial Thickness (μm) of Different Annular Analyzed Zones by Multiple Linear Regression Analysis

Confounding Factor	Average ET		Central		Paracentral		Mid-peripheral		Peripheral	
	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value
Age, y	−0.077	<0.001	–	–	−0.062	0.003	−0.099	<0.001	−0.071	<0.001
Duration of treatment, mo	–	–	−0.075	0.020	–	–	–	–	−0.060	0.031
No. of medications	−1.060	0.012	−1.339	0.007	−1.722	<0.001	−1.104	0.013	–	–

ET, epithelial thickness.

Discussion

The main finding of this study was significantly lower ET in eyes treated with topical antiglaucoma medications than in that in healthy eyes. Patient age, duration of therapy, and number of antiglaucoma medications applied were shown to affect the ET of different analyzed zones in patients with glaucoma.

In previous studies, the "Pachmetrywide" scan mode has been used to map the CET of the 9-mm diameter zone in healthy eyes.[18] The investigators found that the CET was greater in inferior and nasal meridians than in the superior and temporal meridians, and the CET decreased toward the peripheral zones.[19] Similarly, these horizontal and vertical asymmetries were observed in both the patient and control groups in the present study. These findings reconfirmed the accuracy of the 9-mm diameter ET map obtained using this widefield OCT.

Our study showed that the average ET of all 25 sectors across the 9-mm diameter zone was significantly lower in the patient group than in the control group. These results were consistent with those in the studies conducted by Dogan et al. and Montorio et al.[14,15] However, they only described the ET changes in a 6-mm diameter zone; the ET of the peripheral cornea was not examined in their studies. Additionally, we found that the reduction in ET was non-uniform across the 9-mm diameter zone in glaucomatous eyes. Most ET thinning with a decrease >2.5 μm occurred within a 6-mm diameter, except for the superior sectors of the peripheral zone. This phenomenon may be because the proliferation of the peripheral epithelium is more rapid than that of the central epithelium.[20] The remarkable ET thinning in the superior sectors could be explained by the influence of the eyelid and toxicity of antiglaucoma medication. As suggested in previous studies, a greater friction during blinking and the persistent depression of upper eyelid in superior cornea may lead to the epithelial thinning.[21,22] Moreover, we speculated that the long-term usage of antiglaucoma medications could make the epithelium more vulnerable to the mechanical effects of the eyelid.

Although the type, number, and duration of glaucoma medication were considered to affect the CET, findings have been inconsistent among studies.[14] Our results showed that the combination of antiglaucoma medications with PGA led to further ET thinning than treatment with PGA monotherapy. The correlation and linear regression analysis also demonstrated that the number of antiglaucoma medications related to the ET within the 7-mm diameter zone. Similarly, Dogan et al. and Batawi et al.

reported a negative correlation between the number of antiglaucoma medications and CET.[12,14] These observations could be attributed to the effect of active components and the BAK of antiglaucoma drops.

Our study found that the ET was associated with the duration of treatment and number of eye drops applied in the patient group; the ET of the central, paracentral, and peripheral zones was significantly lower in patients treated with antiglaucoma medications for more than 2 years than in those treated for less than 1 year. Multiple linear analysis also revealed that the duration of treatment significantly influenced the ET of the central and peripheral zones. Conversely, previous studies did not find a significant correlation between the treatment duration and amount of ET thinning.[14,15] The authors presumed that the epithelial thinning might happen in the early period of treatment.[15] In a similar study, using a combination of OCT and scanning electron microscopy, Cennamo et al. found that the ET thinning was only observed in glaucomatous eyes with early and mild change in the epithelial microvilli.[13] Taken together, we believe that these conflict between our and previous studies' conclusions might be caused by the difference in treatment duration, where 16 patients treated for less than 12 months were included in this study.

In the present study, the ET of the central zone did not correlate with patient age. This finding is in accordance with a study conducted by Batavi et al. who evaluated the central ET in eyes with primary open-angle glaucoma (POAG) using Cirrus HD-OCT.[12] In contrast, Montorio et al. reported that the CET increases with increasing age. The authors suggested that chronic use of antiglaucoma medications and age-related alterations would induce a decrease in the number of microvilli, which subsequently results in minor epithelial edema and an increase in ET.[15] Moreover, we found for the first time that there were significant correlations between patient age and mean ET in the paracentral, mid-peripheral, and peripheral zones in glaucomatous eyes. Interestingly, Yang et al. and Kim et al. demonstrated that the central CET was less susceptible to the influence of age than the paracentral and mid-peripheral CET in healthy eyes.[23,24] One possible explanation is the decrease in the regenerative capacity of limbal stem cells with aging.[25] Another explanation is the accumulated damage of limbus from sunlight exposure and eyelid blinking,[26] these mechanisms both leads to epithelial thinning in a large part of the cornea. However, the central corneal epithelium itself has the capacity to proliferate and migrate to maintain homeostasis by scattering stem cells across the central cornea; this may explain why age has no effect on central ET.

One major strength of our study is the evaluation of OSD in all participants. The high prevalence of OSD has been reported to be associated with chronic topical antiglaucoma therapy.[4,27,28] Accordingly, our results showed a significant difference in the OSD indicators between patients and healthy controls. The average OSDI score of patients was also comparable to the results of other studies, which was below 12 in patients with mild and moderate glaucoma.[28,29] Interestingly, we found that only the fluorescein staining grade was associated with the ET in the central and paracentral zones, indicating that abnormal fluorescein corneal staining might be a strong predictor of CET thinning. This disagreement between corneal staining severity and OSDI scores was in line with previous studies conducted in glaucoma cohorts.[4,30,31]

Another strength here is the evaluation of ET in the 7–9-mm diameter zone using the novel widefield OCT. To our knowledge, most previous studies merely focused on the ET changes of the 6-mm diameter zone in glaucomatous eyes because of the limitations of former generations of OCT. As shown above, in the present study, the ET of the peripheral zone was not only significantly attenuated, but also related to the duration of treatment and age in patients with glaucoma. These phenomena indicate that the corneal epithelium might be vulnerable in older patients who have long-term use of topical antiglaucoma medications.

This study also had several limitations. First, the thickness of the tear film, which was reported to be 4.79 ± 0.88 μm in a previous study,[32] was included in the ET data in this OCT. The gravity induced nonuniform distribution of tear film may contribute to a falsely thick ET reading in inferior cornea.[33] Second, although a wide variety of patients with glaucoma treated with different antiglaucoma medications were enrolled in this study, the number of patients with non-PGA treatments was relatively small. Finally, because of the cross-sectional design, the precise influence of different antiglaucoma medications on corneal ET could not be evaluated; a prospective longitudinal study with newly diagnosed patients with glaucoma is required in the future to elucidate this matter.

In conclusion, the current study demonstrated a thinner CET in the 9-mm diameter zone in patients treated with topical antiglaucoma drugs than that in healthy controls. We also found that patient age, duration of treatment, and number of medications influenced the CET of different analyzed zones. The wide corneal epithelial thickness mapping could be an effective, convenient, and comprehensive method for assessing the ocular surface damage in glaucomatous eyes, especially in the peripheral cornea. Meanwhile, these results reminded us that it was essential to protect the corneal epithelium from the early stage of topical antiglaucoma treatment, particularly in eyes treated with multiple IOP-lowering medications.

Acknowledgments

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