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Effect of Demographic Variables on the Regional Corneal Pachymetry

Nauman Hashmani, MBBS, Sharif Hashmani, FCPS, Asif Murad, BSc, Noureen Asghar, MBBS, and Mahnoor Islam, MBBS

Purpose: The measurement of corneal thickness by corneal pachymetry provides valuable information in the setting of corneal disease; however, spectral-domain optical coherence tomography (SD-OCT)-based assessment of different corneal sectors has been scarce in Pakistan.

Design: We aimed to obtain a whole-corneal thickness map using SD-OCT and to evaluate its correlation with age, sex, and axial length.

Methods: Our study included 214 subjects with healthy corneas; each eye was scanned with an SD-OCT covering a 9-mm diameter, and reproducibility was evaluated in a subset of 50 participants by means of an identical scan protocol repeated by 2 different OCT operators.

Results: Our analysis revealed corneal thickness to be thinnest inferotemporally whereas thickest in the superior and superonasal quadrants. No statistically significant differences could be detected between male and female participants with respect to corneal thickness, age, intraocular pressure, axial length, and refractive errors. However, we identified a significant negative correlation between age and corneal thickness in all corneal sections, excluding the inner and middle superior, inner superonasal, and inner and middle superotemporal quadrants. Conversely, the correlation between axial length and corneal thickness was found to be positive in the central region ($P = 0.03$, $R = 0.149$), the outer inferotemporal quadrant ($P = 0.012$, $R = 0.171$), throughout the temporal quadrant ($P = 0.024$, $R = 0.154$ for inner; $P = 0.025$, $R = 0.153$ for middle; $P = 0.006$, $R = 0.186$ for outer), and in the inner superotemporal quadrant ($P = 0.018$, $R = 0.162$).

Conclusions: Different corneal sectors may interact heterogeneously with patient-related characteristics. This may provide incentive to evaluate whole-corneal thickness as a distinct parameter for clinical identification of disease processes.

Key Words: corneal mapping, corneal thickness, pachymetry, SD-OCT

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Several instruments are available on the market to evaluate corneal pachymetry (CP). These include the corneal topography, ultrasound, and the optical coherence tomography (OCT). Ultrasound pachymetry is the most commonly used technique to measure corneal thickness. However, ultrasound pachymeters require direct contact with the cornea and scanning reliability depends heavily on the experience and ability of the operator to align the probe with the focal spot over the cornea.[1,2] The topography and the OCT have alleviated these limitations of the ultrasound.[3]

CP has been used extensively in diagnosing corneal diseases such as keratoconus. Additionally, the planning of certain surgical procedures, such as photorefractive keratectomy and laser in situ keratomileusis, requires this modality to predict the safety and planning of the procedures. In particular, pachymetry provides essential information while selecting the type of refractive surgery, calculating ablation depth, and assessing the danger of postoperative ectasia.[4] Lastly, CP is essential in glaucoma as well, as the thickness of the cornea has influence on the measurement of intraocular pressure (IOP).

Our group has previously published an evaluation of corneal epithelial maps using the OCT[5] and pachymetry using the Oculus Pentacam.[6] Work has been done on pachymetry maps using various modalities including the spectral-domain optical coherence tomography (SD-OCT). No work has been done to evaluate regional differences in the cornea in Pakistani eyes and observe the effect of demographic variables. Also, we evaluated the reproducibility of this technique.

METHODS

Selection of Patients

This prospective clinical study included the participation of 214 healthy subjects evaluated at 2 operating centers of Hashmanis Hospital, Karachi, Pakistan. Informed consent was obtained from each participant after explaining the nature and possible consequences of this study. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Hashmanis Hospital.

Patients with any preexisting ocular pathology, history of cataract, ocular hypertension, ocular trauma, previous ocular surgery, ocular medication use, amblyopia, and contact lens were categorically excluded from the analysis. Additionally, those with a history of visual field loss (assessed via clinical examination), systemic disease or pregnancy were also excluded. All patients were screened using an anterior segment tomography device (Pentacam HR; Oculus, Wetzlar, Germany), so as to rule out corneal diseases, dystrophies, and keratoconus.

