Spectral-Domain OCT Analysis of Regional Epithelial Thickness Profiles in Keratoconus, Postoperative Corneal Ectasia, and Normal Eyes

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Abstract

PURPOSE—To assess corneal microarchitecture and regional epithelial thickness profile in eyes with keratoconus, postoperative corneal ectasia, and normal unoperated eyes using spectral-domain optical coherence tomography (SD OCT).

METHODS—Regional corneal epithelial thickness profiles of eyes with keratoconus (KC) and postoperative corneal ectasia (Ectasia) were measured with anterior segment SC OCT (Optovue RTVue-100, Optovue Inc., Fremont, CA) and compared retrospectively to those of normal eyes (Control). Epithelial thickness was assessed at 21 points, 0.5 mm apart, across the central 6-mm of the corneal apex in the horizontal and vertical meridians.

RESULTS—One hundred twenty eyes were evaluated, including 49 eyes from 29 patients with KC, 32 eyes from 16 patients with Ectasia, and 39 eyes from 21 control patients. Average epithelial thickness at the corneal apex was 41.18±6.47μm (range 30 to 51 μm) in eyes with KC, 46.5±6.72μm in eyes with ectasia (range 34 to 60 μm), and 50.45±3.92 μm in normal eyes (range 42 to 55 μm). Apical epithelial thickness was significantly thinner in eyes with KC (p <.0001) and ectasia (p=.0007) than it was in controls. Epithelial thickness ranges in all other areas varied widely for KC (SD, range 21 to 101 μm) and ectasia (SD, range 30 to 82 μm) compared to controls (SD, range 43 to 64), p = .0063

CONCLUSION—Central epithelial thickness was, on average, significantly thinner in ectatic corneas compared to controls; however, both central and regional epithelial thickness was highly irregular and variable in corneas with keratoconus and postoperative corneal ectasia. These thickness variations may alter preoperative topographic features and measurements in unpredictable ways, especially steepest K values. Regional epithelial thickness cannot be assumed to be uniform in ectatic corneas and therefore may require direct measurement when considering

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treatments for which underlying stromal thickness is particularly important, such as corneal collagen cross-linking or topography-guided excimer laser ablation.

New treatment modalities are demonstrating significant potential efficacy for ectatic corneal disorders such as keratoconus and postoperative corneal ectasia, including corneal collagen cross linking (CXL), intracorneal ring segments (ICRS), and limited topography-guided laser ablation, with variable success rates.[1-7] While these ectatic diseases comprise a heterogeneous population, the end stage histopathological changes are quite similar.[8] Histopathologic analysis of corneal ectasia have shown thinning of the epithelium, usually overlying the steepest portion of the cornea, breaks in Descemet's membrane, fragmentation of Bowman layer, and scarring.[8,9] The corneal epithelium has a rapid cell turnover and is highly reactive to asymmetries in the shape of the underlying stromal surface. Epithelial layer remodeling may therefore have a significant impact in corneal topographic measurements, corneal warpage patterns, and early detection of corneal ectatic processes.[10,11]

CXL and ICRS both require a minimum corneal depth to prevent corneal endothelial damage for CXL or segment extrusion for ICRS. In both procedures, corneal thickness is routinely initially measured with the epithelium intact and again centrally only after epithelial debridement only centrally in CXL. Topography-guided ablations utilize topographic data obtained with the epithelium intact. Thus, incorrect assumptions of regional epithelial thickness can affect outcomes in all of these procedures.

Central measurements of epithelial and stromal layers have been described with confocal microscopy, optical pachymetry and anterior segment optical coherence tomography in normal eyes.[12-15] Recently, a very high-frequency (50-MHzVHF) digital ultrasound with resolution of 21 μm has been used for three dimensional epithelial thickness analysis for the central 8 to 10-mm diameter in normal eyes, patients with keratoconus and post LASIK patients.[11,16-18]

In this study we used spectral domain optical coherence tomography (SD OCT) to evaluate and compare the regional corneal epithelial thickness profiles in patients with keratoconus, postoperative corneal ectasia and normal eyes to determine the relative thickness consistency and predictability for each condition.

