

# Corneal Epithelial Mapping Characteristics in Normal Eyes Using Anterior Segment Spectral Domain Optical Coherence Tomography

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**Purpose:** The detailed mapping characteristics of the corneal epithelial thickness (CET) in normal eyes from a Middle Eastern population were investigated in relation to age, sex, intraocular pressure, and keratometric power (K).

**Methods:** A retrospective cross-sectional and analytical study was conducted using spectral domain optical coherence tomography (OCT). We calculated the CET in 124 subjects in 17 zones within a 6 mm circle. Exclusion criteria included subjects with dry eyes, keratoconus, previous eye surgery, glaucoma, and irregular corneas.

**Results:** A total of 124 individuals was composed of 64 males and 60 females. The mean age of this population was 45.52, ranging from 18 to 79 years. The central CET was thicker in the central 2 mm than the other zones of the cornea except the nasal, inferior-nasal, inferior and inferior-temporal zones, respectively. Males have thicker CET than females in all zones except in the peripheral nasal zone. We found a positive and significant correlation between age and CET in the central, superior-peripheral, inferior-paracentral, and inferior-temporal paracentral zones. Additionally, a medium-positive correlation was detected between increasing age and the variability of epithelial spectral domain in different zones. No link between CET and intraocular pressure was found.

**Conclusions:** This study analyzed 17 CET zones within the central 6 mm, where the central epithelium is resistant to aging. The CET was thinner superiorly than inferiorly. This may help in decision-making in refractive procedures and in the prediction of corneal diseases.

**Translational Relevance:** OCT novel algorithms are noninvasive methods for measuring CET and have been demonstrated to be useful in refractive surgery planning and follow-up, as well as a robust tool for diagnosing potential corneal ectasia.

## Introduction

The corneal epithelium as a part of the ocular surface has an important structure and function in health and sickness. It provides a protective layer consisting of five to seven epithelial cells; the basal corneal epithelial cells maintain regenerative capability during normal homeostasis whereas the limbal stem cells provide a further source of epithelial regeneration under epithelial stress or injury.<sup>1</sup> In addition, the corneal epithelium has a refractive power of about +1.03 diopter (D) and +0.85 D in the central 2 and 3.6 mm, respectively, as demonstrated by Simon et

al.<sup>2</sup> Corneal epithelium displays a nonuniform pattern over different corneal zones to compensate for abrupt changes in stromal contour irregularities; although this will result in a smoother refractive surface, it still may induce astigmatism.<sup>2</sup>

Recent advances in in vivo high-resolution imaging have resulted in renewed research interest in corneal epithelial thickness (CET) as a sensitive marker of the health of the eye. The corneal epithelial thickness has been measured using a variety of techniques, including very high frequency ultrasound scanning, optical coherence tomography (OCT), optical pachymetry, confocal microscopy, and focusing confocal microscopy. Each of these studies quantified

the average thickness of the central epithelial layer. Additionally, some studies included measurements of epithelial thickness in the peripheral cornea, but the number of points measured in the periphery was limited.<sup>3–8</sup> Early studies of CET have not demonstrated a difference in various corneal meridians.<sup>5,9</sup> The CET not only plays an important role in the total refractive power of the cornea, but it also exhibits early changes in abnormal corneal metabolism and disease, for instance, lack of nutrients and or oxygenation levels in the cornea.<sup>4,5,10,11</sup>

The recent invention of spectral domain OCT anterior segment imaging is gaining popularity and has become an integral part of many ophthalmic practices worldwide. It is essential for defining normal and diseased corneas, as it is highly reproducible and reliable.<sup>12</sup> The uses of anterior segment OCT scanning include dry eye assessment, tear film measurement, keratoconus screening, which has a characteristic doughnut pattern associated with localized central thinning encircled by an annulus of thick epithelium (Fig. 2A), postrefractive ectasia diagnosis and follow-up, preoperative assessment in transepithelial photorefractive keratectomy, phototherapeutic keratectomy, and flap thickness after LASIK, among other uses in infectious and immune corneal disorders.<sup>13–17</sup>

Although numerous studies have been conducted on corneal pachymetry and its role in measuring intraocular pressure and detecting keratoconus, there are relatively few publications on the role of each part of the cornea in various eye conditions.<sup>18–22</sup> The effect of age in isolation of other confounding factors such as dry eyes and levels of sex hormones is not fully clear.<sup>23–25</sup> Additionally, there has been controversy regarding the CET's relationship to age, particularly in certain corneal areas where the central zone epithelium appears to remain unchanged with age.<sup>1,3,23</sup> This study aimed to determine whether age, intraocular pressure, sex, refraction, and net corneal power have any influence on certain zones of the corneal epithelium in normal eyes and set a baseline for future research in Jordan and other Middle East countries. This will aid in the decision-making process for corneal refractive surgery and in identifying specific corneal conditions such as keratoconus and those refractive surgeries that depend on CET in achieving good results.

## Methods

### Study Design and Subjects

A cross-sectional retrospective study was conducted between January 2015 and June 2021 at Amman Eye

Clinic to measure the corneal epithelial thickness. The subjects were recruited voluntarily while at the clinic for consultations or accompanying their significant others. On obtaining an informed consent, a full ocular examination was performed to rule out corneal abnormalities such as scarring, keratoconus, and previous intraocular surgery, high myopes and hyperopes among others. In the majority of cases ( $n = 97$ ), best-corrected visual acuity or automated refraction (Topcon KR-8000; Topcon, Tokyo, Japan) was performed.

### Ethical Approval

This study received approval from Institutional Review Board at Applied Science University (2021-PHA-41) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects or their guardian(s) for imaging, intraocular pressure (IOP) measurement, and dry eye assessment at the time of the first clinic visit.