Participants with refractive errors between −6 and +5 diopters were included, in addition to subjects with a best-corrected visual acuity of >0.8 and IOP of <22 mm Hg. Lastly, those with significant dry eyes (ie, with a Schirmer test value of

From the Department of Ophthalmology and Visual Sciences, Hashmanis Hospital, Karachi, Pakistan.
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Correspondence: Noureen Asghar, JM-75, OFF MA Jinnah Road, Jacob Lines, Karachi, Pakistan. E-mail: noureen.asghar07@gmail.com.
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<5 mm) and patients on systemic medications were also excluded.

Technical Information

One eye was considered for each participant, and if both eyes were eligible, only 1 was chosen randomly. The population enrolled in this study was ensured to have no history of preexisting ocular disease. To confirm this, ophthalmologic tests were performed on each participant to rule out pathologies. These tests included autorefraction (Topcon KR-800, Tokyo, Japan), keratometry, best-corrected visual acuity using a Snellen chart, IOP using an air-puff tonometer (Reichert 7CR, Reichert, Inc., Depew, NY), dilated fundus examination, slit-lamp examination, axial length measurement (Wavelight OB-820, WaveLight, Erlangen, Germany), and the commercially available SD-OCT device (Avanti RTVue XR; Optovue, Inc., Fremont, CA). For each eye included, 1% tropicamide was used to dilate the pupil for the examination of the fundus and to perform posterior segment OCT. The eye was then allowed to return to its nondilated state and scanned by an experienced OCT operator.

Optical Coherence Tomography

Each eye was scanned with an SD-OCT device; the anterior segment module was employed in conjunction with newly released commercially available software, which allowed CP to cover a 9-mm diameter. The machine scans at an axial resolution of 5 μm, a beam width of 22 μm, and a light source centered at 840 nm.

For optimal scan quality, patients were asked to blink before each scan to ensure that the tear film would be spread out smoothly, to stare at the target, and to avoid blinking during measurements. Moreover, only high-quality images centered at the corneal vertex and free of motion artifact were accepted for analysis. Any eyes with evidence of signal blockage, as indicated by a net pattern over the area, were excluded.

Classifications

All corneal maps were divided into 4 zones: a central zone, inner zone, middle zone, and outer zone. Except for the central zone, the zones were further subdivided into 8 sectors: superior, superotemporal (ST), temporal, inferotemporal (IT), inferior, inferonasal, nasal, and superonasal (SN). An example of the regions is shown in Figure 1.

Reproducibility

For each patient, an identical scan protocol was repeated by 2 different OCT operators to evaluate interobserver reproducibility. A subset of 50 patients from the cohort was included in this experiment.

Statistical Analysis

Data were collected on Google forms and subsequently imported into the statistical software (SPSS v23; IBM, Armonk [NY], US); all further analyses were computed in this software. Normality was judged both visually and via statistical tests (Shapiro Wilk/ Kolmogorov–Smirnov test). Continuous variables

