

Effect of Age and Gender on Corneal Epithelial Thickness in Refractive Surgery Candidates

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Purpose: To investigate the effect of age and gender on corneal epithelial thickness in healthy refractive surgery candidates.

Methods: A retrospective, single-centered cross-sectional study in which we used the Anterior Segment (AS-OCT), MS39 -a device well-suited for corneal epithelial assessment, to measure the corneal epithelial thickness (CET) at five anatomical regions: the central zone and four peripheral quadrants (superior, inferior, nasal, and temporal) in consecutive healthy individuals evaluated for refractive surgery evaluation.

Results: A total of 181 right eyes of individuals were divided into two groups based on their gender, and further into their age groups. The CET was significantly thicker in males compared to females in all four quadrants ($p < 0.005$). Age also influenced the epithelial thickness, as with increasing age there was a thicker CET, in the inferior ($p < 0.05$), nasal ($p < 0.05$), temporal ($p < 0.001$) and superior quadrants ($p < 0.05$). No significant correlation was found with the central CET ($p = 0.06$).

Conclusion: Corneal epithelial thickness varies between males and females in all quadrants with males having significantly thicker epithelium. In addition, age is a factor that significantly influences the CET, showing an increase with advancing age. Refractive surgeons should take this into consideration especially when planning transepithelial refractive procedures.

Keywords: cornea, epithelium, thickness, gender, age

Introduction

The cornea, consisting of five main layers, is the anterior transparent covering of the eye that refracts light to the photoreceptors of the retina.¹ The outermost layer of the cornea, the corneal epithelium (CE) has the remarkable ability to regenerate with a complete turnover every 6 days on average.^{1,2} Given its critical role in the healing process after refractive surgery, the thickness, shape, and remodeling effect of the corneal epithelium are important factors to consider in ensuring the accuracy and predictability of refractive surgeries.³

Refractive surgery, such as laser-assisted in situ keratomileusis (LASIK) and transepithelial photorefractive keratectomy (t-PRK), is popular for correcting visual impairments such as myopia, hyperopia, and astigmatism.⁴ Thus, it is important to understand the various factors that can impact the accuracy and predictability of these procedures. One such factor is the corneal epithelial thickness (CET), which plays a crucial role in the healing process after surgery.⁵ Recent studies have demonstrated that the CET can affect postoperative refraction and that astigmatic correction might be reduced in patients with thick epithelium.⁶

There are several imaging modalities to measure the CET, including very high-frequency ultrasound⁷ and confocal microscopy,⁸ however, the recently introduced spectral domain-anterior segment optical coherence tomography (AS-OCT), can measure the CET in a non-contact fashion with high repeatability and accuracy.^{9,10} AS-OCT, combines

spectral-domain OCT with Placido disc corneal topography, provides information about epithelial thickness, corneal elevation, pachymetry, and dioptric power.¹¹ In this study, we used the AS-OCT, MS-39, a device well-suited for corneal epithelial assessment, which integrates these capabilities and has been shown to offer reliable and reproducible measurements in clinical settings.¹²

Previous studies have suggested that CET may be influenced by factors such as gender and age, however, the results of these studies have been inconsistent.^{12–14} In addition, to date, there has been a lack of research that specifically examines healthy individuals who seek refractive surgery, as prior studies have been conducted on individuals from various age groups, but not those who are candidates for refractive surgery.

Candidates for refractive surgery are a distinct group due to strict ocular and systemic eligibility criteria, including stable refraction, sufficient corneal thickness, and normal corneal topography, with exclusion factors such as keratoconus, high refractive errors, elevated IOP and systemic conditions that may affect healing.^{15,16} Additionally, they often have unique psychosocial characteristics, including high motivation to reduce dependence on glasses but sometimes unrealistic expectations and low tolerance for postoperative complications.¹⁶ Their elective status and need for rigorous screening highlight the importance of careful assessment to ensure safety and patient satisfaction.¹⁷

In this study, we investigated how the CET is affected by gender and age in healthy refractive surgery candidates.

Methods

This retrospective, single-centered cross-sectional study was conducted at the Care-Vision Laser Center, Tel-Aviv, Israel, and approved by the Barzilai Medical's center ethics committee. Patient informed consent was not required, as the study was retrospective and based solely on anonymized data. Confidentiality was ensured according to institutional and ethical standards. This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

181 Israeli candidates for refractive surgery, aged 18 to 60, who came to the clinic consecutively for pre-refractive surgery evaluation were included. The data were collected between January 2019 and April 2023. Only the right eye data used for this study, but both eyes were measured by anterior segment optical coherence tomography (AS-OCT, MS-39 CSO, Scandicci, Italy). The right eye was selected to avoid inter-eye correlation and to ensure statistical independence of the data points, as measurements from both eyes of the same subject are not truly independent. This method is commonly applied in ophthalmic studies assessing corneal and epithelial thickness using OCT devices.^{18,19}

CET was measured using the MS-39 with an axial resolution of approximately 3–5 μm , enabling precise epithelial mapping. Scans were performed in a controlled setting with patients seated comfortably and fixating on an internal target. For each eye, three consecutive scans were acquired, and the mean value was used for analysis. Quadrants were defined as superior, inferior, nasal, and temporal, in addition to the central zone.