PATIENTS AND METHODS

Patients with progressive keratoconus (KC) and postoperative corneal ectasia (Ectasia) presenting for the U.S. FDA corneal collagen crosslinking clinical trial (ClinicalTrials.gov identifier # NCT00567671, physician-sponsored IND with approval from the Emory University Institutional Review Board) from May 2009 to June 2010 were evaluated in this study. Keratoconus cases were classified for severity using the grading scheme proposed by McMahon et al.[19] These eyes by definition had no clinical evidence of scarring, as that was a specific exclusion criterion for the CXL study. Normal eyes of candidates for refractive surgery were used as the control group and evaluated under separate Emory IRB approval.

SPECTRAL-DOMAIN OCT ANALYSIS OF CORNEAL ARCHITECTURE

A spectral-domain OCT device (Optovue RTVue-100; Optovue Inc, Fremont, CA) with a scan rate of 26,000 axial scans per second, axial resolution of 5 μm, transverse resolution of 15 μm, and an add-on lens (CAM-L mode: 6.0-2.0 mm) was used to assess the regional corneal architecture and epithelial thickness profile in KC, Ectasia, and normal eyes. OCT mean corneal power was measured by the SD OCT Pachymetry map with the additional corneal power software (Cpwr) and corneal tomography was obtained by Scheimpflug imaging (Pentacam, Oculus).

The specific imaging capture technique for this study has been previously described.[20] Briefly, patients were asked to fixate on the target light source, and consecutive images were acquired with the patient's forehead and chin stabilized by a headrest. Images were obtained in duplicate to confirm thickness measurement reproducibility. Measurements with deviation > 3 μm in central corneal thickness were repeated.

Anatomical landmarks for the epithelium and Bowman layer were identified by direct visualization of the area of increased reflectivity corresponding with the epithelium-Bowman interface. The high-resolution cross-line scan OCT tool of the add-on lens was used to measure the epithelial thickness. The flap tool and manual measurement tool were used in this study. The SD OCT measurements include the tear film. The flap tool measurement setting is perpendicular to either the front or back surfaces of the cornea and the minimum thickness difference between mouse clicks is 4 μm. The aspect ratio of the window display should be adjusted to 1:1 scale for perpendicular appearance of the flap tool. The actual measurement values do not change as the measurements are calculated independently to the display. In highly aberrated eyes (severe keratoconus cases) the flap tool did not reliably find the front and back surfaces of the cornea in the peripheral regions, so the manual measurement tool was used for these cases. We manually adjusted the aspect ratio of the display window to 1:1 scale to acquire perpendicular measurements.

In a previous study, we used high-resolution cross-line scans in the vertical and horizontal meridians and SD OCT pachymetry maps to evaluate eyes with keratoconus before and after epithelium removal on the day of the crosslinking treatment.[21] Spectral domain OCT anatomical landmarks for epithelium and Bowman were confirmed from this analysis. The area of increased reflectivity corresponding Bowman's interface was intact after epithelium removal. An intact solid white line was observed in all cases. Therefore, our intended target for epithelial measurement was the anterior most portion of the solid white line, and we avoided including Bowman layer and the anterior stroma, since the Bowman layer itself can overestimate the epithelial thickness measurements by 8 to 19 μm.[22,23] Spectral domain OCT anatomical landmarks for the epithelium and Bowman layer are demonstrated in Figure 1.

The OCT scans were centered on the apex of the cornea, and both horizontal and vertical high-resolution cross-sectional images were acquired. Measurements exactly at the corneal apex were avoided, as both internal and interface reflectivity is high and contrast is poor. The flap tool coordinate "0.00" was used to mark the highest point in the meridian.

Epithelial thickness was assessed at 21 points 0.5 mm apart across the central 6-mm of the cornea in the horizontal and vertical meridians. Regularity and morphology of the corneal epithelial thickness were assessed.

STATISTICAL ANALYSIS

The JMP® 9.0. software (SAS Institute Inc.) was used for statistical analysis. Student's t test was used to evaluate independent samples, and Pearson correlation coefficient and analysis of variance (ANOVA) were used to compare peripheral to central measurements across the cornea. P values < .05 were considered statistically significant.

RESULTS

One hundred twenty eyes from 66 patients were evaluated, including 49 eyes from 29 patients with keratoconus, 32 eyes from 16 patients with ectasia, and 39 eyes from 21 control patients. Patient demographics are shown in Table A. There were significant differences in age, spherical equivalent, mean Sim-Ks measured by Scheimpflug tomography (Pentacam), OCT mean corneal power (Cpwr), and thinnest corneal point (SD-OCT).