### Patient Selection

Patients aged between 18 to 79 years were enrolled in this study. These include volunteers, patients asking for refractive surgery or cataract consultations, and patients seeking comprehensive ophthalmology examinations. A total of 124 individuals were selected who fit the criteria for normal cornea (Figs. 1A–D) among 452 examined individuals between January 2015 and June 2021. The nationalities of participants of this study included 80 Jordanians, 33 Iraqis, and 11 from other Arab Gulf region citizens.

The medical records and scans were reviewed for the following exclusion criteria:

#### Scan-Related Reasons ( $n = 77$ )

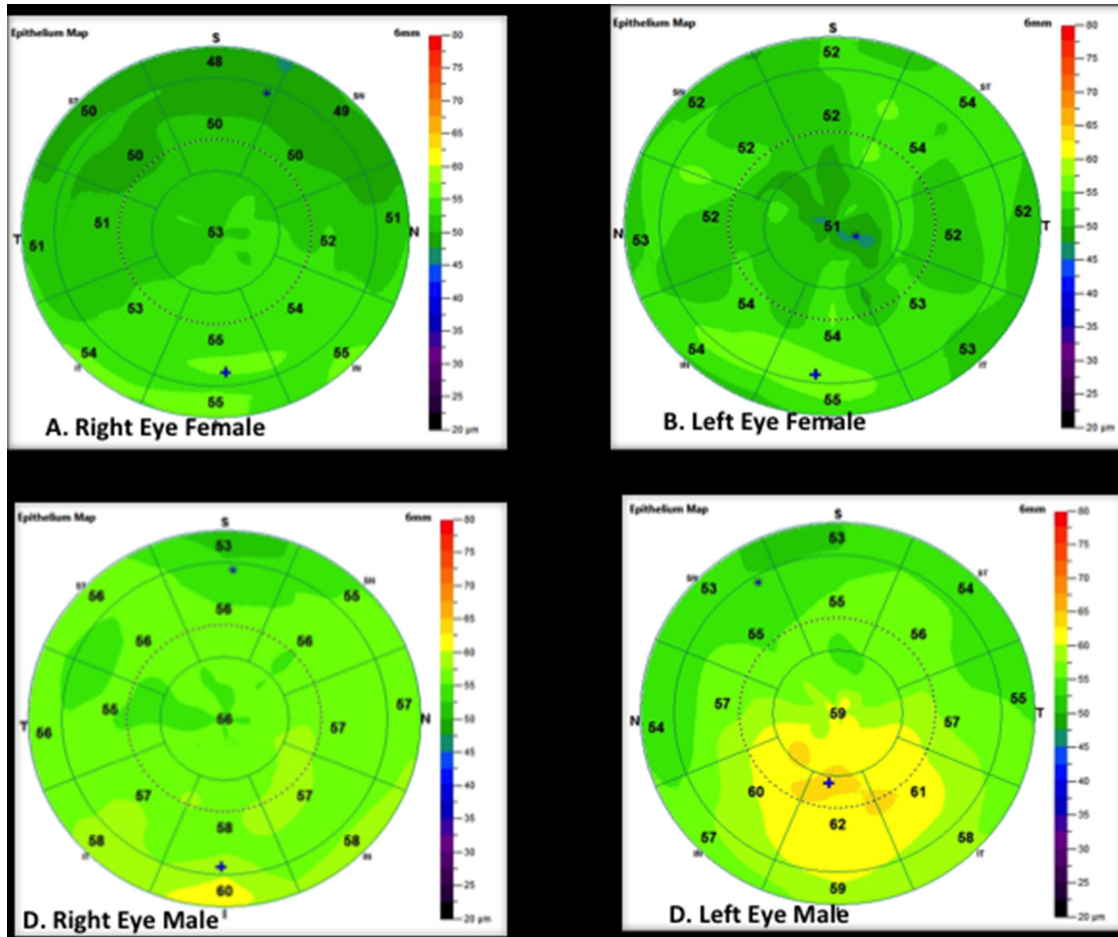
These reasons included inadequate scan coverage of the cornea, poor signal (Fig. 2D), off-centered scans, or highly irregular scans (Fig. 2B).

#### Eye-Related Reasons ( $n = 192$ )

These included previous intraocular surgery, postrefractive surgery, corneal scarring (Fig. 2C), dystrophy, dellen, pterygium, high refractive errors (Myopia  $> 6D$ , Hyperopia  $> 4D$ , or Astigmatism  $> 3D$ ), glaucoma, or keratectasia and keratoconus detected by Scheimpflug tomography.

#### Dry Eye Disease ( $n = 51$ )

Participants with a tear film breakup time shorter than five seconds, a Schirmer I test result  $< 10$  mm/5 min, or a positive corneal staining/pooling were also excluded to reduce the risk of corneal



**Figure 1.** Epithelial Maps (6 mm Ø). A through D shows normal variations of epithelial thickness among right, left eyes, males and females. Note the nonuniform distribution of epithelium.

epithelial cell damage. However, the following conditions were included in the study: macular scarring, age related cataract, macular degeneration, newly diagnosed diabetic patients and retinitis pigmentosa.

