Epithelial Thickness Profile Change After Combined Topography-Guided Transepithelial Photorefractive Keratectomy and Corneal Cross-linking in Treatment of Keratoconus

Xiangjun Chen, MD; Aleksandar Stojanovic, MD; Xiaorui Wang; Jing Liang, MD; Di Hu, MD; Tor Paaske Utheim, MD, PhD

ABSTRACT

PURPOSE: To evaluate corneal epithelial remodeling after topography-guided transepithelial photorefractive keratectomy (PRK) combined with corneal collagen cross-linking (CXL) in the treatment of keratoconus.

METHODS: Retrospective analysis of the epithelial thickness distribution changes in 53 keratoconic eyes of 44 patients. Manifest refraction, maximum (K_{max}) and minimum (K_{min}) keratometry obtained by Placido topography, corneal irregularity index (IRI) measured by Scheimpflug topography, and the epithelial thickness profile over the central 5-mm zone obtained by anterior-segment spectral domain optical coherence tomography (SD-OCT) were evaluated preoperatively and at 1 to 3, 3 to 6, and more than 6 months postoperatively.

RESULTS: Preoperatively, the epithelial thickness at the thinnest area (Min_{Area}) was 48.8 ± 4.4 μm, correlating negatively with K_{max} (r = -0.310, P < .05) and IRI (r = -0.362, P < .05). At more than 6 months postoperatively, epithelial thickening of 5.5 ± 5.1 μm occurred at the thinnest area (Min_{Area}). There was no significant change in the epithelial thickness in other areas, resulting in a decrease of difference in epithelial thickness between Min_{Area} and the rest of the paracentral areas of 5.5 ± 4.3 μm. Corrected distance visual acuity, refractive astigmatism, K_{max}, K_{min}, and IRI all improved after the treatment (P < .05).

CONCLUSIONS: A significant epithelial thickness profile change occurred after the treatment due to an increase in thickness at the preoperatively thinnest area. Because the thickness in other areas remained largely unchanged, the treatment resulted in a more even epithelial thickness distribution. This may be attributed to regularized postoperative corneal stromal shape.

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The clinical evaluation of corneal epithelial thickness profile is becoming more important in the diagnosis of keratoconus and in corneal therapeutic refractive surgery.[1-3] The corneal epithelium in normal eyes is mostly evenly distributed, being only slightly thicker inferiorly and nasally than superiorly and temporally.[4-8] In eyes with irregular stromal surface due to any pathology or after corneal refractive surgery that results in a non-physiologic stromal shape, the epithelium remodels, attempting to establish a smoother anterior corneal surface.[9] This process results in thinning above the relatively elevated corneal area and thickening above the relatively depressed regions. It is hypothesized that the magnitude of the epithelial compensation is determined by the curvature gradient.[9-11] Characterized by conical ectasia, keratoconus is a degenerative disorder of the cornea that results in irregular corneal optics and associated vision loss.[12,13] The epithelial profile in keratoconus is reported to be doughnut-shaped with localized central thinning over the apex of the cone, surrounded by an annulus of thickened epithelium around the cone.[6,14]

Corneal collagen cross-linking (CXL) is a minimally invasive procedure for treating keratoconus and iatrogenic keratectasia by increasing the biomechanical stability of the

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corneal stroma.[15-19] It has been shown that corneal epithelial thickness changes occur after CXL.[2,20,21] Kanellopoulos and Asimellis[21] first analyzed the epithelial thickness distribution measured by spectral-domain optical coherence tomography (SD-OCT) after combined treatment with photorefractive keratectomy (PRK) and CXL (Athens protocol). They compared a group of keratoconic eyes that underwent the combined treatment with untreated keratoconic eyes and found a thinner but more homogeneous epithelium in the former group. Because the epithelial thickness profile has a much wider range of deviation in keratoconic eyes than in normal virgin eyes,[6] a direct comparison of its distribution before and after the treatment may more readily reveal information about the behavior of epithelial remodeling in keratoconus. To our knowledge, the current study is the first to analyze the epithelial thickness distribution changes after the treatment with CXL combined with topography-guided PRK by directly comparing preoperative and postoperative data in the same group of eyes. We also correlated the epithelial thickness profile changes with topographic/tomographic measurements.

PATIENTS AND METHODS

This retrospective study comprises 53 keratoconic eyes (27 right eyes and 26 left eyes) of 44 patients (6 female and 38 male) treated with topography-guided transepithelial PRK followed by high fluence, short duration CXL (accelerated CXL) within the same session at the University Hospital of North Norway, Tromsø, Norway. Inclusion criteria were: clinical diagnosis of progressive keratoconus, no other ocular pathology, no epithelial defects, and no previous surgery. A specific exclusion criterion, relevant to this study population, was estimated residual corneal thickness of less than 400 microns after the topography-guided transepithelial PRK. The study was approved by the regional ethics committee (REK-NOR) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients for anonymous use of data for analysis and publication.