Table 1 shows the epithelial thickness profiles at various regions throughout the cornea for each group. Average epithelial thickness at the highest point in the meridian was significantly thinner in eyes with keratoconus ($P < .0001$) and ectasia ($P = .0007$) than in normal eyes. There were also statistically significant differences at 0.5, 1.0, and 1.5 mm above and at 0.5, 1.0, 1.5, in the meridian ($P < .05$). The thickest point in all groups was found 2.5 mm below the corneal apex and nasally displaced. There were no statistically significant differences between groups at this thickest point.

The corneal epithelium was statistically significantly thinner in both the vertical (Figure 2A) and horizontal (Figure 2B) meridians in multiple locations in eyes with keratoconus and ectasia compared to normal eyes ($P < .05$). Epithelial thickness was not, on average, thicker in eyes with keratoconus or ectasia at any location compared to normal eyes (Table 1). Table 2 demonstrates the wide range of standard deviations for eyes with keratoconus and ectasia compared to a relatively tight range for normal eyes. Focal areas of significantly thickened epithelium were noted in eyes with keratoconus and ectasia paracentrally and peripherally, which occurred in an unpredictable fashion relative to the thickness of the underlying stroma.

Figure 3 demonstrates significant regional epithelial thickness profile variability, with localized areas of thickened and thinned epithelium in an unpredictable fashion observed in mild (Figures 3A and 3B), moderate (Figures 3C and 3D), and severe (Figures 3E and 3F) keratoconus throughout the central 6 mm of the cornea and the relationship between SD-OCT and Scheimpflug imaging (high-resolution cross-line scans, sagittal curvature, and pachymetry map).

DISCUSSION

In this study, anterior segment spectral-domain OCT demonstrated significant irregularity, variability, and alterations in regional epithelial and total corneal thickness profiles in both keratoconus and ectasia populations compared to the epithelial thickness profiles of normal eyes. Epithelial remodeling can be observed in several corneal diseases such as corneal scars, corneal dystrophies, post-refractive surgery, corneal melts, and ectatic corneal disorders.

The epithelium was statistically significantly thinner over the corneal apex in eyes with keratoconus and postoperative corneal ectasia. Focal central epithelial thinning is suggestive but not pathognomonic for keratoconus. Epithelial thickening in keratoconus has been associated with breaks in Bowman layer, and the stromal thinning has been related to the number of breaks in Descemet's membrane,[9] which may account for the cases we found with thickened epithelium overlying stromal thinning (Figure 3), in contrast to what has been reported in other series.[18] In some regions, high-resolution cross-sectional scans revealed areas of epithelial thickening "filling space" in a way that partially compensates for stromal irregularities. Specifically, we observed the epithelium to be thin over areas in which the anterior stromal curvature is steep and the surface elevated, while the epithelium tended to be thicker over areas in which the curvature is flat (or concave). These observations lead to the conclusion that the overall corneal thickness does not predict the underlying stroma thickness in eyes with KC and ectasia, and thicker epithelium can occur in regions of thinner stroma when those stromal regions do not correlate with the steepest area of the cornea. Further, this epithelial hypertrophy associated with stromal thinning occurred in mild, moderate, and severe keratoconus cases; thus, severity level cannot predict this epithelial irregularity. It would be interesting to see what these corneas would look like with "head-on" images generated by ultra high-frequency (50-MHzVHF) digital ultrasound compared to to the cross-sectional views currently available with the SD OCT. A new pattern software may soon be widely available for the Optovue system that will allow this "head-on" view; in initial studies Li and colleagues have reported averaged epithelial thickness patterns that significantly differ from normal eyes, with significantly lower central and minimum thicknesses and a higher deviation across the cornea similar to the averaged findings in our study.

It seems logical that thinned epithelium overlies thin, protruding stroma and thickening epithelium overlying thin, concave stroma and that this may occur with reasonable predictability. However, regardless of specific anatomic remodeling patterns, localized epithelial remodeling patterns cannot currently be predicted based on any other technique other than direct measurement. Neither corneal curvature nor whole cornea thickness can predict localized regions of stromal concavity or epithelial thickening. Therefore, the epithelial thickness distribution is functionally, clinically unpredictable, resulting in the need to directly measure regional epithelial thickness profiles in situations where significant difference from expected patterns could have clinical significance. Specific situations where this variability would be important include CXL treatments and/or ICRS placement in thinner corneas and topography-guided ablations.