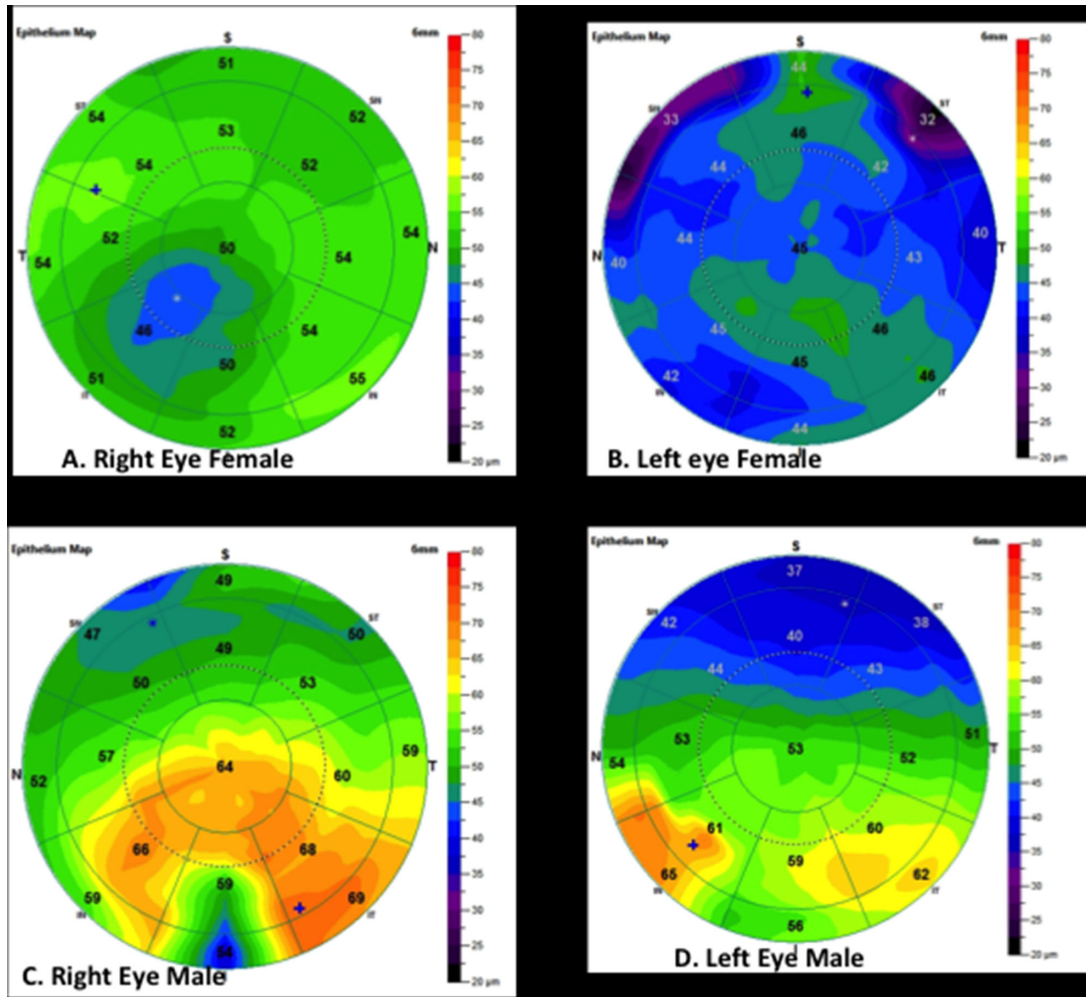
### Final Eye Selection Criteria

Any eye that met any of the exclusion criteria was removed from the study; the rest of the scans were reviewed for segmentation errors and signal strength index. Furthermore, each scan was reviewed for keratoconus by the keratoconus logistic regression formula =  $0.543 \times \text{minimum} + 0.541 \times (S-I) - 0.886 \times (SN-IT) + 0.886 \times (\text{Minimum} - \text{Median}) + 0.0198 \times Y_{\text{min}}$ , developed by Qin et al.<sup>21</sup> As a consequence, any case that showed a high risk for keratoconus warranted a review of the refraction and topography, as well as a repeat of the slit lamp and OCT anterior segment (AS) tests in certain instances. Forne fruste keratoconus cases were ruled out as well (n = 7) (Fig. 2A).

### Anterior Segment-OCT Measurement of the Corneal Epithelial Thickness

The CET measurements were acquired with the anterior segment platform of the Optovue Avanti 70,000 A-scans/second (Optovue, Fremont, CA, USA) spectral-domain OCT with the add-on lens of the corneal adaptor (CAM-L module, S/N 43412). Eight meridional B-scans per capture, each of which had 1024 A-scans, and an axial resolution of 5 µm covering an area of 6 mm in diameter were obtained. Subjects were asked to open their eyes wide while the scan was running, and no attempt was made to open their eyes by the operator, to prevent errors in corneal curvature or alter the results. After good fixation and centration, a scan was obtained in just a few seconds. All readings were obtained before the tear-film breakup time; Schirmer testing and ophthalmic examinations were performed.

The CET maps were generated automatically and divided into a total of 17 zones: one central zone



**Figure 2.** Examples of excluded scans. (A) Abnormal thinning with suspicion of keratoconus. (B) Irregular epithelial surface with severe variations and irregularities. (C) Abnormal inferior corneal dryness and thickening of epithelium. (D) Superior epithelium is highly irregular and thin, possible marginal thinning.

with a diameter of 2 mm, eight paracentral zones forming a circle 3 mm wide, and eight outer peripheral zones forming an outer circle of 1 mm width. Data were compiled into Excel sheets manually, along with demographic information and subject characteristics. The data were checked for accuracy and the presence of missing values or outliers.

**Manifest and Subject Refraction**

A total of 96 patients had automated and subjective refraction. Sphere, cylinder and axis were reported. The Mean sphere equivalent was calculated using the equation = (±) sphere + (–) cylinder power/2. Cylinder power was always in the (–) sign.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS Statistics for Mac, Version 28.0.0.0 (IBM

Corp., Armonk, NY, USA). The data were checked for normality and homogeneity using Kolmogorov-Smirnov and Levene’s tests, respectively. Descriptive statistics including mean, range, and standard deviations were calculated. To determine whether there was a difference in the CET between different zones in comparison with the central area, the analysis of variance (ANOVA) test was used to compare quantitative data between the different paracentral and peripheral zones to the center epithelium thickness. To limit Type I error, a Holm-Bonferroni (HB) was adjusted for three comparisons: for the center, paracentral and peripheral zones in each octant. Both linear and multiple regression models were carried out to determine the effect of age, IOP, sex, and corneal net power on the CET in different zones of the corneal epithelial map. Student independent *t* tests were performed to determine whether there was a difference in CET between women and men. Other independent variables included

in the analyses were keratometry (K), flat K and steep K, K average, sphere, cylinder, mean sphere equivalent, corneal pachymetry in the center, net corneal power, and corneal curvatures.

