Clinical Interventions in Aging

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ORIGINAL RESEARCH

Age-Related Changes in Corneal Epithelial Thickness Measured with an Ultrasound Pachymeter

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Background: There is increasing research on the aging process of the cornea and its effect on the corneal parameters measured objectively. Nevertheless, the association of corneal epithelial thickness (CET) with age has yet to be fully illustrated.

Purpose: We aimed to measure CET in healthy subjects to determine its age-related variation by using an ultrasound device.

Patients and Methods: A total of one hundred and three subjects were enrolled in this study and grouped according to age: Group < 30 years, 31–40 years, 41–50 years, 51–60 years, 61–70 years, and > 71 years. The CET and total central corneal thickness (CCT) of each subject were measured by the Sonogage Corneo-Gage Plus 2 (Cleveland, Ohio) ultrasound pachymeter. The relationships between thickness values, laterality, age groups, and gender were analyzed using the Jonckheere-Terpstra test. The Partial correlation test was employed to assess the effect of age on the CET and CCT.

Results: The mean CET was 47.88±1.15μm, with no statistically significant gender-related difference between right and left eyes. In addition, the CCT difference detected between female and male eyes was insignificant. The difference in mean CET across age groups was statistically significant (p =0.029). The difference in mean CET of left eyes across age groups was statistically significant (p=0.031). The mean CET and left CET of the oldest group were significantly thinner than the younger groups.

Conclusion: Ultrasound pachymeter of the corneal epithelium demonstrated that there was no correlation between age and CCT, or gender. The CET becomes thinner with age in the central zone in both genders and there is no difference between males and females. Based on these results, age has a negative effect on CET. These findings could offer further insight into age-related changes in the cornea.

Keywords: aging, cornea, epithelium, gender, pachymeter, ultrasound

Introduction

The corneal epithelium has a role in determining total corneal refractive power. Its structure is altered under various pathologies such as keratectasia, contact lens usage, keratoconjunctivitis sicca, and limbal stem cell deficiency.[1]

A complete understanding of the biological features of the corneal epithelium may provide greater insight into normal and diseased ocular surfaces.[2]

Concordantly, there is increasing research on the aging process of the cornea, and its effect on the corneal parameters that can be objectively measured. Various imaging methods, such as confocal microscopy, very high frequency (VHF) ultrasound, and optical pachymetry have been used to measure the average thickness of the corneal epithelium (CET).[3]

Nevertheless, an association of the CET with age has yet to be fully illustrated. Some authors who used VHF digital ultrasound and spectral domain- optical coherence tomography (OCT) reported no correlation between CET and age,[4,5] but another large-scale study reported a statistically significant decrease in CET with age.[2]

Two recent studies using OCT found that the CET becomes thinner with increasing age in the paracentral and mid-peripheral zones. The authors using spectral domain-anterior segment OCT also reported that there is a reduction in epithelial thickness in the central zone.[1,6]

Received: 10 June 2022
Accepted: 6 September 2022
Published: 28 September 2022

The reasons for these variable results may be related to different study populations and measurement techniques.[7]

One possible reason for the lack of consistency in the results of older studies is omitting the control of confounding factors having the potential to affect CET measurements. For example, gender should be controlled when the study objective is to evaluate the correlation between the CET and age, because studies reported the corneal epithelium being thinner in women than in men.[1] Another study found no significant difference between males and females regarding CET in all age groups.[6]

Both VHF digital ultrasound and confocal microscopy use invasive techniques needing, anesthesia. The noncontact and high-speed features make Spectral Domain-OCT a preferred device for measuring CET.[8] However, it is a limitation that the tear film is included in the CET value measured by OCT,[7] whereas the tear film is not included by VHF ultrasound devices with examinations being accomplished under normal saline immersion.[9]

This study aimed to determine age-related changes in CET in healthy individuals using a VHF ultrasound pachymeter after controlling for gender.

Materials and Method

In this cross-sectional observational study, the subjects were recruited from a population of individuals seeking routine eye examination at the ophthalmology outpatient clinic of the Altintepe Medical Center, Istanbul, Turkey, between November 2012 and June 2013.