Reinstein and co-authors characterized the epithelial thickness profile of 56 normal eyes using a very high-frequency (VHF) digital ultrasound.[16] The mean epithelial thickness at the corneal apex was 53.4±4.6 μm and the epithelium was 5.9 μm thicker inferiorly and 1.3 μm thicker nasally at the 3 mm radius. In our study the corneal epithelium in normal eyes was slightly thicker inferiorly and nasally (Figure 2) but no statistically significant differences were found. Reinstein et al. also analyzed the epithelial thickness profile of 54 eyes with keratoconus using the Artemis VHF digital ultrasound system.[11,18] The mean epithelial thickness at the corneal apex was 45.7±5.9 μm. The authors reported a localized zone of epithelial thinning surrounded by an annulus of thickened epithelium over the region of the cone ("donut shape") in all cases. Kanellopoulos and co-authors reported a larger variation in epithelial thickness in keratoconus patients and overall thickening of the corneal epithelium in the center of the pupil, with the epithelium being 3.1 μm thicker, using the Artemis-II.[24] The authors also reported a variation of ±3-4 μm in both corneal and epithelial thickness measurements, compared to the values (0.58 μm) reported by Reinstein and colleagues.[25] In our case series we observed localized areas of thickened epithelium overlying a thinner stroma occurring particularly in moderate and severe keratoconus cases, with thinner epithelium across the corneal apex.

Reinstein et al.[11] reported the efficacy of using these epithelial findings to distinguish true ectatic disease from pseudokeratoconus with epithelial thickening in an otherwise normal cornea. If the findings of regional epithelial thickness variability found in this study proved to be applicable to less advanced ectatic disease presentations, this could be relevant to refractive surgical screening and partially explain the occurrence of postoperative ectasia in patients seemingly without risk factors and with normal topographic findings.[26-28]

In SD OCT, a Fourier transformation is used to extract the frequency spectrum of the signal, which is used to generate the high resolution scans. With SD OCT it is possible to measure all echoes of light from different delays simultaneously allowing for significant increases in speed and sensitivity.[29-31] Faster acquisition times minimize artifacts from eye motion. There are several implications of the increased speed and sensitivity offered by SD OCT, including images with a lower signal to noise ratio (SNR) compared to time-domain OCT (TD OCT)[29-31] as well as excellent axial resolution images (axial resolution of 5 μm). Three-dimensional epithelial and total corneal maps can be generated by interpolating thickness profiles from different meridians.[32] However, the resolution of the cross-sectional scans is superior to the pachymetry map scans. In addition, OCT-based corneal topography and pachymetry maps seem promising for evaluating highly irregular corneas despite corneal opacities, as demonstrated by Li et al[33] and Nakagawa et al.[34]

Despite outstanding axial resolution, the manual task of identifying Bowman layer based on a visual interpretation of the image may be limited by the resolution of the flap and manual tools. It is important to clarify that the epithelial thickness measurements using SD OCT include the tear film, whereas VHF digital ultrasound measurements do not, since these are performed using an immersion technique. However, one of the advantages of SD OCT compared to VHF digital ultrasound includes its short time of image acquisition and ease of use allowing clinicians to integrate this technology to their clinic workflow. This is in contradistinction to VHF digital ultrasound, which requires an immersion technique.

Utilizing corneal epithelial thickness profile analysis in the clinical setting may aid in interpretation of corneal topography in clinical and subclinical corneal ectasia, corneal warpage in contact lens wear patients and residual refractive errors after refractive surgery explained by epithelial remodeling. Furthermore, the direct visualization of areas of reactive epithelial thickening underlying a thin residual stromal bed may improve the safety and efficacy of a number of corneal procedures including epithelium-off cross-linking treatments, corneal intacts and inlays, femtosecond laser lamellar corneal transplants and pockets.

In conclusion, SD OCT high resolution cross-sectional scans demonstrated significant differences in regional corneal epithelial thickness profiles in eyes with keratoconus and postoperative corneal ectasia compared to normal eyes, with significant regional variability and unpredictability in these ectatic eyes.