(51.6%) and 60 females were included for analysis. The mean age of this population was  $45.52 \pm 17.64$  ranging from 18 to 79 years. Most of the individuals were more than 50 years old (44%) and had a lower magnitude of refractive errors ( $-0.5 \pm 2.3$  D) and higher mean intraocular pressures ( $16.9 \pm 4.1$  mm Hg)

## Results

Data were compiled from the medical records and scan results. Table 1 presents the refractive error, IOP, and demographic characteristics of the study population. A total of 124 individuals composed of 64 males

### Epithelial Thickness in the 17 Corneal Zones

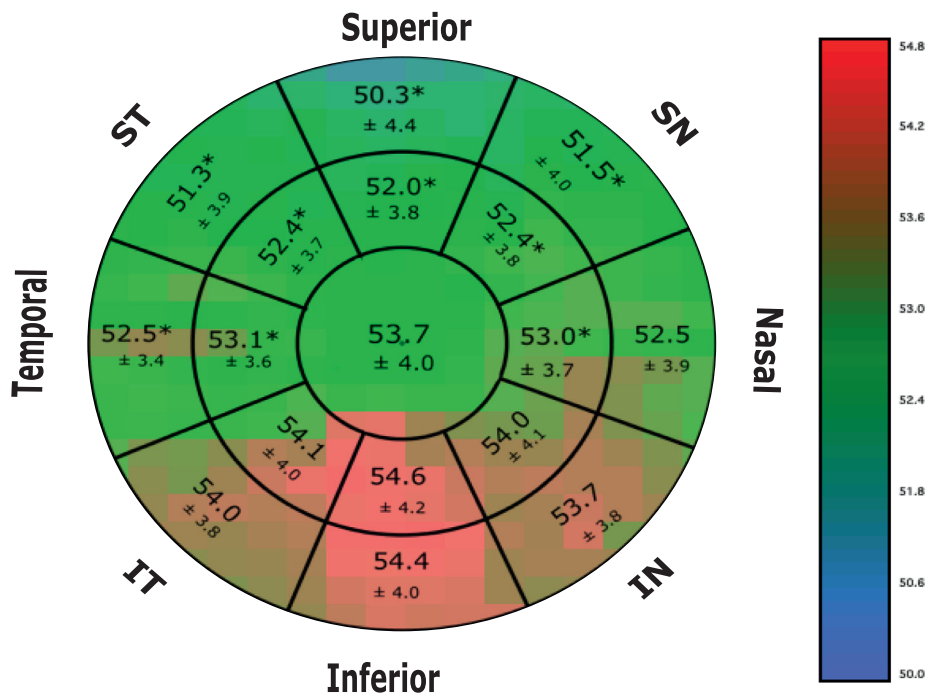
To determine whether the differences in the means of the epithelial thickness maps were statistically significant in all of the 17 zones that comprise the 6 mm

**Table 1.** Descriptive Statistics of the Study Population Per Age Group

| Age group | Patients, n | Sex, M/F | Refractive Error, SD    | IOP, mm Hg, SD          |
|-----------|-------------|----------|-------------------------|-------------------------|
| 18–29     | 33          | 15/18    | $-2.0 \pm 1.6$ (n = 27) | $15.3 \pm 3.1$ (n = 20) |
| 30–39     | 16          | 10/6     | $-1.8 \pm 1.8$ (n = 12) | $17.3 \pm 3.3$ (n = 14) |
| 40–49     | 20          | 14/6     | $-1.8 \pm 2.1$ (n = 14) | $16.3 \pm 2.0$ (n = 18) |
| >50       | 55          | 25/30    | $-0.5 \pm 2.3$ (n = 35) | $16.9 \pm 4.1$ (n = 44) |
| Total     | 124         | 64/60    | $-1.3 \pm 2.1$ (N = 88) | $16.5 \pm 3.5$ (N = 96) |

Tests for normality and homogeneity using Kolmogorov-Smirnov and Levene’s tests were not statistically significant.

### Epithelial Thicknesses Mapping 6 MM (17 zones)



**Legends:**

- SN:** Superior-Nasal
- IN:** Inferior-Nasal
- IT:** Inferior-Temporal
- ST:** Superior-Temporal

\* indicates Statistically Significant result

**Figure 3.** Schematic drawing of Epithelial thickness mapping in normal subjects (n = 124).

diameter circle, variance analysis (one-way ANOVA) was performed. According to the mean thickness displayed in Figure 3, we observed that the epithelium becomes thinner as it extends out from the center, as expressed in the superior, superior nasal, temporal, and superior temporal zones. To minimize type I errors in the octants above, an HB sequential approach was used with three comparisons per octant. According to Table 1 in supplemental file 2, the temporal epithelial zone was not statistically significant when the HB test was used. As indicated in Figure 3, CET was thin in the following order: superior, superior temporal, and superior nasal (50.3, 51.3, and 51.54 μm). On the other hand, when it moved outward toward the paracentral zones, the inferior epithelium was thicker than the central epithelium, as shown in Figure 3.

**Sex**

Independent sample *t*-testing shows that males have significantly thicker corneal epithelia as compared to

females, with a mean difference of 1.7 μm and range from 1.1 to 2.3 μm (*P* < 0.05) in all zones studied with exception of the outer nasal zone (peripheral 5–6 mm), where *P* was not significant (*P* = 0.062) as presented in Table 2.