During the evaluation, we also measured: refraction, uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), pachymetry, slit lamp examination, tonometry, and tomography.

We included in this study candidates for refractive surgery between the ages of 18–60. The exclusion criteria were any previous ocular surgery, history of cataracts, vitreoretinal disease, visual field loss as indicated by clinical examination, glaucoma, ocular hypertension amblyopia evidence of systemic disease, or pregnancy. Furthermore, patients with any corneal abnormalities, scars or diseases, dystrophies, keratoconus, and form fruste keratoconus were excluded as well. The data was collected using Microsoft Excel version 16.0 (Microsoft Corporation, Redmond, Washington, USA).

Statistical Analysis

The data are presented as mean and standard deviation for quantitative variables and as frequencies and percentages for categorical variables.

The associations between gender and clinical measurements for each age segment were examined using either a *t*-test for independent samples or Pearson correlation as appropriate.

P-values <0.05 were considered statistically significant.

The demographic information and data were compiled using Microsoft Excel 16.0. Data were analyzed using IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp.

Results

In our study, a total of 181 right eyes of individuals were divided into 2 groups based on their gender with 87 males and 94 females, and further into two age groups of 18–30 and 31–60. Corneal epithelial thickness (CET) was measured in various regions and was found to be significantly thicker in males compared to females in all quadrants ($p < 0.05$, Figure 1A). In the central region, males exhibited a CET that was $3.07 \mu\text{m}$ thicker than females ($P < 0.001$). Similarly, in the superior quadrant, males had a CET that was $3.28 \mu\text{m}$ thicker than females ($P < 0.001$), while in the nasal quadrant, the difference was $2.65 \mu\text{m}$ with males having a thicker CET ($P < 0.001$). In the inferior quadrant, males displayed a CET that was $2.93 \mu\text{m}$ thicker than females ($P < 0.005$), and in the temporal quadrant, males had a CET that was $3.51 \mu\text{m}$ thicker than females ($P < 0.001$, Figure 1B and C). The pachymetry measurements showed that males had an average corneal thickness of $538.73 \mu\text{m}$, while females averaged $528.51 \mu\text{m}$ ($P < 0.05$).

In the 18–30 age group, there were 59 participants, while the 31–60 age group included 122 participants. Significant age-related differences in epithelial thickness were observed, with older age associated with thicker epithelium in all quadrants except the central zone, where the thickness was greater but did not reach statistical significance (Figure 2A). In the central region, the older group exhibited a CET that was $0.88 \mu\text{m}$ thicker than the younger group ($P = 0.06$). In the superior quadrant, the older group had a CET that was $1.98 \mu\text{m}$ thicker than the younger group ($P < 0.05$), while in the nasal quadrant, the difference was $1.99 \mu\text{m}$ with the older group exhibiting a thicker CET ($P < 0.005$). In the inferior quadrant, the older group had a CET that was $3.12 \mu\text{m}$ thicker than the younger group ($P < 0.005$), and in the temporal

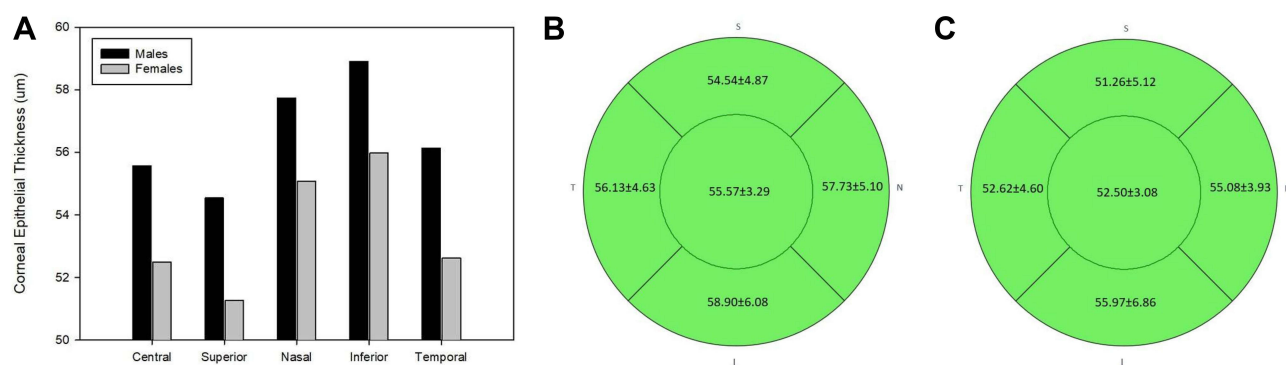


Figure 1 (A) depicts the CET for males and females in the various corneal regions. (B) depicts the epithelial thickness maps for males. (C) depicts the epithelial thickness maps for females.