All patients underwent complete ophthalmologic evaluation preoperatively and postoperatively, including slit-lamp biomicroscopy, Scheimpflug-based corneal topography/tomography (Precisio; iVIS Technology, Taranto, Italy), Placido-based corneal topography and wavefront aberrometry (Nidek OPD II; Nidek Co. Ltd, Aichi, Japan), eye tonometry (Icare tonometer; Revenio Group Corporation, Helsinki, Finland), corrected distance visual acuity (CDVA), subjective spectacle refraction, and SD-OCT (RTVue; Optovue, Inc., Fremont, CA) corneal scanning. The OCT imaging preceded other examinations to avoid potential artifacts.

THE RTVUE-100 SD-OCT

Employing the RTVue-100 SD-OCT system with a corneal adaptor module, the cornea was imaged by using a pachymetry pattern, running on software version A6 (9.0.27).[22] All scans were performed across a diameter of 6 mm, centered over the pupil image. Only the data within the central 5 mm were analyzed in the current study, which included nine sectors: one 2-mm central circle and eight paracentral octants within an annulus between 2- and 5-mm circles (**Figure 1**). Data output included thickness maps of the total cornea and the epithelium. Epithelial thickness at the central, superior, and inferior region, minimum (Min) and maximum (Max) values, the difference between minimum and maximum epithelial thickness (Min-Max), and map standard deviation (St Dev) were recorded from the output of the measurements. Furthermore, for the current study, we defined a minimum epithelial thickness area (Min_{Area}) as either the pupil central 2-mm diameter zone or the continuous paracentral zones with epithelial thickness of 3 µm or greater thinner than the adjacent zones, depending on the location of the thinnest epithelium preoperatively. The area of the remaining zones in the paracenter was defined as $Para_{Rest}$. The postoperative epithelial thickness measurements at the same areas were calculated and compared to those of the preoperative values. Three measurements were obtained on a single visit, of which the two best quality images were chosen, and the average value was used for further analysis.

SURGICAL PROCEDURE

One surgeon performed all surgeries (AS). The protocol for topography-guided transepithelial PRK has been described elsewhere.[23,24] To plan the treatment, the patient's refraction, corneal elevation, pachymetry data, dynamic pupilometry, and the pupil, iris, and scleral vessel registration information were imported into Corneal Interactive Programmed Topographic Ablation (CIPTA) software. Our main aim was to reshape the irregular corneal surface into an optically regular aspheric surface by treating corneal higher order aberrations to provide better quality of vision and better CDVA. Partly reducing the lower order refractive error was only our secondary goal, followed under the constraints of the available corneal tissue. For the purpose of tissue saving, surgical design using a small optical zone of 3.3 ± 1.4 mm (range: 1.2 to 6.3 mm) with a relatively large transition zone (mean total ablation zone: 8.3 ± 0.6 mm, range: 7 to 9 mm) was applied. The large transition zone was planned to reduce the curvature gradient within the treatment zone and between the treated and non-treated cornea, with an aim to minimize regression.[25-27] In addition to the refractive part as described above, the ablation plan also consisted