**Effect of Age on the CET**

Linear regression was used to test the effect of age on corneal epithelial thickness. Table 3 shows a positive and significant correlation between age and CET in the central, superior-peripheral, paracentral inferior, and paracentral inferior-temporal zones. Figure 4 showed the positive linear regression line between the central (2 mm) epithelium with age. In addition, a Pearson correlation was used to test the relationship between age and epithelium standard deviation (SD). We found that the determinant coefficient was significant (*r* = 0.441, *P* < 0.001) indicating a medium positive relationship between the two variables.

**Table 2.** Differences in Epithelial Thickness by Sex

| Zone              | Male (n = 64 μm) | Female (n = 60 μm) | Difference μm | <i>P</i> Value |
|-------------------|------------------|--------------------|---------------|----------------|
| Center            | 54.8 ± 3.9       | 52.6 ± 3.7         | 2.2           | <0.001*        |
| Superior          |                  |                    |               |                |
| Paracentral       | 53.0 ± 3.5       | 51.0 ± 3.9         | 2             | <0.001*        |
| Peripheral        | 51.2 ± 4.3       | 49.4 ± 4.2         | 1.8           | <0.01*         |
| Superior nasal    |                  |                    |               |                |
| Paracentral       | 53.3 ± 3.4       | 51.4 ± 3.9         | 1.9           | 0.002*         |
| Peripheral        | 52.3 ± 3.8       | 50.7 ± 4.0         | 1.6           | 0.014*         |
| Nasal             |                  |                    |               |                |
| Paracentral       | 53.8 ± 3.4       | 52.1 ± 3.8         | 1.7           | 0.004*         |
| Peripheral        | 53.1 ± 4.0       | 52.0 ± 3.6         | 1.1           | 0.062          |
| Inferior nasal    |                  |                    |               |                |
| Paracentral       | 54.8 ± 4.1       | 53.0 ± 3.9         | 1.8           | 0.006*         |
| Peripheral        | 54.4 ± 3.7       | 52.9 ± 3.8         | 1.5           | 0.014*         |
| Inferior          |                  |                    |               |                |
| Paracentral       | 55.5 ± 4.0       | 53.7 ± 4.3         | 1.8           | 0.009*         |
| Peripheral        | 55.2 ± 3.6       | 53.6 ± 4.3         | 1.6           | 0.017*         |
| Inferior temporal |                  |                    |               |                |
| Paracentral       | 54.9 ± 3.7       | 53.3 ± 4.2         | 1.6           | 0.015*         |
| Peripheral        | 54.6 ± 3.6       | 53.4 ± 3.8         | 1.2           | <0.05*         |
| Temporal          |                  |                    |               |                |
| Paracentral       | 54.1 ± 3.5       | 52.1 ± 3.5         | 2             | 0.001*         |
| Peripheral        | 53.3 ± 3.3       | 51.7 ± 3.3         | 1.6           | 0.036*         |
| Superior temporal |                  |                    |               |                |
| Paracentral       | 53.6 ± 3.4       | 51.3 ± 3.6         | 2.3           | <0.001*        |
| Peripheral        | 52.3 ± 3.8       | 50.3 ± 3.7         | 2             | <0.001         |

\*Significant at 0.05.

**Table 3.** Linear Regression of Age on Corneal Epithelial Thickness (*n* = 124)

| Zone              | Reg. Equation                    | R Value | P* Value |
|-------------------|----------------------------------|---------|----------|
| Center            | $51.70 + 0.04 \times \text{age}$ | 0.197   | 0.028*   |
| Superior          |                                  |         |          |
| Paracentral       | $52.4 - 0.01 \times \text{age}$  | 0.037   | 0.683    |
| Peripheral        | $52.5 - 0.05 \times \text{age}$  | 0.195   | 0.030*   |
| Superior-Nasal    |                                  |         |          |
| Paracentral       | $52.18 + 0.01 \times \text{age}$ | 0.023   | 0.801    |
| Peripheral        | $52.82 - 0.03 \times \text{age}$ | 0.125   | 0.170    |
| Nasal             |                                  |         |          |
| Paracentral       | $51.9 + 0.02 \times \text{age}$  | 0.113   | 0.210    |
| Peripheral        | $51.6 - 0.02 \times \text{age}$  | 0.096   | 0.287    |
| Inferior-Nasal    |                                  |         |          |
| Paracentral       | $52.2 + 0.02 \times \text{age}$  | 0.16    | 0.074    |
| Peripheral        | $52.9 + 0.02 \times \text{age}$  | 0.09    | 0.330    |
| Inferior          |                                  |         |          |
| Paracentral       | $52.6 + 0.05 \times \text{age}$  | 0.19    | 0.035*   |
| Peripheral        | $53.7 + 0.02 \times \text{age}$  | 0.073   | 0.420    |
| Inferior-Temporal |                                  |         |          |
| Paracentral       | $52.3 + 0.04 \times \text{age}$  | 0.18    | 0.046*   |
| Peripheral        | $52.8 + 0.03 \times \text{age}$  | 0.124   | 0.170    |
| Temporal          |                                  |         |          |
| Paracentral       | $52.14 + 0.02 \times \text{age}$ | 0.107   | 0.240    |
| Peripheral        | $52.53 - 0.0 \times \text{age}$  | 0       | 0.998    |
| Superior-Temporal |                                  |         |          |
| Paracentral       | $52.45 + 0.0 \times \text{age}$  | 0       | 0.999    |
| Peripheral        | $53.06 - 0.04 \times \text{age}$ | 0.173   | 0.055    |

\*Indicates significance.