Acknowledgments

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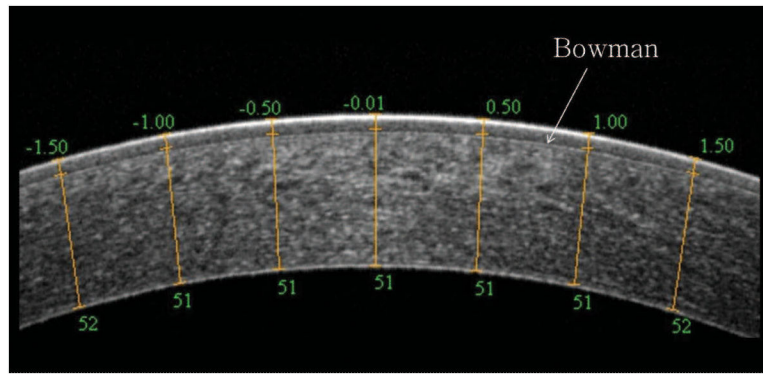
Figure 1.
Spectral-domain OCT anatomical landmarks for epithelium-Bowman layer interface.
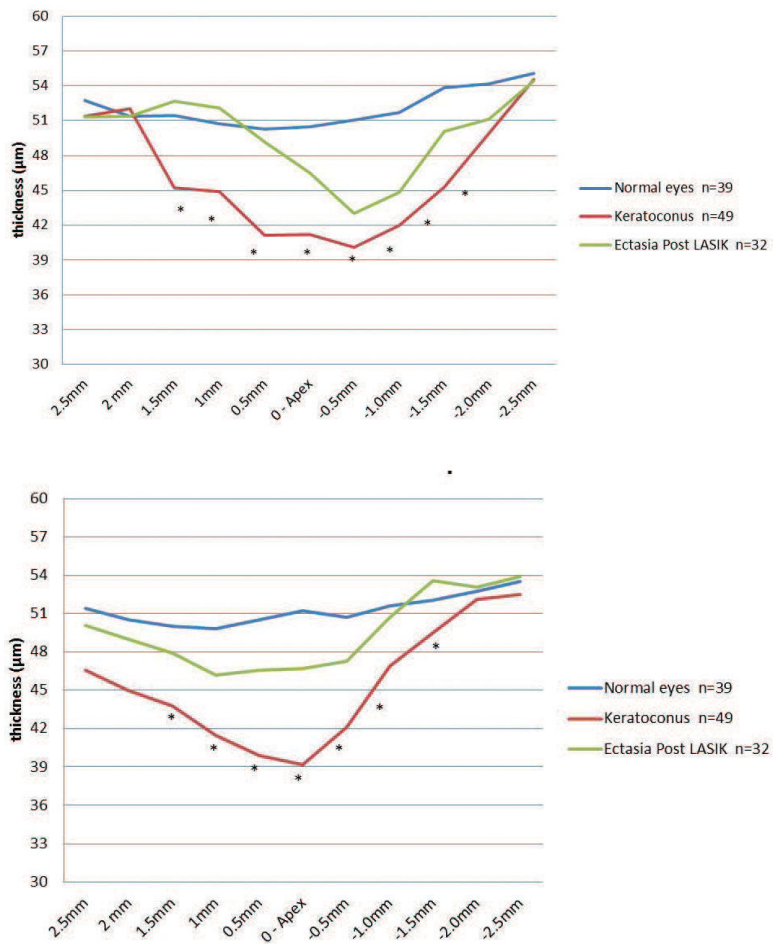
Figure 2.
Cornea epithelial thickness across the central 6-mm of the corneal apex in the (A) vertical and (B) horizontal meridian in normal eyes, keratoconus and postoperative corneal ectasia. *p < .05 (ANOVA, JMP® 9.0 - SAS Institute Inc.)
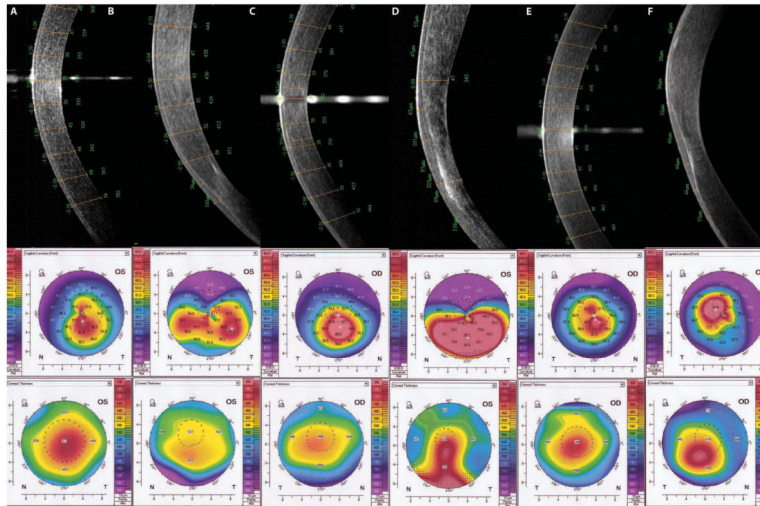
Figure 3.
Relationship between spectral-domain OCT cross-sectional high resolution scans across the central 6-mm of the corneal apex in the vertical meridian and Scheimpflug imaging (sagittal curvature and regional thickness mapping) in mild (Fig. 3 A and B), moderate (Fig. 3 C and D), and severe (Fig. 3 E and F) keratoconus. Irregularities of the corneal epithelium and localized area of thickened epithelium are observed.