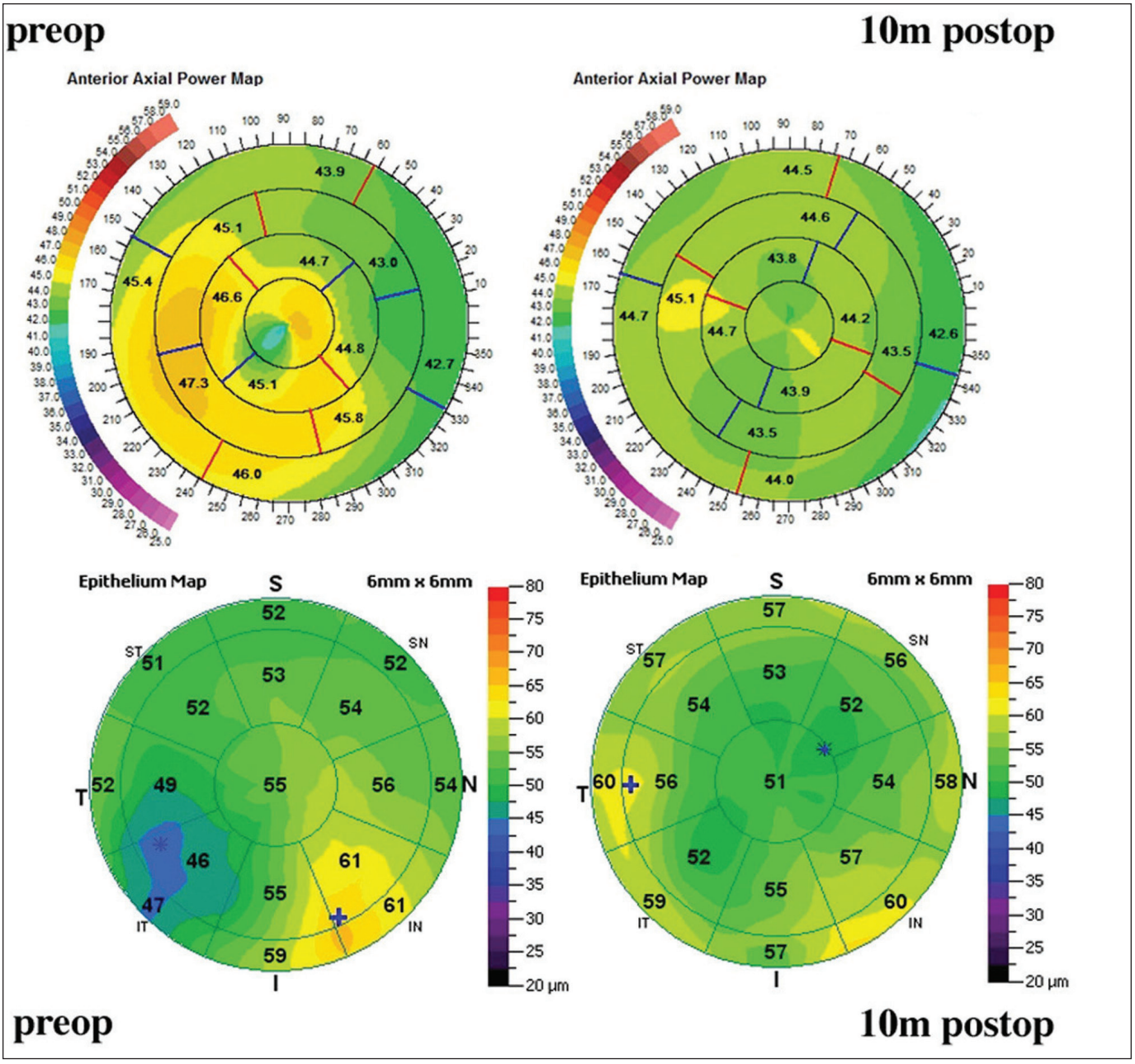

Figure 1. Corneal axial curvature map obtained by Scheimpflug tomographer (upper row) and epithelial thickness mapping obtained by spectral-domain optical coherence tomography (SD-OCT) (lower row) of one eye preoperatively (left) and 10 months postoperatively (right).

of a lamellar part, which was aimed at removal of the epithelium and simultaneous preservation of its smoothing effect, achieved by its previous remodeling during the development of keratoconus. Hence, the superior portion of the lamellar ablation consisted of only epithelium, whereas the inferior portion (cone area) partially included stroma, above which the epithelium grew thinner under remodeling. The depth of the lamellar part was decided by using the information from the preoperative epithelial thickness map obtained by OCT, whereas the 'refractive' ablation map was produced on the basis of Scheimpflug topography. The sum of the two had to be no less than the epithelial thickness at any point throughout the area of the treatment to ensure that the surface after ablation would be beneath the thickest point of the epithelium. This way, no epithelium rested at the surface after ablation, and at the same time minimal use of stromal tissue was achieved (**Figure 2**).

The refractive and lamellar parts were merged by the CIPTA software and executed in a single, uninterrupted

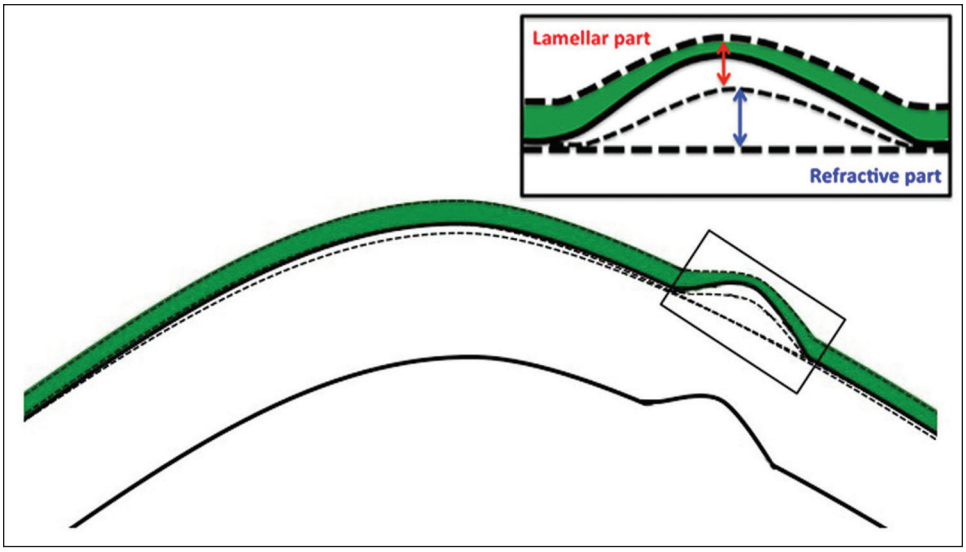

Figure 2. Schematic drawing of the ablation plan of the topography-guided transepithelial ablation in keratoconic eyes. The green layer represents the epithelium. The top and bottom dashed lines represent the epithelial surface and the desired postoperative surface. The spaces between the top and middle dashed lines represent the lamellar part of the ablation, and the space between the middle and bottom dashed lines represents the refractive part of the ablation. The lamellar part of the ablation in the area of the cone consists of both the epithelium and stroma, due to the epithelial thinning over the cone.