**Table 4.** The Predictor Effect of IOP on Epithelial Thickness by Linear Regression (*n* = 124)

| Zone              | Reg. Equation                     | R Value | P Value |
|-------------------|-----------------------------------|---------|---------|
| Center            | $54.42 - 0.053 \times \text{IOP}$ | 0.045   | 0.662   |
| Superior          |                                   |         |         |
| Paracentral       | $53.51 - 0.105 \times \text{IOP}$ | 0.094   | 0.364   |
| Peripheral        | $51.38 - 0.086 \times \text{IOP}$ | 0.063   | 0.545   |
| Superior-Nasal    |                                   |         |         |
| Paracentral       | $53.17 - 0.06 \times \text{IOP}$  | 0.054   | 0.599   |
| Peripheral        | $52.52 - 0.07 \times \text{IOP}$  | 0.06    | 0.563   |
| Nasal             |                                   |         |         |
| Paracentral       | $54.42 - 0.05 \times \text{IOP}$  | 0.045   | 0.662   |
| Peripheral        | $52.64 - 0.02 \times \text{IOP}$  | 0.018   | 0.863   |
| Inferior-Nasal    |                                   |         |         |
| Paracentral       | $54.60 - 0.06 \times \text{IOP}$  | 0.052   | 0.614   |
| Peripheral        | $54.50 - 0.07 \times \text{IOP}$  | 0.061   | 0.555   |
| Inferior          |                                   |         |         |
| Paracentral       | $55.20 - 0.06 \times \text{IOP}$  | 0.047   | 0.651   |
| Peripheral        | $55.10 - 0.06 \times \text{IOP}$  | 0.051   | 0.623   |
| Inferior-Temporal |                                   |         |         |
| Paracentral       | $55.68 - 0.12 \times \text{IOP}$  | 0.101   | 0.336   |
| Peripheral        | $55.46 - 0.16 \times \text{IOP}$  | 0.931   | 0.354   |
| Temporal          |                                   |         |         |
| Paracentral       | $55.57 - 0.17 \times \text{IOP}$  | 0.16    | 0.119   |
| Peripheral        | $55.03 - 0.17 \times \text{IOP}$  | 0.177   | 0.084   |
| Superior-Temporal |                                   |         |         |
| Paracentral       | $54.64 - 0.15 \times \text{IOP}$  | 0.139   | 0.177   |
| Peripheral        | $53.12 - 0.13 \times \text{IOP}$  | 0.166   | 0.259   |

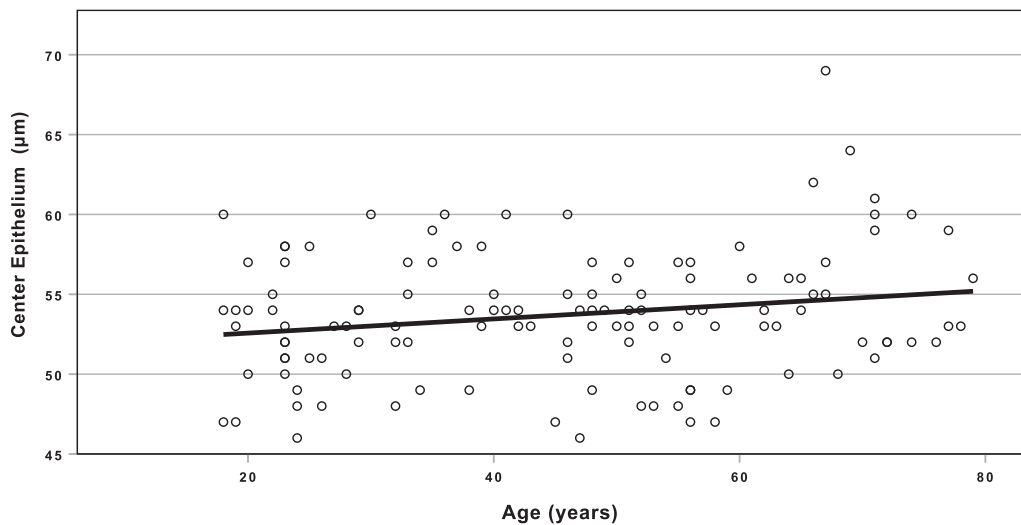
\*Indicates statistically significant result.

### Intraocular Pressure

To study the predictive relationship between intraocular pressure as an independent variable and

CET, it was compared to the different corneal epithelial zones using linear regression. As shown in Table 4, there was no perceptible link.

Linear Regression of Epithelium at Center (2mm) with Age



**Figure 4.** A Positive linear relationship between increasing age and central epithelial thickness. The graphs of the other 16 zones are appended in Supplementary file 1.

**Table 5.** Correlation Between Refractive Errors, Keratometry and Age Groups

| Variable | Age Groups | n  | Mean | SD  | F     | P Value* |
|----------|------------|----|------|-----|-------|----------|
| Sphere   |            |    |      |     | 4.6   | <0.01*   |
|          | 18–29      | 28 | −1.7 | 1.6 |       |          |
|          | 30–39      | 13 | −1.0 | 1.8 |       |          |
|          | 40–49      | 16 | −1.1 | 1.9 |       |          |
|          | >50        | 40 | 0.04 | 2.1 |       |          |
| Cylinder |            |    |      |     | 3.018 | 0.034*   |
|          | 18–29      | 27 | −0.6 | 0.5 |       |          |
|          | 30–39      | 14 | −1.1 | 1.1 |       |          |
|          | 40–49      | 16 | −1.0 | 0.5 |       |          |
|          | >50        | 40 | −0.9 | 0.5 |       |          |
| Flat K   |            |    |      |     | 3.103 | 0.03*    |
|          | 18–29      | 27 | 43.0 | 1.6 |       |          |
|          | 30–39      | 14 | 42.8 | 1.6 |       |          |
|          | 40–49      | 15 | 41.9 | 1.2 |       |          |
|          | >50        | 40 | 43.3 | 1.4 |       |          |
| Steep K  |            |    |      |     | 3.134 | 0.029*   |
|          | 18–29      | 27 | 43.8 | 1.7 |       |          |
|          | 30–39      | 14 | 44.1 | 2.0 |       |          |
|          | 40–49      | 15 | 42.7 | 1.1 |       |          |
|          | >50        | 40 | 44.2 | 1.6 |       |          |

\*P is significant at 0.05.