Exclusion criteria included history of ocular surface or intraocular surgery and the use of topical and systemic medications that could potentially disrupt the ocular surface health, contact lens use, suspicion of keratectasia, ongoing anterior segment pathology, ocular disease having the potential to alter the optical property or preclude proper viewing of the fixation target of the measuring devices, and a best-corrected visual acuity worse than 20/40. Before inclusion in the study, all subjects underwent a complete ocular examination that included assessment of the manifest refraction, corneal topography, biomicroscopy, applanation tonometry, and indirect ophthalmoscopy. Topography and keratometry were assessed using Orbscan II (Bausch & Lomb, Salt Lake City, Utah).

Ethics Approval and Consent to Participate

Informed consent was obtained from each subject after a thorough explanation. The ethical approval has been taken from Turkish Red Crescent Association, Altintepe Medical Center, Clinical Research Ethics Review Committee. This ethics committee was affiliated with the Provincial Education and Training Hospital Institutional Ethics Committee, Turkey (56 / Ethics / 2012).

Human and Animal Rights

No animals were used for studies that are the basis of this research. This research was conducted on humans in accordance with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

Power Calculation and Sample Size

Subjects were divided into six age groups: < 30, 31–40, 41–50, 51–60, 61–70, and > 71 years.

The size of each age group was determined based on a rule of thumb (10 cases per predictor).[10]

However, we were not able to recruit 20 cases for the oldest group as planned. G*Power (version 3.1.9.7) software (17 March 2020 - Release) was used to calculate the achieved power of the obtained sample size.

Simple linear regression was used to determine a potential association between age and corneal epithelial thickness, and the adjusted r^2 value was found to be 0.139. The power calculation is based on the adjusted r^2 value (obtained from this linear regression analysis), a sample size of 206 eyes (103 healthy participants), ($\alpha = 0.05$), *F*-test, and 2 predictors (including age and central corneal thickness). The effect size was automatically calculated based on r^2 where the effect size $f^2 = (1/1- r^2)$. For adjusted $r^2 = 0.139$, the effect size of $f^2 = 0.16$ was in the medium range.

A priori power analysis calculated the total sample size required for the study as 63. The achieved actual power (1-β) was (0.80), indicating a good power and therefore an adequate sample size. Because of the aforementioned calculation and as regarded by the researchers,[11] we aimed to recruit at least 120 samples as the minimum size.

Single-point, hand-held central corneal thickness (CCT) and CET measurements were taken with a VHF ultrasound pachymeter (Corneo-Gage Plus 2, Sonogage, Cleveland, Ohio), which has a 50-MHz transducer and higher resolution than conventional 20-MHz pachymeter, enabling it to measure CET in addition to CCT.[12]

The pachymeter was calibrated in advance of each reading. The subject was seated with the head upright and eyes in the primary position of gaze. After a topical anesthetic drop, proparacaine hydrochloride 0.5% ophthalmic solution (Alcaine ®) was instilled in the eyes, the probe was carefully aligned perpendicularly to and lightly touching the cornea. This pachymeter allows only a 5-degree angulation margin to permit the best measurements, which helps to achieve a more consistent perpendicular probe position.[13]

All measurements were performed by an experienced ophthalmic technician between 10.00 am and 12.00 pm and at least 2 hours after eye-opening to keep diurnal variation to a minimum. The first measurement was omitted, and the probe remained touching the cornea until continuous measurements were grouped within 5 µm. The smallest of these measurements was taken as the CCT.[14] CCT values were recorded in microns.

Ultrasound CET measurement was performed first. At least 10 measurements of CET were made for each of the average recorded values. CCT was measured by determining the minimum of 10 consecutive central corneal measurements.

Statistical Analysis

Statistical analysis of data was performed using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY).

Before beginning analysis, the right and left eyes of the population were selected at random using Microsoft Excel's random number function for the CCT and CET of the right and left eyes. While the normality of the distribution was verified using the Shapiro Wilk test, homogeneity of variance was assessed using Levene's Test for Equality of Variances. A bootstrapped independent samples *t*-test was used to proceed with the comparison of two independent groups according to quantitative data analysis. Comparisons between groups were conducted with the Mann–Whitney *U*-test with significance tested by Monte Carlo simulation. The nonparametric Jonckheere-Terpstra test with significance tested by Monte Carlo simulation was used to compare more than two groups according to quantitative data analysis, and subsequently, post hoc Dunn's test was applied. Quade's non-parametric analysis of covariance was used to test the interaction effects of factors, i.e., gender with two levels and age with six levels in CCT and CET. A partial correlation test was used to determine the association of age with CCT and CET after controlling for gender.