ablation by use of 1-KHz, high-resolution, 0.6-mm dual flying spot laser (iRES; iVIS Technology). The programmed maximum stromal ablation depth was 61.9 ± 17.3 µm (range: 26 to 113 µm). Immediately after the ablation, the ultrasound pachymetry measurement was taken and the stroma was saturated by topically applied 0.17% riboflavin-5-phosphate as one drop every 3 minutes. In cases where the measurements showed values less than 400 µm despite an estimated residual corneal thickness of at least 400 µm, the swelling with hypotonic 0.25% riboflavin solution was applied to induce a slight corneal edema until a 400-µm thickness was achieved.[28] The ultraviolet-A (UVA) light irradiation was then initiated with 18 or 12 mW/cm^2 power with effective irradiation time of 5 or 7.5 minutes, using either a high intensity UVA illuminator (Peschke CCL-VARIO Meditrade GmbH) or the KXL system (Avedro, Inc., MA). In both cases, the UV-radiation zone size was 9 mm. At the end of the surgery, one to two drops of a dexamethasone with chloramphenicol mixture (Spersadex med Kloramfenikol; Laboratoires Thea, Clermont-Ferrand, France) and one drop of bromfenac 0.9% (Yellox; Croma-Pharma GmbH, Leobendorf, Austria) eye drops were applied, followed by a bandage contact lens (Acuvue Oaysis; Johnson & Johnson Vision Care, Inc., Jacksonville, FL). Bromfenac 0.9% twice a day was used 2 days before and 3 days after the surgery. Dexamethasone with chloramphenicol four times a day was used in the first 2 weeks, and then replaced by low potency steroid rimexolone 1% (Vexol; Alcon Laboratories, Surrey, United Kingdom) eye drops in tapering doses for another 3 weeks. The bandage contact lens was removed from the cornea between postoperative days 5 to 7.

Data Analysis

Preoperative and postoperative topographic/tomographic parameters analyzed in the current study included maximum (K_{max}) and minimum (K_{min}) simulated keratometric values obtained from the OPD Scan II, and the irregularity index (IRI) measured by the Precisio. The IRI is defined as the maximum height difference between the real cornea and its best-fit aconic surface within the central 6-mm zone. It is an indication of 'how irregular' the corneal surface is. Corneal higher order aberrations within the central 5-mm zone were recorded from OPD Scan II. Mean epithelial thickness measured at the center, paracenter, superior, inferior, Min_{Area}, $Para_{Rest}$, and the difference between Min_{Area} and $Para_{Rest}$ (Min_{Area}-$Para_{Rest}$) were registered on all visits. The epithelial thickness data for left eyes were reflected in the vertical axis and superimposed onto the right eye values so that nasal/temporal characteristics could be combined.

Statistical analyses were performed using IBM SPSS Statistics (version 22; IBM Corp., Armonk, NY). The Shapiro–Wilk test was used to test the normality of the data distribution. The paired *t* test or Wilcoxon signed-rank test was used to examine preoperative and postoperative differences. The Pearson or Spearman correlation coefficient was applied to seek possible correlations between different parameters. In all analyses, a *P* value of less than .05 was considered statistically significant.

RESULTS

At the time data were collected, 22 eyes, 41 eyes, and 48 eyes had follow-up data available at 1 to 3 months (1.8 ± 0.3 months; range: 1 to 2 months), 3 to 6 months (4.4 ± 1.3 months; range: 3 to 6 months), and more than 6 months (15.0 ± 5.3 months; range: 7 to 31 months) postoperatively, respectively. Among these, 39 eyes had a follow-up time of 12 months or longer. No statistically significant difference in age, preoperative topographic/tomographic parameters, or epithelial thickness param-

TABLE 1
Postoperative Refractive and Topographic Changes

Parameter	CDVA (logMAR)	Sphere (D)	Cylinder (D)	SE (D)	K_{max} (D)	K_{min} (D)	K_{max}-K_{min} (D)	IRI (μm)
Preoperative measurements (n = 53)								
Mean ± SD	0.16 ± 0.18	0.77 ± 1.90	-3.25 ± 2.01	-0.85 ± 1.82	47.19 ± 3.58	43.82 ± 2.62	3.38 ± 2.63	36.3 ± 14.9
Range	-0.08 to 1.00	-3.75 to 5.50	-8.75 to -0.50	-7.38 to 4.13	41.00 to 58.25	37.25 to 53.75	0.25 to 12.25	12.00 to 71.00
Postoperative changes								
1 to 3 months (n = 22)	-0.08 ± 0.23	-1.08 ± 2.12[a]	1.61 ± 2.51[a]	-0.24 ± 1.74	-2.45 ± 3.21[a]	-0.97 ± 2.27[a]	-1.48 ± 1.48[a]	-10.5 ± 9.9[a]
3 to 6 months (n = 41)	-0.08 ± 0.12[a]	-0.97 ± 2.07[a]	1.70 ± 2.07[a]	-0.15 ± 2.12	-2.15 ± 2.48[a]	-1.02 ± 1.88[a]	-1.12 ± 1.23[a]	-10.7 ± 6.9[a]
> 6 months (n = 48)	-0.12 ± 0.20[a]	-0.82 ± 2.07[a]	1.53 ± 1.99[a]	-0.05 ± 2.01	-2.43 ± 2.45[a]	-1.11 ± 1.67[a]	-1.33 ± 1.41[a]	-13.2 ± 10.2[a]