### Keratometry and Net Corneal Power (CPNet)

The data analyzed were found to be normal and linearly distributed. Means  $\pm$  standard deviation of flat K, steep K, and CPNet were, respectively,  $42.9 \pm 1.5$  D,  $43.8 \pm 1.8$  D, and  $42.8 \pm 1.5$  D. The relationship between these values in all of the 17 zones and the CET was investigated using Pearson product-moment correlation coefficient. There was no correlation between central epithelium thickness and either flat K ( $r = -0.002$ ,  $N = 121$ ,  $P = 0.988$ ), steep K ( $r = 0.072$ ,  $N = 121$ ,  $P = 0.483$ ), or CPNet ( $r = 0.066$ ,  $N = 121$ ,  $P = 0.468$ ). Notably, a small negative correlation was detected only between thickness of the superior peripheral epithelium and CPNet ( $r = -0.229$ ,  $N = 121$ , and  $P = 0.011$ ).

### Refractive Errors, Keratometry and Age

The one-way ANOVA test showed a significant difference between the age groups with the sphere, cylinder, flat K, and steep K as shown in Table 5. These findings suggest that people have different corneal parameters as they become older.

## Discussion

Corneal epithelial thickness in the center ranges from 46 and 62  $\mu\text{m}$  using a variety of imaging instruments including anterior segment optical coherence tomography, confocal microscopy and very high frequency (VHF) digital ultrasound.<sup>1,5,8,10,12,15,26–28</sup> Over VHF digital ultrasonography and confocal microscopy, the advantage of OCT is that it is a noninvasive, repeatable, and fast investigation. There is no risk of corneal abrasion, epithelial compression, or infection transfer between participants.<sup>8,29</sup> On the other hand, one benefit of contact measurement devices is that they eliminate the variable thickness of the tear film, which is reported to be between 2 and 7  $\mu\text{m}$  in thickness.<sup>3,30,31</sup> In the current study, central CET in normal individuals was found to be  $53.7 \pm 4.0$   $\mu\text{m}$ , which is similar to other studies in Table 6.<sup>7,32</sup> The similarity between CET results between the Optovue OCT machine is a good example of a reliable resolution and a well-selected cohort of normal subjects.<sup>5,7,23,32,33</sup> Regarding our results and those reported from other studies as presented in Table 6, we could conclude that *no ethnic* difference was detected.

The corneal epithelial layer profile in this study was nonuniform and variable in thickness at different zones of the cornea Figure 1, which is similar to other studies.<sup>7,23,28,31,32</sup> Although older research did not show any differences between cornea locations, the current study demonstrated that superior epithelium is thinner than inferior one.<sup>5,9</sup> This is consistent with previous literature.<sup>11,32,37,38</sup> This vertical nonuniformity of CET was discussed in detail by Reinstein et al.<sup>1,31</sup>; the possible explanations in short include mechanical chaffing and abrasion caused by the accelerated movement of the upper eyelid crossing the visual axis, prolonged compression by the upper eyelid, and shorter tear film transit time caused by gravity resulting in thinner and less-nourished epithelium superiorly.<sup>1,7,31,39</sup> Furthermore, contrary to previous reports, no significant differences in nasal and temporal epithelial thickness at the paracentral and peripheral zones were detected.<sup>9,39</sup> Nonetheless, Reinstein et al.<sup>1</sup> reported thicker nasal epithelia compared to temporal epithelia. Equally important, the corneal epithelium can alter its thickness to establish and maintain a smooth, symmetrical optical surface and alternatively conceal the presence of an irregular stromal surface as seen in asymmetric LASIK flaps, microstriae, myopia, hyperopia, radial keratotomy, post-LASIK, corneal crosslinking patients and intra-corneal stromal rings.<sup>8,11,15,32,37</sup> This suggests that corneal epithelium nonuniformity may play a role in refrac-