A summary of quantitative variables is presented in tables as average (standard deviation), range (minimum-maximum), and median (25th percentile – 75th percentile). The data were analyzed with a 95% confidence level, and a p-value of less than 0.05 was considered to be statistically significant.

Results

A total of 206 eyes of 103 healthy subjects (72 women, 31 men) with a mean age of 48.87 ± 18.36 years for males and 49.18±15.77 for females took part in the study (Table 1).

Table 1 shows the descriptive statistics of the measured variables. Mean CET measurements were 47.68±0.99µm and 47.93±1.2µm in male and female subjects, respectively (Table 1).

The central CET and CCT values did not differ significantly between the men and women in the study (Table 2).

The differences between CCT and CET between the right and left eyes were calculated and described in Table 2. The average CCT of the right eye was thinner than that of the left eye in the total subject and female subject groups, and this difference was statistically significant (p = 0.001 and p=0.003, respectively). There were no significant differences between the CET of the right and left eyes in the total and gender subject groups (Table 2).

Analysis of the relationship between CCT, CET, and left, and right eyes are tabulated in Table 3. The mean (±standard deviation) CET for all eyes was 47.88±1.15µm. CET ranged from 46 to 52µm for all eyes (Table 3). The mean (±standard deviation) CET was 47.91±1.16µm for right eyes and 47.8±1.12µm for left eyes (Table 4).

Table 5 shows the distribution of the median right, left, and total CET and CCT of the total subjects in different age groups. There is a statistically significant difference in randomly chosen CET between age groups (p=0.029). Comparing

Table 1 Statistics of Measured Variables from All Subjects

Variable	Females	(n = 72)	Males	(n = 31)
	Mean ± SD	Range	Mean ± SD	Range
CET, µm	47.93±1.2	46–52	47.68±0.99	46–50
CCT, µm	545±34.43	479–648	545.55±33.34	459–598
Age, y	49.18±15.77	17–81	48.87±18.36	16–82

Table 2 Gender Differences in CET and CCT

	Total	Female	Male	p
Subject number(n)	103	72	31	
Subject age Mean (SD.) (min - max)	49.09 (16.50) (16–82)	49.18 (15.77) (17–81)	48.87 (18.36) 16–82)	0.932 t
CCT* Median (q1 / q3)	537 (521 / 571)	534 (521 / 564.5)	540 (520 / 578)	0.583u
CET* Median (q1 / q3)	48 (47/49)	48 (47/49)	48 (47/49)	0.578u
Right CCT* Median (q1 / q3)	537 (518/567)	534.5 (519.5 / 563)	541 (513 / 578)	0.799u
Left CCT* Median (q1 / q3)	540 (521 / 571)	536.5 (521 / 567.5)	543 (520 / 579)	0.687u
p value (right vs left)	0.001w	0.003w	0.238w	
Right CET* Median (q1 / q3)	48 47/49)	48 (47/49)	48 47/48)	0.393u
Left CET* Median (q1 / q3)	48 (47/48)	48 (47/48)	47 (47/48)	0.535u
p value (right vs left)	0.322w	0.273w	0.940w	

Notes: t Independent samples *t*-test (Bootstrap), u Mann Whitney *U*-test (Monte Carlo),w Wilcoxon Signed Ranks Test (Monte Carlo). q1: percentile 25, q3: percentile 75, * randomly selected between right and left sides.
Abbreviation: SD, standard deviation.