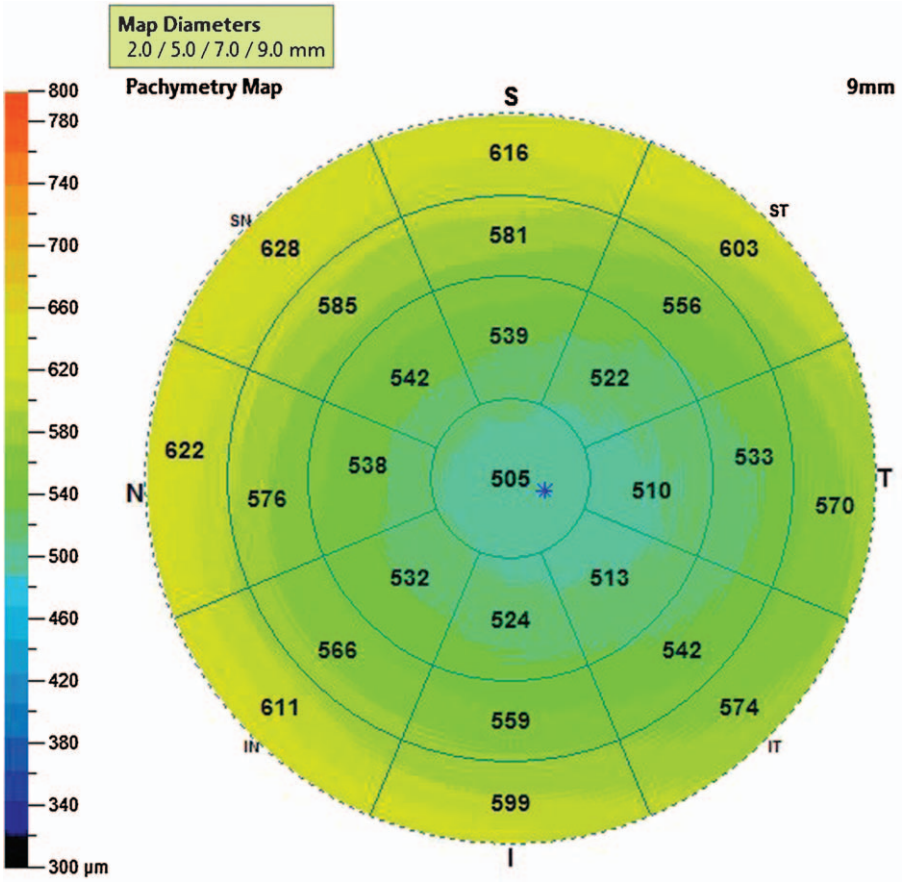

FIGURE 1. This pachymetry map represents variation in the thickness of different corneal sectors.

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were represented by means and standard deviations, whereas differences between sexes were calculated using the independent *t* test. To assess differences between central and peripheral corneal thickness, the 1-way analysis of variance test was used. A Pearson product moment correlation coefficient was used to correlate age, keratometry, and axial length with corneal thickness, and a partial correlation used to measure an adjusted *P* value. In addition, interobserver reproducibility was estimated with the help of 2 tests: the coefficient of variation (CV) and the intraclass correlation coefficient (ICC). Finally, a multiple regression model was constructed, wherein a P value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Table 1 provides a summary of general patient-related characteristics divided into 5 age groups. Of the 214 included participants, the majority were males (n = 110; 51.4%), whereas female patients constituted a slightly smaller proportion (n = 104 females; 48.6%). The mean age of the cohort was 40.0 years (range = 20–70 years). The 50 patients considered for the reproducibility experiment, however, included an equal number of males and females. The mean age of the reproducibility subset was 39.0 ± 15.0 years.

Corneal Thickness by Sector

Table 2 summarizes relevant information about the corneal thickness of each corneal location. Corneal thickness was found to be thinnest at the IT region in all sectors, with mean values of 529.2 ± 32.4 μm, 556.4 ± 35.1 μm, and 588.1 ± 37.2 μm in the inner, middle, and outer locations, respectively. The superior quadrant was found to be the thickest in the inner, middle, and outer locations with means of 557.5 ± 33.8 μm, 601.3 ± 35.3 μm, and 645.4 ± 38.4 μm, respectively.

Additionally, our analysis identified uniformly lesser values toward the center as compared to the periphery. The outermost section of the cornea was between 13.1% and 24.1% thicker than the central, with the superior quadrant showing the largest value.

Keratometry

The means for the K1 and K2 values were 44.5 ± 1.4 and 45.1 ± 1.7, respectively. There was no correlation between pachymetry and K1 ($r = -0.08$, $P = 0.25$) and K2 ($r = 0.07$, $P = 0.27$).