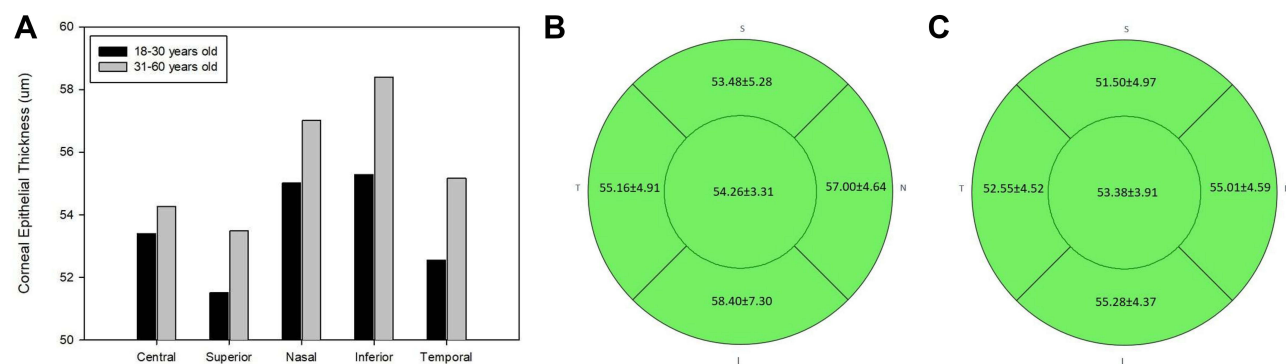


Figure 2 (A) depicts the CET for the age group in the various corneal regions. (B) depicts epithelial thickness maps for the older group. (C) depicts epithelial thickness maps for the younger group.

quadrant, the older group had a CET that was 2.61 μm thicker than the younger group ($P < 0.001$, Figure 2B and C). The pachymetry measurements showed that the older group had an average corneal thickness of 532.63 μm , while the younger group had an average of 535.06 μm . However, this difference was not statistically significant ($p = 0.32$).

Discussion

The CE plays a crucial role in maintaining the integrity and function of the cornea. It acts as a first line of defense against external threats, and its thickness affects the cornea's optical properties.^{1,20} CE thickness distribution has clinical significance, particularly in refractive surgery such as Trans-PRK planning, and it also influences postoperative refraction.^{21–24}

The impact of age and sex on CE thickness, particularly in healthy individuals undergoing refractive surgery, remains unclear as past studies' results were inconclusive.^{25–27}

The aim of our study was to provide insights into the variation of CE thickness in different age and gender groups. Examining refractive surgery candidates, we aimed to provide important information for the surgical planning of refractive surgery procedures. Previous studies have shown that the corneal epithelium may compensate for underlying stromal irregularities or localized thinning. As this relationship has already been well-established, our focus was placed specifically on mapping epithelial thickness across age and gender groups, rather than re-evaluating the correlation with stromal thickness.^{8,28}

The results of our study, suggest that there is a significant difference in corneal epithelial thickness between males and females, with males having thicker corneal epithelium.

A study that could support the results of our study was conducted by Mohammad Abusamak²⁹ aimed to examine the intricate mapping features of corneal epithelial thickness (CET) in healthy eyes of a Middle Eastern population in association with age, gender, intraocular pressure, and keratometric power (K). A retrospective, cross-sectional, and analytical investigation was carried out using SD-OCT. CET was measured in 124 participants across 17 regions within a 6 mm diameter circle. The central CET was denser in the central 2 mm than in other corneal areas, except for the nasal, inferior-nasal, inferior, and inferior-temporal zones. Similar to our study males exhibited a thicker CET than females in all regions except the peripheral nasal area. As in our study, they also report a positive correlation between age and CET in the superior, inferior, nasal and temporal paracentral zones.

A similar study that looked at age and CET changes was conducted by Colakoglu and Cosar.³⁰ In this study, 103 participants were enrolled and classified according to age groups: below 30 years, 31–40 years, 41–50 years, 51–60 years, 61–70 years, and over 71 years. The corneal epithelial thickness (CET) and total central corneal thickness (CCT) of each participant were assessed using the Sonogage Corneo-Gage Plus 2 ultrasound pachymeter.