Table 3 Measured Variables in the Present Study

Variable	Mean ± SD	Range
CET (µm)	47.88 ± 1.15	46–52
CCT (µm)	545.17 ± 34.03	459–648

Table 4 Statistics of Measured Variables According to All Right versus All Left Eyes

Variable	Right Eyes Mean ± SD	Left Eyes Mean ± SD
CET (µm)	47.91±1.16	47.8±1.12
CCT (µm)	544.8±34.35	545.53±33.87

Table 5 CCT and CET in All Right and All Left Eyes According to Age Groups

		Right CCT Median (q1/q3)	Left CCT Median (q1/q3)	Right CET Median (q1/q3)	Left CET Median (q1/q3)	CCT* Median (q1/q3)	CET* Median (q1/q3)
Age group (years)	≤30 n=32	529 (518.5/569.5)	530 (522/568)	48 (47/48.5)	48 (47/48)	530 (521/569.5)	48 (47/49)
	31–40 n=26	530 (512/537)	531 (511/540)	48 (47/48)	48 (47/49)	529 (511/537)	48 (48/49)
	41–50 n=48	536.5 (519/570.5)	539 (522.5/578)	48 (47/49	48 (47/49)	537 (521.5/575)	48 (47/49)
	51–60 n=42	555 (536/562)	555 (538/568)	48 (47/49)	48 (47/48)	555 (536/562)	48 (47/49)
	61–70 n=40	536.5 (513/566)	537 (512/575)	47.5 (47/49)	47.5 (47/48)	536.5 (513/575)	48 (47/49)
	>70 n=18	545 (513/570)	544 (516/567)	47 (47/47)	47 (46/47)	545 (516/570)	47 (47/47)
	p value	0.344	0.535	0.123	0.031	0.444	0.029
Pairwise Comparisons	>70 vs ≤30	ns.	ns.	ns.	0.008	ns.	0.004
	>70 vs 31–40	ns.	ns.	ns.	0.003	ns.	0.007
	>70 vs 41–50	ns.	ns.	ns.	0.003	ns.	0.003
	>70 vs 51–60	ns.	ns.	ns.	0.011	ns.	0.01
	>70 vs 61–70	ns.	ns.	ns.	0.036	ns.	0.018
	All other Comparisons	ns.	ns.	ns.	ns.	ns.	ns.

Notes: Jonckheere-Terpstra Test (monte carlo); Post Hoc Test: Dunn's Test, q1: percentile 25, q3: percentile 75, *Randomly selected between right and left sides, ns.:not significant.

the measured parameters in the 2 age groups, ie, above 70 years old and each younger age group revealed a statistically significant difference with lower CET values in the > 70 group ($p < 0.05$). The Left CET displayed a similar significance between the > 70 and each younger age group ($p = 0.031$) (Table 5).

Box plots reveal the correlation between age groups and CET and the left CET (Figure 1 and 2, respectively). The line within the box marks the median. The boundaries of the box indicate the 25th and 75th percentiles.

As can be deduced from the table below, there was no statistically significant difference between males and females regarding CCT and CET in all groups of age. Likewise, there were no interaction effects of age and gender on CCT and CET, meaning that trends in age-related thickness changes were very similar for males and females (p=0.575) (Table 6).

A significant negative correlation between left CET and randomly selected CET with age was found in our study (r= −0.203, p=0.041 and r=−0.215, p=0.030, respectively) (Table 7).

Discussion

With the advent of new ophthalmic instrumentation, the measurement of the CET has been facilitated in routine clinical practice. Using an ultrasound prototype, Reinstein et al measured the average CET as 50.7±3.7μm.[4] Similarly, by using a VHF pachymeter, we found the mean CET in 206 normal eyes to be 47.88±1.15μm. The difference between the mean thickness values of Reinstein et al's and ours may be due to the thinning effect of Benzalkonium Chloride containing Proparacaine solution used to numb the cornea in the present study. In previous research, corneal epithelium was found to be significantly less thick in glaucoma patients receiving eyedrops and was influenced by the use of β-blockers, prostaglandin analogs, and Benzalkonium Chloride.[7]