CDVA = corrected distance visual acuity; D = diopters; SE = spherical equivalent; K_{max} = maximum simulated keratometry; K_{min} = minimum simulated keratometry; IRI = irregularity index; SD = standard deviation
[a]*Statistically significant changes from preoperative measurements.*

eters was found between the eyes with or without follow-up longer than 12 months.

The mean age of the patients at the time of surgery was 31.0 ± 10.1 years (range: 13 to 50 years). Preoperative refractive and topographic/tomographic measurements are summarized in **Table 1**. No adverse events were reported intraoperatively or postoperatively. No eyes demonstrated progression of keratoconus during the follow-up period. Postoperatively, a significant improvement in CDVA and decrease in refractive astigmatism, K_{max}, K_{min}, and IRI were seen ($P < .05$ in all comparisons with preoperative measurements) (**Table 1**). Corneal root mean square higher order aberrations decreased significantly from 2.08 ± 0.88 to 0.84 ± 0.50 μm postoperatively ($P = .000$). Coma-type (S3+5+7) and spherical-type (S4+6+8) aberrations decreased from 1.96 ± 0.83 to 0.74 ± 0.50 μm and from 0.63 ± 0.39 to 0.35 ± 0.18 μm, respectively ($P = .000$). A demarcation line was present in 42 (79%) eyes with an average depth of 292.1 ± 87.5 μm.

Epithelial Thickness Profile Change and Its Correlation With Topographic/Tomographic Data

The epithelial thickness profile change is shown in **Figure 3** and **Table 2**. Preoperatively, the epithelial thickness at the center and Min_{Area}, the minimum epithelial thickness, the Min-Max, and the Min_{Area}-$Para_{Rest}$ correlated negatively with K_{max} and IRI ($P < .05$), whereas the St Dev correlated positively with K_{max} and IRI ($P < .05$) (**Table 3**, **Figure 4**).

Postoperatively, there was epithelial thickening at Min_{Area}; however, the epithelial thickness at $Para_{Rest}$ and center did not show a statistically significant change, leading to a decrease in Min_{Area}-$Para_{Rest}$ by 5.5 ± 4.3 μm at more than 6 months postoperatively (**Table 2**). The amount of epithelial thickening at the Min_{Area} area correlated negatively with its preoperative value ($r = -0.449$, $P < .01$), optical zone ($r = -0.329$, $P < .05$), and total ablation zone size ($r = -0.433$, $P < .01$), and correlated positively with preoperative IRI ($r = 0.310$, $P < .05$).

DISCUSSION

Topography-guided PRK followed by CXL has been reported to be safe and effective in arresting keratectasia progression and in improving corneal optic regularity in keratoconus.[24,29] In line with these reports, the current study demonstrated a significant improvement in CDVA and a decrease in refractive astigmatism, keratometry values, IRI, and corneal HOAs after the combined treatment. Recently developed three-dimensional corneal epithelial mapping by SD-OCT allows in vivo, non-contact, quantitative measurement of the epithelial thickness profile.[4,5] Epithelial thickness distribution using SD-OCT has been studied in normal