Correlation with Age, Sex, and Axial Length

No statistically significant differences could be detected between male and female participants with respect to age ($P = 0.314$), IOP ($P = 0.422$), axial length ($P = 0.413$), and refractive errors ($P = 0.775$). The relationship between corneal thickness and sex is elaborated in Table 3, which shows no significant correlation in any sectors.

The impact of age on corneal thickness is displayed in Table 4; our analysis identified a significant negative correlation between age and corneal thickness in all sections, with the exception of the inner and middle locations of the superior quadrant, the inner location of the SN quadrant, and the inner and middle locations of the ST quadrant. Interestingly, the strength of the correlation was seen to increase from the center toward the periphery (inner location < middle location < outer location) for each relevant quadrant.

Conversely, the correlation between axial length and corneal thickness was found to be positive (Table 5), and was significant in the central region ($P = 0.03$, $R = 0.149$), the outer location of the IT quadrant ($P = 0.012$, $R = 0.171$), throughout the temporal quadrant ($P = 0.024$, $R = 0.154$ for inner; $P = 0.025$, $R = 0.153$ for middle; $P = 0.006$, $R = 0.186$ for outer), and in the inner location of the ST quadrant ($P = 0.018$, $R = 0.162$).

Reproducibility

The CVs for the inner, middle, outer, and whole circles ranged from 0.005 to 0.008, 0.006 to 0.009, 0.009 to 0.019, and

TABLE 1. General Characteristics

Age Group, y	Patients, n	Sex, M/F	Refractive Error, D	IOP, mm Hg	Axial Length, mm
20–29	54	28/26	-0.8 ± 1.5	14.4 ± 2.4	23.6 ± 1.1
30–39	63	22/41	-0.5 ± 1.3	15.3 ± 3.1	23.5 ± 1.0
40–49	44	27/17	0.2 ± 1.4	15.7 ± 2.9	23.4 ± 0.9
50–59	36	21/15	0.9 ± 1.4	14.9 ± 3.1	23.3 ± 0.8
60+	17	12/5	1.0 ± 1.3	15.3 ± 3.3	23.2 ± 0.6
Total	214	110/104	-0.0 ± 1.5	15.1 ± 2.9	23.4 ± 0.9

D indicates diopters; F, female; IOP, intraocular pressure; M, male; mm, millimeter; mm Hg, millimeters of mercury; n, number; y, years.

TABLE 2. Thickness by Section

Section	Inner, μm	Middle, μm	Outer, μm	*P* value
Central	520.1 ± 32.6			
Superior	557.5 ± 33.8	601.3 ± 35.3	645.4 ± 38.4	<0.001
Superior nasal	557.5 ± 33.6	597.6 ± 34.7	637.8 ± 38.8	<0.001
Nasal	549.3 ± 32.4	584.5 ± 33.8	626.3 ± 37.2	<0.001
Inferior nasal	541.8 ± 31.8	574.6 ± 32.6	612.7 ± 38.0	<0.001
Inferior	535.3 ± 32.2	566.9 ± 34.3	602.5 ± 34.6	<0.001
Inferior temporal	529.2 ± 32.4	556.4 ± 35.1	588.1 ± 37.2	<0.001
Temporal	531.2 ± 32.3	557.3 ± 34.1	590.9 ± 37.9	<0.001
Superior temporal	545.3 ± 33.0	580.9 ± 35.0	620.1 ± 39.2	<0.001

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TABLE 3. Difference in Corneal Thickness by Sex