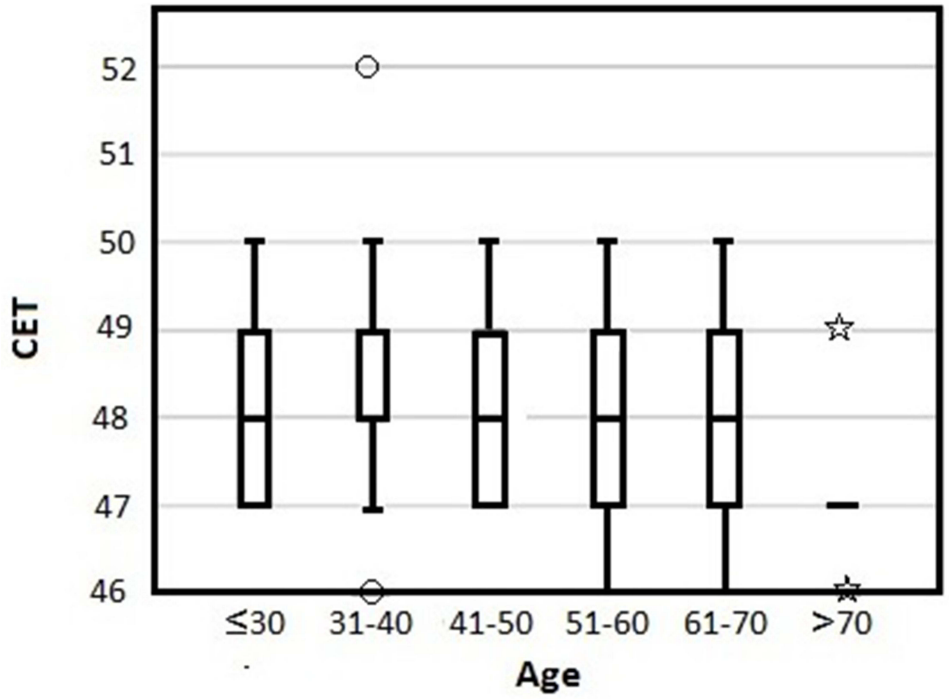

Figure 1 The correlation between age groups and CET.

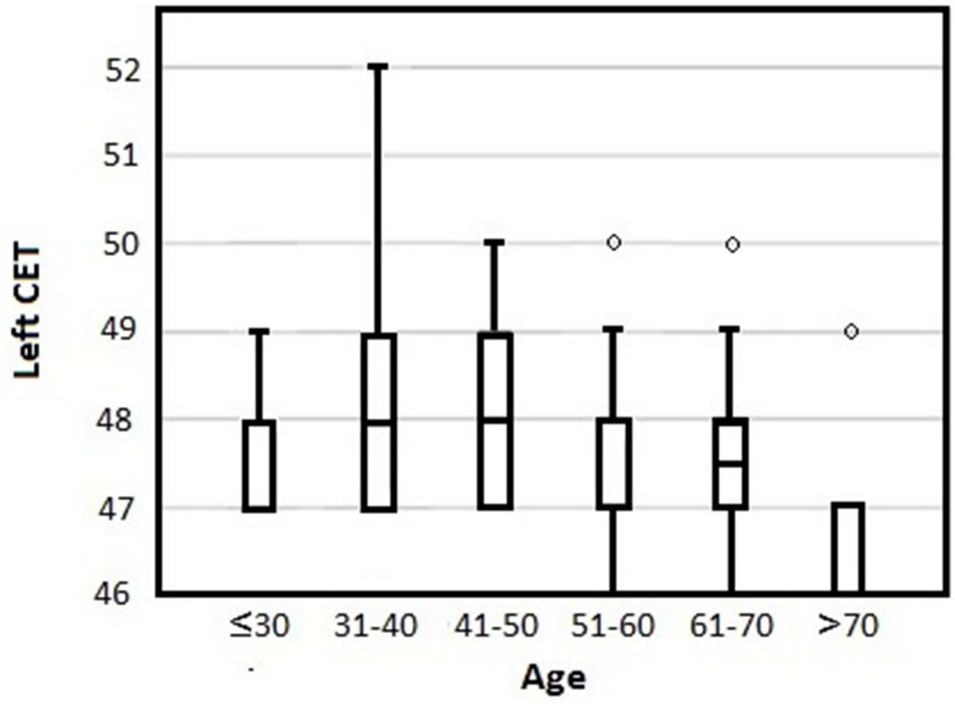

Figure 2 The correlation between age groups and the left CET.

CET has been previously reported to vary between 48±5 μm and 59.9±5.9 μm.[4] The mean CET value found in our study falls outside of the low end of this range formed by a variety of measurement techniques.