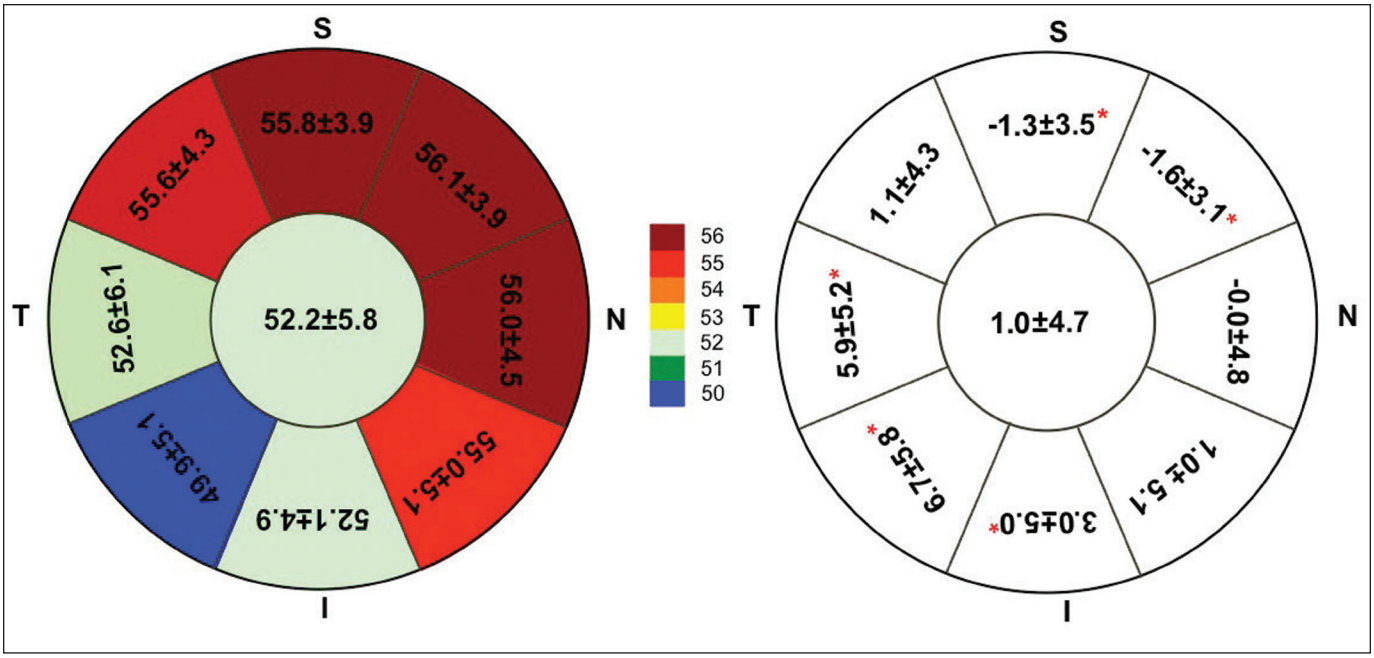

Figure 3. Average preoperative epithelial thickness distribution (left) and its change at > 12 months postoperatively (right) within the central 5-mm area (n = 39). Values marked with * represent statistically significant change postoperatively.

eyes,[5,30] long-term contact lens wearers,[31] dry eyes,[32,33] keratoconic eyes,[6] and eyes after refractive surgery.[4,22] Reinstein et al.[2] proposed that epithelial profile map could be a useful adjunct to topography in monitoring patients after CXL. In this study, we investigated changes in the corneal epithelial thickness profile in keratoconic eyes after topography-guided transepithelial PRK followed by CXL.

Reinstein et al.[7] found the thinnest point of the epithelium in normal eyes to be, on average, at 0.33 mm temporally and 0.9 mm superiorly from the corneal vertex. In keratoconic eyes, several studies[1,6,8,14,34,35] demonstrated thinning of the epithelium in the temporal inferior area and larger thickness variation, which is in accordance with the current study. Furthermore, we found that both epithelial thickness at the Min_{Area} and its difference from the surroundings (Min_{Area}-$Para_{Rest}$) correlated significantly with K_{max} and IRI: the steeper and more irregular the corneal shape is, the thinner the epithelium at the cone apex and the larger its variation from the surroundings will be. Vinciguerra et al.[11] and Reinstein et al.[10] hypothesized that the amount of epithelial remodeling is determined by the rate of curvature change at the stromal surface. It would have been of interest to correlate the epithelial thickness variation in keratoconic eyes to the curvature gradient maps, but the topographers used in the current study do not support the curvature gradient mapping.

Studies regarding the epithelial thickness profile change after CXL are scarce.[2,20,36] Using SD-OCT 3 months after CXL in 17 keratoconic eyes and 14 eyes with postoperative ectasia, Rocha et al.[20] showed reduced peripheral epithelial thickness and decreased regional variation. Using Artemis VHF digital ultrasound, Reinstein et al.[2] reported thickening of the peripheral epithelium in two eyes after CXL for post-LASIK ectasia. Despite the inconsistency in thinning/thickening of the peripheral epithelium, both demonstrated more uniform regional epithelial thickness distribution after CXL, most likely due to a more regular postoperative stromal shape.

After combined treatment by topography-guided PRK and accelerated CXL, the current study revealed significant postoperative thickening of the epithelium at Min_{Area} with the amount of thickening correlating negatively with the preoperative epithelial thickness, optical zone size, and total ablation zone size. These findings were consistent with our previously reported postoperative epithelial thickness change after topography-guided PRK in treatment of myopia.[4] However, the epithelial thickening patterns were somehow different; in the current study, the epithelial thickening was limited to the preoperatively thinnest area, whereas the thickness at the center and the rest of the paracentral sections did not show significant changes. This was not the case after topography-guided PRK in the treatment of myopia,[4] where the epithelial thickness increased centrally by 5.20 ± 3.43 µm and paracentrally by 5.72 ± 3.30 µm. The reason for the difference in the epithelial remodeling pattern between the two studies is presumably the different starting points: regular versus irregular corneal surface and healthy versus pathologic keratoconic cornea. Additionally, the subsequent

TABLE 2
Postoperative Epithelial and Stromal Thickness Changes (µm)