Section	Male (n = 110)	Female (n = 104)	*P* value
Central	520.9 ± 34.6	519.2 ± 30.5	0.694
Superior			
Inner	560.8 ± 35.4	554.1 ± 31.8	0.151
Middle	604.4 ± 37.5	598.0 ± 32.7	0.184
Outer	647.0 ± 42.8	64.38 ± 33.2	0.548
Superior nasal			
Inner	558.5 ± 35.4	556.4 ± 31.8	0.661
Middle	598.7 ± 37.2	596.5 ± 32.0	0.635
Outer	638.1 ± 41.6	637.5 ± 35.9	0.907
Nasal			
Inner	549.3 ± 34.7	549.2 ± 29.8	0.975
Middle	584.4 ± 36.7	584.7 ± 30.7	0.951
Outer	626.2 ± 40.9	626.4 ± 32.9	0.972
Inferior nasal			
Inner	541.6 ± 34.1	542.0 ± 29.4	0.922
Middle	574.1 ± 35.0	575.2 ± 30.0	0.802
Outer	612.0 ± 39.9	613.4 ± 36.1	0.790
Inferior			
Inner	535.0 ± 33.8	535.5 ± 30.5	0.906
Middle	566.9 ± 36.6	566.8 ± 31.8	0.990
Outer	602.3 ± 35.4	602.7 ± 33.9	0.932
Inferior temporal			
Inner	529.6 ± 33.8	528.8 ± 31.1	0.864
Middle	556.0 ± 35.7	556.8 ± 34.6	0.867
Outer	588.4 ± 38.3	587.8 ± 36.2	0.908
Temporal			
Inner	532.5 ± 33.2	529.8 ± 31.5	0.550
Middle	558.7 ± 35.2	555.9 ± 33.0	0.550
Outer	592.7 ± 40.2	588.9 ± 35.5	0.468
Superior temporal			
Inner	547.3 ± 34.1	543.2 ± 31.8	0.372
Middle	584.5 ± 36.6	577.0 ± 32.9	0.119
Outer	624.7 ± 40.7	615.3 ± 37.2	0.080

TABLE 4. Effect of Age on Corneal Thickness

Section	Regression Equation	*R* Value	*P* Value	Adjusted *P* Value
Central	534.3–0.36*age	0.140	**0.041**	0.079
Superior				
Inner	565.2–0.19*age	0.072	0.292	0.431
Middle	613.7–0.31*age	0.112	0.101	0.150
Outer	667.1–0.55*age	0.180	**0.008**	**0.012**
Superior nasal				
Inner	568.4–0.28*age	0.104	0.129	0.192
Middle	614.6–0.43*age	0.157	**0.022**	**0.030**
Outer	662.1–0.62*age	0.200	**0.003**	**0.005**
Nasal				
Inner	564.7–0.39*age	0.152	**0.026**	**0.042**
Middle	606.9–0.57*age	0.211	**0.002**	**0.003**
Outer	657.7–0.80*age	0.271	**<0.001**	**<0.001**
Inferior nasal				
Inner	557.5–0.40*age	0.158	**0.021**	**0.035**
Middle	597.0–0.57*age	0.219	**0.001**	**0.002**
Outer	638.8–0.66*age	0.219	**0.001**	**0.002**
Inferior				
Inner	550.7–0.39*age	0.154	**0.024**	**0.041**
Middle	587.2–0.52*age	0.190	**0.005**	**0.008**
Outer	630.0–0.70*age	0.254	**<0.001**	**<0.001**
Inferior temporal				
Inner	544.9–0.40*age	0.154	**0.024**	**0.045**
Middle	579.5–0.59*age	0.211	**0.002**	**0.004**
Outer	619.3–0.79*age	0.269	**<0.001**	**<0.001**
Temporal				
Inner	546.4–0.39*age	0.151	**0.027**	**0.056**
Middle	579.9–0.57*age	0.212	**0.002**	**0.005**
Outer	622.7–0.81*age	0.269	**<0.001**	**<0.001**
Superior temporal				
Inner	556.3–0.28*age	0.107	**0.120**	**0.216**
Middle	595.1–0.36*age	0.130	**0.057**	**0.092**
Outer	640.7–0.52*age	0.168	**0.014**	**0.022**

Note: Values in bold represent statistical significance.

0.006 to 0.011, respectively. The ICC ranged from 0.980 to 0.995, 0.970 to 0.994, 0.809 to 0.973, and 0.950 to 0.990, respectively. The CV and ICC for the center of the cornea were 0.005 and 0.992, respectively. This information is shown in Table 6.