Table 1

Demographics and clinical features of Study Population

Parameters	KC (n=49)	Ectasia (n=32)	Control (n=39)	P Values
Age (SD) range	36.0±7.5	45.6±7.9	35.8±6.4	p=0.0054
Gender [number (%) male]				
SE (D) range	−4.20±4.39	−5.05±6.11	−3.58±3.62	
Mean Sim-K (D) range	50.5±5.96	44.21±5.06	43.40±1.32	p<.0001
OCT Cpwr (D) range	50.12±6.88	43.36±5.20	43.37±1.21	p<.0001
Thinnest CT (μm) Range	424.6 ±62.1	406.5 ±47.6	524.3 ±14.2	p<.0001

KC = keratoconus group

Ectasia = postoperative ectasia group

Control = normal control group

SD – Standard deviation

SE –Spherical equivalent

D – Diopters

μm – microns

Sim-K – Mean Sim-Ks measured by Scheimpflug tomography (Pentacam, Oculus)

OCT Cpwr – Mean corneal power measured by the SD OCT Pachymetry map with the additional corneal power software (Cpwr)

CT – total corneal thickness in microns

Table 2

Mean epithelial thickness across the central 6-mm of the corneal vertex in the vertical axis in normal eyes, keratoconus and postoperative corneal ectasia.

	2.5 mm	2 mm	1.5 mm	1 mm	0.5 mm	K apex	−0.5mm	−1.0 mm	−1.5mm	−2.0mm	−2.5mm
Normal eyes n=39	52.73±3.92	51.36±5.3	51.45±3.72	50.72±4.7	50.27±4.6	50.45±3.9	51.04	51.68±3.5	53.81±4.9	54.19±5.2	55.09±4.5
Keratoconus n=49	51.36±5.7	50.36±5.9	50.00±5.7	47.38±5.2	43.89±6.2	41.18±6.5	40.1±7.8	42.00±11	47.81±10	50.14±6.6	54.55±6.1
Postoperative Corneal Ectasia n=32	51.34±5.3	52.31±6.6	53.84±9.5	53.09±9.4	48.84±7.9	46.5±6.7	45.31±8.3	45.87±7.6	50.59±6.1	52.78±8.2	54.43±7.3
ANOVA	$p = 0.61$	$p = 0.42$	$p = 0.049$	$p = 0.0013$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p = 0.007$	$p = 0.0165$	$p = 0.005$	$p = 0.085$

SD – Standard deviation

μm – Epithelial thickness in microns

ANOVA - JMP® 9.0 - SAS Institute Inc

Need to have a legend for "2.5mm" etc. for the measurements

Table A

Demographics and clinical features of Study Population

Parameters	KC (n=49)	Ectasia (n=32)	Control (n=39)	P Values
Age (SD) range	36.0±7.5	45.6±7.9	35.8±6.4	0.0054
SE (D) range	−4.20±4.39	−5.05±6.11	−3.58±3.62	0.421
Mean Sim-K (D) range	50.5±5.96	44.21±5.06	43.40±1.32	<.001
OCT Cpwr (D) range	50.12±6.88	43.36±5.20	43.37±1.21	<.001
Thinnest CT (μm) Range	424.6 ±62.1	406.5 ±47.6	524.3 ±14.2	<.001

KC = keratoconus group

Ectasia = postoperative ectasia group

Control = normal control group

SD – Standard deviation

SE – Spherical equivalent

D – Diopters

μm – microns

Sim-K – Mean Sim-Ks measured by Scheimpflug tomography (Pentacam, Oculus)

OCT Cpwr – Mean corneal power measured by the SD OCT Pachymetry map with the additional corneal power software (Cpwr)

CT – total corneal thickness in microns