Parameter	Superior	Inferior	Center	Min	Max	St Dev	Min-Max	Min_{Area}	$Para_{Rest}$	Min_{Area} - $Para_{Rest}$	Paracenter	$Stroma_{Min}$
Preoperative measurements (n = 53)												
Mean ± SD	55.7 ± 3.7	52.5 ± 4.2	52.3 ± 5.5	43.7 ± 5.8	61.7 ± 4.0	4.6 ± 1.6	-18.2 ± 6.0	48.8 ± 4.4	55.8 ± 3.5	-7.0 ± 3.1	54.1 ± 3.6	441.8 ± 29.6
Range	46.5 to 64.5	39.0 to 63.0	39.0 to 68.0	31.0 to 57.0	53.0 to 70.0	1.7 to 9.9	-33.0 to -7.0	39.0 to 61.0	46.3 to 65.0	-15.25 to -0.7	43.7 to 62.8	400.5 to 521.5
Postoperative changes												
1 to 3 months (n = 22)	-2.3 ± 3.7[a]	2.1 ± 4.5[a]	-1.6 ± 5.3	3.8 ± 5.9[a]	-0.3 ± 4.3	-1.2 ± 1.6[a]	4.3 ± 5.8[a]	4.5 ± 6.1[a]	-1.9 ± 3.7[a]	6.3 ± 4.6[a]	-0.11 ± 3.9	-42.0 ± 23.6[a]
3 to 6 months (n = 41)	-0.9 ± 3.8	2.4 ± 5.0[a]	-0.2 ± 5.2	2.6 ± 6.0[a]	1.5 ± 4.8[a]	-0.4 ± 1.5	1.5 ± 5.7	4.3 ± 5.7[a]	-0.5 ± 3.8	4.7 ± 4.5[a]	0.8 ± 4.1	-35.4 ± 20.2[a]
> 6 months (n = 48)	-0.3 ± 3.6	3.1 ± 4.6[a]	1.0 ± 4.8	3.1 ± 5.1[a]	2.2 ± 5.2[a]	-0.6 ± 1.7[a]	1.3 ± 6.1	5.5 ± 5.1[a]	0.0 ± 3.5	5.5 ± 4.3[a]	1.2 ± 3.9[a]	-25.7 ± 23.3[a]

St Dev = map standard deviation; Min_{Area} = minimum epithelial thickness area; $Para_{Rest}$ = remaining zones in the paracenter; $Stroma_{Min}$ = minimum stromal area; SD = standard deviation
[a]*Statistically significant difference from preoperative measurement.*

TABLE 3
Correlation Between Epithelial Thickness and Topographic/ Tomographic Data

Parameter	*r*	*P*
K_{max}		
Inferior	-0.201	.149
Center	-0.465	.000
Min	-0.340	.013
Min-Max	-0.337	.013
St Dev	0.412	.002
Min_{Area}	-0.310	.024
Min_{Area}-$Para_{rest}$	-0.327	.017
IRI		
Inferior	-0.393	.004
Center	-0.290	.035
Min	-0.500	.000
Min-Max	-0.439	.001
St Dev	0.441	.001
Min_{Area}	-0.362	.008
Min_{Area}-$Para_{rest}$	-0.337	.014

K_{max} = maximum simulated keratometry; St Dev = map standard deviation; Min_{Area} = minimum epithelial thickness area; $Para_{Rest}$ = remaining zones in the paracenter; IRI= irregularity index

CXL procedure performed after the topography-guided PRK may have altered the corneal epithelial remodeling behavior. Kanellopoulos and Asimellis[37] investigated the epithelial thickness profile changes after high myopic femtosecond laser-assisted LASIK with or without concurrent high-fluence CXL (UVA fluence of 30 mW/cm^2 for a total of 80 seconds). The comparison of matched myopic correction subgroups treated for myopia greater than -7.00 D indicated significantly less thickening of the epithelium paracentrally in eyes treated with concurrent CXL, indicating that the application of CXL might have played a role in preventing postoperative epithelial thickening, which is commonly found in healthy eyes.[4,22]

Kanellopoulos and Asimellis[21] compared the epithelial thickness profile between 175 keratoconic eyes treated with the Athens protocol and 193 untreated keratoconic eyes. They found a thinner central epithelium (47.78 ± 7.36 vs 52.09 ± 6.80 µm) and lower average thickness difference between the minimum and maximum epithelial thickness (-19.94 ± 7.21 vs -21.83 ± 12.07 µm) in the group of eyes treated with the Athens protocol (1 year after the treatment) than in the group of untreated keratoconic eyes. Contrary to our results, their data showed a lower superior, inferior, and mean epithelial thickness in eyes treated with the Athens protocol; however, it was