Furthermore, the possible factors that could influence CET include many demographic, ethnic, and ophthalmic characteristics. The effect of age on CET has yet to be fully revealed.[6]

Table 6 Variation of the CCT and CET Between Males and Females of the Same Age Group

		Right CCT Median (q1/q3)	Left CCT Median (q1/q3)	Right CET Median (q1/q3)	Left CET Median (q1/q3)	CCT* Median (q1/q3)	CET* Median (q1/q3)
Female							
Age groups	≤30	532 (524/571)	532 (527/571)	48 (47/49)	48 (47/48)	532 (524/571)	48 (47/49)
	31–40	524 (512/532)	529 (511/533)	48 (47/48)	48 (47/49)	524 (511/530)	48 (48/49)
	41–50	530.5 (518/551)	535 (522/550)	48 (47/49)	48 (47/48)	531.5 (521/550)	48 (47/49)
	51–60	556 (536/562)	558 (538/568)	48 (47/49)	48 (47/49)	556 (536/562)	48 (47/49)
	61–70	534 (515/568)	532 (511/576)	47 (47/49)	48 (47/49)	534 (515/576)	48 (47/49)
	>70	545 (516/567)	544 (516/567)	47 (47/47)	47 (47/47)	545 (516/567)	47 (47/47)
p value		0.315	0.491	0.243	0.147	0.356	0.078
Male							
Age groups	≤30	518.5 (510/568)	525 (518/565)	48 (47/48)	47.5 (47/48)	525 (518/568)	48 (47/49)
	31–40	540.5 (522/562)	545.5 (525/565)	47.5 (46.5/48)	48 (47.5/49)	544 (523.5/565.5)	48 (47.5/48)
	41–50	556.5 (534/578)	563 (529/584)	48 (48/49)	48.5 (47/49)	561 (534/578)	48.5 (48/49)
	51–60	546.5 (535/583)	545.5 (532/583)	47.5 (47/48)	47 (47/48)	545.5 (535/583)	47.5 (47/48)
	61–70	539 (511/555)	543 (513/555)	48 (47/49)	47 (47/48)	539 (511/555)	48 (47/48)
	>70	541.5 (501.5/574)	548 (510.5/573)	47 (47/47)	46.5 (46/48)	549.5 (509.5/574.5)	47 (46.5/48)
p value		0.775	0.850	0.308	0.118	0.894	0.240

Notes: p (gender*age)=0.575 q. Jonckheere-Terpstra Test (monte carlo); Post Hoc Test: Dunn's Test, q1: percentile 25, q3: percentile 75, *Randomly selected between right and left sides.

Table 7 Correlations of Age with CCT and CET

Age	r	p
Right CCT	0.025	0.8
Left CCT	0.015	0.881
Right CET	−0.135	0.176
Left CET	−0.203	**0.041**
CCT*	0.03	0.768
CET*	−0.215	**0.03**

Notes: Partial Correlation Test, r: Correlation coefficient, *Randomly selected between right and left sides.

The mean CET for the right eyes was higher than the thickness for the left eyes, without any statistical significance. Wu and Wang reported a statistically insignificant thinner epithelial thickness of the right eye than the left eye in myopic eyes.[8] We can deduce from these findings that there is no lateral predilection for CET.

Many articles have reported the male cornea is thicker than the female cornea.[2] The present study findings parallel these reports, but the gender difference in this study was of no statistical significance.

In their study, Samy et al controlled gender to look for the correlation of CET with age[6] because there are some reports of the cornea being thinner in women than in men.[1] Our data do not confirm these reports and show that the CET was almost the same in both genders, male mean CET measurement (47.68±0.99 μm) being smaller than the female one (47.93±1.2 μm) with no statistical significance. Samy et al found no statistically significant gender differences regarding CET in all the measured areas in all groups of age. There was significant thinning in the central zone in both genders in

different age groups. Thinning of the central 2 mm of CET, a finding of their study,[6] is defined as an uncommon one not reported in the relevant articles.[1]

The present study also has a strength in that we controlled for gender when assessing the correlation between age and CET. In addition, we included in the present study only healthy Turkish subjects of all ages; hence ethnicity was not expected to be a potential confounder.

While Yang et al reported thinning of the CET with age, in a study including healthy Korean subjects, the results demonstrated that the CET did thin with age in paracentral and mid-peripheral except for the central zone.[1,2] Other studies report no correlation between the CET and age.[4,15]

The lack of consistency may be due to the omission of controlling for confounding factors affecting CET assessment. Our results are in agreement with the remarks of researchers reporting a decrease in CET with aging.