DISCUSSION

Analyzing demographic variations in corneal thickness likely plays an essential role in the diagnosis and prognostication of ocular diseases; identification of the normal corneal architecture with respect to patient-related characteristics helps validate pathological changes in conditions such as glaucoma or keratoconus. However, although a number of studies have offered figures for central or peripheral thickness alone, wide corneal thickness assay is necessary for the comparison of different meridians. Thus, the purpose of our study was to demarcate the corneal sectors in terms of not only thickness, but also their correlation with age, sex, and axial length.

Available literature has defined a wide range of mean corneal thickness in normal subjects from 514 to 575 μm[7–10]; however, the heterogeneous use of traditional and evolving techniques across institutes, including high-frequency ultrasound, ultrasonic pachymetry, slit-scanning topography, and OCT, has allowed significant differences in the measurement of corneal thickness due to varying degrees of accuracy. When considering analyses with SD-OCT only, the mean central corneal thickness (CCT) appears to be lower in our patients as compared with European populations.[11] Conversely, previous studies from the Indian subcontinent show similar findings on CCT,[12] indicating the influence of regional factors.

Nonetheless, the vast majority of studies focus primarily on the central region of the cornea, given its stronger association with disease progression. In addition to this, our analysis has identified the central corneal region to be the thinnest sector; Henriksson et al[13] have suggested that a decreasing number of stromal lamellae from peripheral to central loci may account for this anatomical variation. The reduction of epithelial cell layers has also been proposed to contribute to central thinning; however, this may contradict with a previous analysis of our group, demonstrating increased central thickness of the corneal epithelium in comparison with the periphery.[5] Second to the center, the IT quadrant was found to have the lowest average thickness, whereas the superior SN quadrants were identified as the thickest. From a broader perspective, the topographic pattern was characterized by a uniformly decreasing thickness from the periphery towards the center; these findings are unsurprising, in view of several studies in the literature reporting a similar pattern.[14–17]

Although no significant association could be confirmed between corneal thickness and sex, it is interesting to note the contradiction between this and our previous publication. When looking at a large cohort of 5171 eyes using the Oculus Pentacam, we found thicker corneas in females.[6] Perhaps the larger sample

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TABLE 5. Effect of Axial Length on Corneal Thickness

Section	Regression Equation	*R* Value	*P* Value	Adjusted *P* Value
Central	404.3 + 4.92*axial length	0.149	0.030	0.057
Superior				
Inner	451.9 + 4.49*axial length	0.131	0.056	0.076
Middle	514.8 + 3.68*axial length	0.103	0.134	0.202
Outer	536.4 + 3.56*axial length	0.089	0.193	0.335
Superior nasal				
Inner	471.1 + 3.67*axial length	0.108	0.117	0.172
Middle	540.5 + 2.43*axial length	0.069	0.315	0.494
Outer	580.7 + 2.49*axial length	0.061	0.371	0.629
Nasal				
Inner	469.8 + 3.38*axial length	0.103	0.134	0.231
Middle	532.6 + 2.21*axial length	0.064	0.350	0.617
Outer	590.9 + 1.50*axial length	0.040	0.562	0.997
Inferior nasal				
Inner	461.7 + 3.40*axial length	0.105	0.125	0.221
Middle	510.8 + 2.71*axial length	0.082	0.233	0.453
Outer	555.7 + 2.42*axial length	0.063	0.361	0.644
Inferior				
Inner	449.0 + 3.67*axial length	0.112	0.102	0.182
Middle	507.7 + 2.51*axial length	0.072	0.293	0.507
Outer	530.6 + 3.06*axial length	0.087	0.205	0.405
Inferior temporal				
Inner	426.5 + 4.37*axial length	0.133	0.053	0.101
Middle	456.6 + 4.24*axial length	0.119	0.082	0.185
Outer	436.2 + 6.46*axial length	0.171	**0.012**	**0.044**
Temporal				
Inner	412.4 + 5.05*axial length	0.154	**0.024**	**0.049**
Middle	432.6 + 5.30*axial length	0.153	**0.025**	0.066
Outer	422.7 + 7.15*axial length	0.186	**0.006**	**0.025**
Superior temporal				
Inner	417.9 + 5.42*axial length	0.162	**0.018**	**0.030**
Middle	486.6 + 4.01*axial length	0.113	0.100	0.164
Outer	536.4 + 3.56*axial length	0.089	0.193	0.335