**Table 6.** Central Corneal Epithelial Thickness Reported By Previous Investigators

| Study                                      | Normal ( $\mu\text{m}$ ) | Age Range (y)  | Instrument | Axial Resolution   | Commercial Manufacturer | Year |
|--|--------------------------|----------------|------------|--------------------|-------------------------|------|
| Li et al. <sup>34</sup>                    | 50.6 $\pm$ 3.9*          | 24–45          | CFM        | 9 $\mu\text{m}$    | Tandem Scanning         | 1997 |
| Erie et al. <sup>15</sup>                  | 46 $\pm$ 5.0*            | 20–46          | CFM        | ? 9 $\mu\text{m}$  | Tandem Scanning         | 2002 |
| Reinstein et al. <sup>8</sup>              | 53.4 $\pm$ 4.6*          | 20.5–73.5      | VHF US     | 21 $\mu\text{m}$   | Artemis                 | 2010 |
| Urs et al. <sup>3</sup>                    | 55.6 $\pm$ 2.8*          | Not available  | VHF US     | 21 $\mu\text{m}$   | Artemis 2               | 2016 |
| Wang et al. <sup>35</sup>                  | 59.9 $\pm$ 5.9           | 35.6 $\pm$ 9.6 | TD-OCT     | ? 10 $\mu\text{m}$ | Custom-Built OCT        | 2004 |
| Sin & Simpson <sup>12</sup>                | 52 $\pm$ 3.0             | 18–53          | TD-OCT     | 10 $\mu\text{m}$   | Humphrey-Zeiss OCT2000  | 2006 |
| Haque et al. <sup>28</sup>                 | 52.9 $\pm$ 4.1           | 21–45          | TD-OCT     | 10 $\mu\text{m}$   | Humphrey-Zeiss OCT2000  | 2006 |
| Feng et al. <sup>6</sup>                   | 54.7 $\pm$ 1.9           | 20–36          | TD-OCT     | 10 $\mu\text{m}$   | Carl Zeiss OCT          | 2008 |
| Tao et al. <sup>27</sup>                   | 52.5 $\pm$ 2.4           | 24–76          | SD-OCT     | 3 $\mu\text{m}$    | Custom-built OCT        | 2011 |
| Francoz et al. <sup>29</sup>               | 48.3 $\pm$ 2.9*          | 20–66          | SD-OCT     | 3.9 $\mu\text{m}$  | Zeiss Spectralis OCT    | 2011 |
| Reinstein et al. <sup>31</sup>             | 553.4 $\pm$ 3.2          | 19–60          | SD-OCT     | 5 $\mu\text{m}$    | Optovue RTVue-100       | 2010 |
| Temstet et al. <sup>33</sup>               | 53.0 $\pm$ 3.1           | 36.1 $\pm$ 9.4 | SD-OCT     | 5 $\mu\text{m}$    | Optovue RTVue-100       | 2015 |
| Wu et al. <sup>32</sup>                    | 53.3 $\pm$ 2.7           | 18–40          | SD-OCT     | 5 $\mu\text{m}$    | Optovue RTVue-100       | 2017 |
| Normative Data FDA Approval. <sup>36</sup> | 52.9 $\pm$ 3.4           | 18–63          | SD-OCT     | 5 $\mu\text{m}$    | Optovue iVue            | 2017 |
| Hashmani et al. <sup>7</sup>               | 53.9 $\pm$ 3.7           | 20–75          | SD-OCT     | 5 $\mu\text{m}$    | Optovue Avanti XR       | 2018 |
| This study                                 | 53.7 $\pm$ 4.0           | 18–79          | SD-OCT     | 5 $\mu\text{m}$    | Optovue Avanti XR       | 2021 |

TD, time-domain; US, ultrasonography; CFM, confocal microscopy.

\*Pre-corneal tear thickness was excluded.

tive errors as concluded by the study of Simon et al.<sup>2</sup> that should be taken into consideration when planning refractive surgery.

In refractive laser ablations, for instance, trans-epithelial photorefractive keratectomy (Trans-PRK) and phototherapeutic keratectomy, surgeons should consider the vertical variability in mapping of the different zones of the epithelium to maintain accurate refractive results and avoid creating unintended corneal aberrations.

Males have thicker corneal epithelium compared to females due to gonadal hormones that are expressed in the nuclei of corneal epithelial, stromal, and endothelial cells.<sup>40,41</sup> Giuffrè et al.<sup>42</sup> and Fortepiani et al.<sup>43</sup> found that the total corneal thickness in women during their menstrual cycle was thickest at ovulation day and thinnest at end of the menstrual cycle. It seems that no other studies have analyzed the effect of menstruation on corneal epithelial thickness. In the current study, males have thicker CET by a mean of 1.7  $\mu\text{m}$  than females as shown in Table 2. This is consistent with other research.<sup>1,7,23,32</sup> The epithelial thickness difference in corneal central zone between males and females varied between study populations; the current study reported a difference of 2.2  $\mu\text{m}$ , whereas Hashmani et al.,<sup>7</sup> Kanellopoulos and Asimellis,<sup>38</sup> and Wu et al.<sup>32</sup> showed values of 1.9  $\mu\text{m}$ , 1.52  $\mu\text{m}$ , and 1.34  $\mu\text{m}$ , respectively.

The age effect was found to be negligible in the majority of the CET corneal zones, as shown in Table 3. Nonetheless, a positive correlation between age and CET was identified in certain zones, most notably the central, superior peripheral, paracentral inferior, and paracentral inferotemporal. This positive correla-

tion implies that age has a greater effect on epithelial thickness in older subjects than in younger subjects (Fig. 4). Current study results are in line with the findings of Kanellopoulos and Asimellis.<sup>44</sup> On the other hand, some research reported different findings that ranged from no correlation between age and CET to a negative correlation.<sup>1,7,32,45</sup> The most likely explanation is that their study populations were young.<sup>1,32</sup> In addition, another important observation was that the CET standard deviation increased with age in a centrifugal pattern, denoting possible degenerative and hormonal changes.<sup>23,38</sup>

There was no discernible correlation between corneal epithelial thickness and intraocular pressure, which is consistent with the findings of Lee and Ahn,<sup>20</sup> who reported a strong positive correlation between stromal thickness and IOP but not with epithelial thickness.

This study has several limitations, including sample selection bias, because the eye clinic subjects are not representative of the general population. Additionally, anterior segment OCT misrepresents the tear film's thickness. The last constraint is a result of the Optovue software's depiction of continuous data as clustered zones. Because of the lack of continuous data, the data are less suitable for multivariate analysis.

In conclusion, this study analyzed in greater depth 17 zones of the corneal epithelium in the central 6 mm; the corneal epithelial thickness showed significant variability between superior and inferior meridians but not in horizontal meridians. Of interest is the relationship between the corneal epithelial thickness and age, especially in older individuals, where the central zones were not affected by age. When compared

to the inferior epithelium, the superior epithelium was the thinnest; this finding provides a useful guide in refractive surgery decision-making and the assessment of corneal diseases such as keratoconus and trans-epithelial ablations. This is the first study in Jordan to study the characteristics of corneal epithelial thickness in normal subjects. This will add to the literature, because there is a lack of knowledge of normal ocular parameters in the Middle East region.

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