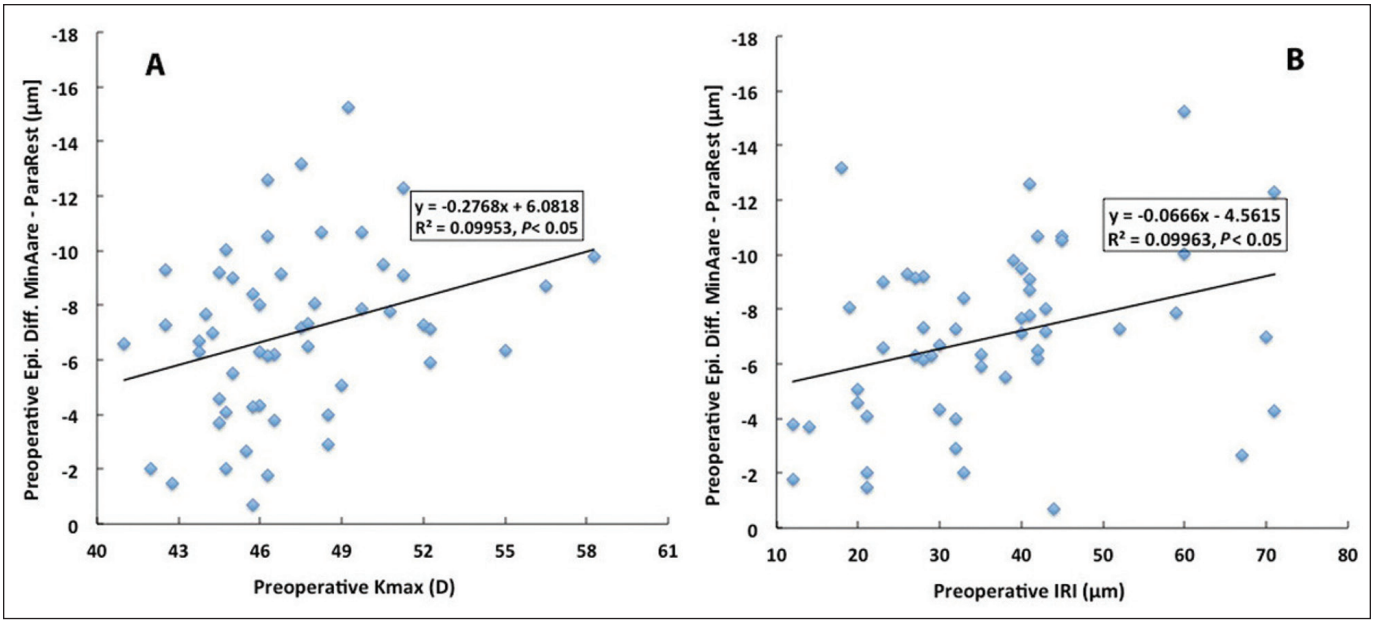

Figure 4. The correlation between preoperative epithelial thickness variation (the difference between the minimum epithelial thickness area [Min_{Area}] and the area of the remaining zones in the paracenter [$Para_{Rest}$]) and (A) maximum keratometry (K_{max}) and (B) corneal irregularity index (IRI). D = diopters

not mentioned whether the differences were of statistical significance. There are several factors that may explain the discrepancy. First, unlike our study, Kanellopoulos and Asimellis did not directly compare the preoperative and postoperative data in the same eyes. Second, the custom ablation design was different between the two types of topography-guided treatments[21,23] (the use of integrated transepithelial approach vs separate phototherapeutic keratectomy for ablating the epithelium, use of different optical zone sizes, programmed steepening of the opposite hemi-meridian in Athens protocol, etc.). Third, the difference in the CXL protocol (the UVA fluence and irradiation duration) may have stimulated different postoperative epithelial remodeling patterns. Finally, the central and paracentral epithelial thickness measurements in the two study groups might have been affected by the difference in the location of the cone in the respective study populations.

Reinstein et al.[38] proposed that the epithelial thickness range between the thickest and thinnest area is related to the degree of stromal irregularity in eyes with irregular astigmatism, and a reduction in epithelial thickness range was achieved in 89% of the eyes treated with transepithelial phototherapeutic keratectomy. In the current study, we demonstrated reduction in epithelial thickness variation (Min_{Area}-$Para_{Rest}$) following the corneal regularization achieved after transepithelial topography-guided PRK combined with CXL. The epithelium over the cone became thicker and the epithelial thickness variation decreased due to reduced need for compensation for stromal bulging, proving that the stromal surface became more regular postoperatively.[39]

Our study established a specific pattern of epithelial remodeling after the combined topography-guided PRK and CXL in keratoconic eyes. Exploring the three-dimensional epithelial morphology following the iatrogenic changes in corneal morphology will broaden our understanding of the epithelial remodeling and may help optimize our treatments. Future studies with a long-term follow-up and larger sample size are warranted.

AUTHOR CONTRIBUTIONS

Study concept and design (XC, AS, TPU); data collection (XC, XW, JL, DH); analysis and interpretation of data (XC, AS, TPU); writing the manuscript (XC, AS, XW, JL, DH); critical revision of the manuscript (XC, AS, TPU); statistical expertise (XC); administrative, technical, or material support (AS); supervision (AS, TPU)

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