Note: Values in bold represent statistical significance

size revealed a small difference among the sexes as there was only a 4-μm difference. Such difference is likely not to be clinically significant.

Current literature presents conflicting information about the relationship between age and corneal thickness. Islam et al[18] have reported an average decline of 4 μm in CCT with each advancing decade, similar to the inverse correlation suggested by Galgauskas et al[19] and our group.[6] It is important to note, however, that these analyses report CCT specifically, whereas our results negated the statistical relationship between CCT and age after adjustment for axial length and localized the correlation with peripheral sectors. Moreover, CCT has also been seen to increase with age in certain populations.[20] It may be reasonable to expect a certain degree of morphological heterogeneity in CCT across ethnic populations and specific age brackets; the pattern of change has been found to vary considerably across decades[18] and even decline progressively in elderly patients.[21]

Another report, while finding increased CCT with the progression of age, confirmed a negative correlation in the superior and nasal quadrants of the same population.[22] As our results concur with not only the notion of declining peripheral thickness with advancing age but also an increase in the strength of this correlation from inner to outer circles, it may be likely that different corneal sectors respond differently to age-related

TABLE 6. Reproducibility of Pachymetry

	Coefficient of Variation				Interclass Correlation Coefficient			
Section	Inner	Middle	Outer	Whole	Inner	Middle	Outer	Whole
Central	0.005				0.992			
Superior	0.006	0.007	0.014	0.008	0.993	0.988	0.954	0.984
Superior nasal	0.005	0.006	0.011	0.006	0.995	0.994	0.948	0.989
Nasal	0.008	0.009	0.012	0.009	0.983	0.974	0.940	0.969
Inferior nasal	0.007	0.008	0.019	0.011	0.980	0.970	0.809	0.950
Inferior	0.005	0.007	0.009	0.006	0.992	0.982	0.973	0.990
Inferior temporal	0.006	0.007	0.016	0.009	0.984	0.981	0.866	0.971
Temporal	0.005	0.009	0.016	0.010	0.993	0.977	0.928	0.976
Superior temporal	0.007	0.007	0.011	0.007	0.986	0.990	0.973	0.990

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changes and require further investigation to establish the extent of such heterogeneity.

To compound this, the literature defines a similar landscape for corneal thickness in the context of axial length. For the central region, most studies demonstrate a lack of a significant association between thickness and axial length.[23–25] In this study, the initial positive correlation between CCT and axial length becomes insignificant when accounting for other characteristics, and the association is ultimately restricted to the ST, IT, and temporal quadrants. In keeping with other studies, this may imply the relative vulnerability of the peripheral cornea to shape alteration[26] and an age-related decline in the epithelial cell density of the peripheral (but not central) cornea.[27]

Finally, the reproducibility of whole-corneal thickness mapping shows values comparable to previous OCT studies.[28] The superior reproducibility of OCT-based techniques likely relates to an element of enhanced precision and lesser dependence on examiner expertise in comparison with other methods such as ultrasound pachymetry,[1,2] thus supporting the role of SD-OCT in the diagnosis of corneal disease and preoperative management before corneal surgery.

In summary, peripheral corneal mapping represents an understudied domain within our understanding of how corneal morphology may interact with integral patient-related characteristics. Given that it demonstrates discrete changes in healthy populations, this provides incentive to evaluate peripheral or whole-corneal thickness as a distinct parameter for the clinical identification of pathogenic processes.

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