Declining metabolic function of the epithelia, and increased local inflammation associated with hormonal changes that occur with aging may both play a role in the thinning that occurs with aging.[16,17]

Kim et al stated that age seemed to not affect the central CET in their study population, and proposed that the central corneal epithelium is less susceptible to the aging effects. The corneal epithelium is sustained by limbal stem cells. The proliferative capacity of these cells has been noted to be reduced with age, which may lead to thinner corneal epithelium in the elderly.[1]

The probe tip displaces the tear film, which may result in thinner CET measurements. The location of the anterior echo reflecting surface may be altered by the applanating probe: the precorneal tear film may be displaced laterally and the epithelium may be thinned by compression.[18]

This is a presumptive limitation of US epithelial thickness assessment and a source of possible uncertainty in our results. Despite this limitation, in contrast to CCT measurements including the stromal layer, the probable compressive effect on the epithelium, containing less compressible epithelial cells only, should be negligible.

Given the fact that the anterior segment OCT is not able to recognize the tear film layer, the inclusion of tear film in epithelial thickness measurements cannot be overemphasized.[19] In that sense, our method could be considered superior to techniques employing anterior segment OCT assessments.

Although there have been studies reporting a higher prevalence of dry eye with age, the evidence is still limited regarding whether the thinner corneal epithelium is related to a tear film thickness decrement.[1]

Subjects with dry eye disease may have been recruited in the older age group. However, the presumption that the observed thinner corneal epithelium in old age is biased by a decrease in tear film thickness is unlikely in our study because of the point contact nature of the probe tip. In a recent report, Kim et al employed anterior segment OCT, a noninvasive technique that measures the tear film and epithelial layer together. Based on their results, Kim et al believed that thinning of the CET with age was not associated with a decrease in tear film thickness. They believed that the likelihood of the reported thinner corneal epithelium in the elderly group being confounded by a decrease in tear film thickness was low, given previous research revealing thicker epithelium in patients with dry eye disease than in normal subjects.[1,20]

Because of the invasive nature of our method, we decided not to use the refractive error of participants as an exclusion criterion to achieve as high a participation rate as possible. Although a potential variable that could affect CET is refractive status, no reports of a correlation between refractive defect and CET have been reported yet.[6,21] Although Ozalp et al[22] reported thinning in corneal epithelial thickness in all quadrants, it was statistically significant only in the superior and superonasal quadrants at the 2–5 mm and 5–6 mm-diameter rings but not in the central 2 mm area that was the area of interest in our study.

Our study has several limitations; namely, the relatively small sample size of some of the age groups. Secondly, our technique is invasive and needs an anesthetic. This may increase the risk of infection and decrease the precision of measurement because of the possible yet not probable contact-related epithelial compression by the probe coming in contact with the cornea.[8]

In general, ocular parameters and more specific corneal parameters are influenced by multiple factors other than age and gender, such as race.[23,24]

Future studies could investigate ethnic variation in the corneal epithelial thickness along with age and gender to set up a race-specific normal range and find the exact effect of race on this critical corneal parameter.

Our research only studied the CET in the central area. It would be interesting to have more studies investigating the central as well as the more peripheral epithelial thickness since some studies revealed prominent thinning of the mid-peripheral CET with age.[1,22]

Conclusion

In conclusion, age seems to influence CET, being negatively associated with aging. These findings could be valuable in corneal refractive interventions, especially in elderly subjects. Knowledge of the age-related changes in epithelial thickness in the normal corneas should help in understanding the corneal aging process, as well as improving the diagnosis of corneal diseases. The advent of state-of-the-art non-invasive imaging modalities having the potential for higher resolution with the capability to differentiate tear film layer from ep'thel'al t'ssue will make it possible to evaluate CET in more detail and confirm its correlative status with aging.

Abbreviations

CET, corneal epithelial thickness; VHF, very high frequency; CCT, central corneal thickness; OCT, optical coherence tomography.

Data Sharing Statement

The data supporting the findings of the article is available within the article.

Acknowledgments

The authors thank the technician, Alaaddin Sari, for his contributions; Huseyin Candan for statistical analysis.

Disclosure

The authors declare no conflicts of interest, financial or otherwise.

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