The average CET was measured at $47.88 \pm 1.15 \mu\text{m}$, and there was no statistically significant difference between right and left eyes based on gender. Furthermore, there was no significant difference in CCT observed between male and female eyes. The difference in mean CET across age groups was statistically significant but unlike our results, it was thinner in the oldest group ($p = 0.029$). Furthermore, the CET becomes thinner with age in the central zone in both genders. This is in contradiction to our study that found that there is no significance change in central CET with age and a significant association between gender and CET. One possible explanation for this discrepancy could be the utilization of AS-OCT in our study, as opposed to the use of ultrasound pachymetry in their study which does not include the tear film in the measurements. However, with US pachymetry the location of the anterior 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.³¹ Thus the non-contact AS OCT might be more accurate.

Another study conducted by Samy, Shaaban, and Badran²⁵ has revealed gender and age-related differences in corneal epithelial thickness among Egyptians. The authors used SD-AS OCT to measure corneal epithelial thickness in a group of healthy adults. In this cross-sectional observational study, 240 eyes from 120 healthy individuals (60 men, 60 women) were examined. Each gender was divided into four age groups: 18–29 years, 30–44 years, 45–59 years, and 60–80 years. SD-AS OCT was used to measure CET at 17 points across a 6.0 mm corneal diameter for each subject. The study found that the CET of the central cornea (2 mm), paracentral, and mid-peripheral zones (2–5 and 5–6 mm, respectively) showed highly significant thinning with age ($P < 0.001$) for both males and females, with no significant difference between the genders.

Comparing the two age groups, below 45 and above 45 years old, revealed statistically significant differences, with lower values of CET in the older group ($P < 0.001$). No differences were observed between males and females in contrast to our study which did find significant differences between genders. A possible explanation for the age effect found in our study is that we used measurements from only the right eye of each patient while they used both eyes. One should note that Colakoglu and Cosar mentioned in their study that the difference in mean CET of left eyes across age groups was statistically significant which could have an effect on the results of the study of Samy, Shaaban, and Badran.³⁰

Recent studies have suggested that CET may also be influenced by sex hormones and growth hormones. A study by McKay et al³² found that estrogen and testosterone receptors are present in the corneal epithelium, suggesting that sex hormones might play a role in regulating its thickness. Additionally, growth hormone has been shown to promote corneal epithelial cell proliferation,³² which could lead to an increase in thickness.

These findings highlight the importance of considering age and sex in the evaluation of corneal epithelial thickness prior to refractive surgery, as hormonal differences or deficiencies could potentially affect epithelial thickness and thus surgical outcomes.

Modern trans epithelial (T-PRK) utilizes an excimer laser to ablate the corneal epithelium and the corneal stroma consecutively. Studies comparing t-PRK to alcohol-assisted PRK have found that both procedures are predictable, effective, and safe, with similar visual outcomes in normal corneas³³ while other studies found that the long-term accuracy was worse for t-PRK.³⁴ Some studies suggest that t-PRK may have better clinical outcomes than Femtosecond LASIK.³⁵ A recent new t-PRK modality relies on multiple population-based studies that demonstrated that the central CET is thinner compared to the periphery.^{14,36} Instead of the traditional uniform epithelial ablation, this procedure ablates 55 microns of corneal epithelium central and 65 microns peripherally.³⁷ However, this modality does not yet consider factors such as the patient's age and gender and their effects on CET. If the epithelial thickness differs from the amount planned to be removed by the laser, it could result in overcorrection or under correction of the refractive error. Including the expected thickness of the corneal epithelium according to gender and age can help in more accurate planning of the required amount of epithelial ablation during t-PRK. Incorporating individual CET data according to demographic profiles may help optimize tissue preservation and reduce the risk of postoperative complications such as ectasia or regression. Knowing the distribution of CET in each individual is especially important in customized T-PRK as the CET varies in different regions of the cornea and this can affect the amount of laser ablation delivered to that region.

As our study demonstrates that there are notable differences in corneal epithelial thickness between men and women, as well as among different age groups, these results could have significant implications for future research in this area. For example, further investigation into the effects of hormonal changes on corneal epithelial thickness could shed light on how sex hormones impact the structure of the cornea. Specifically, researchers could explore the impact of hormonal changes, during pregnancy or menopause, on epithelial thickness.

Our findings highlight those variations in corneal epithelial thickness (CET), influenced by factors such as age and gender, may significantly impact the ablation depth and treatment planning in trans-epithelial photorefractive keratectomy (t-PRK). Failure to account for these variations could lead to suboptimal ablation, resulting in over- or under-correction, which may affect surgical outcomes. Therefore, incorporating individualized CET profiles into t-PRK planning is crucial to optimize tissue preservation, minimize postoperative complications, and enhance the overall success of refractive surgery.

In conclusion, corneal epithelial thickness differs between males and females, with males exhibiting significantly thicker CET across all quadrants. Age also has a significant effect on CET, showing a trend of increased thickness with advancing age. Considering these findings, refractive surgeons should consider these changes when planning t-PRK, as CET is an important factor in this procedure.

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