ARTICLE

Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results

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PURPOSE: To evaluate changes in corneal topography indices after corneal collagen crosslinking (CXL) in patients with keratoconus and corneal ectasia and analyze associations of these changes with visual acuity.

SETTING: Cornea and refractive surgery subspecialty practice.

DESIGN: Prospective randomized controlled clinical trial.

METHODS: Corneal collagen crosslinking was performed in eyes with keratoconus or ectasia. Quantitative descriptors of corneal topography were measured with the Pentacam topographer and included 7 indices: index of surface variance, index of vertical asymmetry, keratoconus index, central keratoconus index, minimum radius of curvature, index of height asymmetry, and index of height decentration. Follow-up was 1 year.

RESULTS: The study comprised 71 eyes, 49 with keratoconus and 22 with post-LASIK ectasia. In the entire patient cohort, there were significant improvements in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature at 1 year compared with baseline (all *P*<.001). There were no significant differences between the keratoconus and ectasia subgroups. Improvements in postoperative indices were not correlated with changes in corrected or uncorrected distance visual acuity.

CONCLUSIONS: There were improvements in 4 of 7 topography indices 1 year after CXL, suggesting an overall improvement in corneal shape. However, no significant correlation was found between the changes in individual topography indices and changes in visual acuity after CXL.

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Corneal collagen crosslinking (CXL) is a promising new treatment to strengthen and stabilize the cornea in cases of keratoconus[1] and ectasia after laser in situ keratomileusis (LASIK).[2–4] The increase in biomechanical strength[5] after CXL slows the progression of keratoconus and ectasia and in many cases improves patients' keratometric and visual acuity outcomes. In our previous report of 1-year CXL outcomes[6] and in other studies,[4,7–10] patients had an improvement in corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), and maximum and average keratometry (K) values.

Because the corneal shape and structure may be altered by CXL, it would be informative to assess resultant changes in quantitative descriptors of corneal topography as a possible concomitant of the improved clinical outcomes. In this prospective randomized controlled study of CXL, the 1-year postoperative changes in topography parameters obtained with a Scheimpflug system were analyzed. The treatment group was also compared with a sham control group and a fellow-eye control group, and results were correlated with 1-year changes in visual acuity.

PATIENTS AND METHODS

Patients were enrolled as part of a multicenter prospective randomized controlled clinical trial performed under guidelines of the U.S. Food and Drug Administration.[A,B] An investigational review board approved and monitored the study, which complied with the U.S. Health Insurance Portability and Accountability Act. All patients provided informed consent.

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As stated in the previous study,[6] the inclusion criteria included age 14 years or older, axial topography pattern consistent with keratoconus or corneal ectasia, an inferior–superior (I–S) ratio greater than 1.5 on topography mapping, a corrected distance visual acuity (CDVA) worse than 20/20, and a diagnosis of progressive keratoconus or LASIK-induced or photorefractive keratectomy–induced ectasia. Progressive keratoconus or ectasia was defined as 1 or more of the following changes over a period of 24 months: an increase of 1.00 diopter (D) or more in the steepest keratometry (K) measurement, an increase of 1.00 D or more in manifest cylinder, or an increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE). Keratoconus severity was classified as mild, moderate, or severe using a grading scheme adapted from McMahon et al.[11]

Exclusion criteria included a history of corneal surgery, corneal pachymetry less than 300 μm (patients with a pretreatment pachymetry measurement between 300 μm and 400 μm received hypotonic riboflavin for stromal swelling[12]), history of chemical injury or delayed epithelial healing, and pregnancy or lactation during the course of the study.

Treatment Group

Patients were initially randomized into a treatment group or a control group. The treatment group received standard riboflavin 0.1%–ultraviolet A (UVA) CXL treatment, according to the methodology described by Wollensak et al.[1] Initially, a topical anesthetic agent was administered and the central 9.0 mm epithelium was removed by mechanical debridement. Riboflavin 0.1% in 20% dextran was then administered topically every 2 minutes for 30 minutes. Riboflavin absorption throughout the corneal stroma and anterior chamber was confirmed by slitlamp examination. Ultrasound (US) pachymetry was performed and, if the cornea was thinner than 400 μm, hypotonic riboflavin in sterile water was administered, 1 drop every 10 seconds for 2-minute sessions, after which US pachymetry was performed to confirm that the stroma had swollen to 400 μm or more. The cornea was aligned and exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm^2. During UVA exposure, isotonic riboflavin administration was continued every 2 minutes. Postoperatively, antibiotic and corticosteroid drops were administered, a soft contact lens bandage was placed, and the eye was reexamined at the slitlamp. The contact lens was removed after the epithelial defect had closed. Antibiotic and corticosteroid drops were continued 4 times daily for 1 week and 2 weeks, respectively. Patients were followed for 12 months postoperatively.

Sham Control Group

The sham control group received riboflavin 0.1% ophthalmic solution alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for 30 minutes. Next, the cornea was exposed to a sham treatment in which the UVA light was not turned on. While the patient was under the UVA light, riboflavin was administered topically every 2 minutes for an additional 30 minutes. The sham control patients were followed for 3 months postoperatively, at which point the study eye crossed over to the treatment group and received full riboflavin–UVA treatment.

Fellow-Eye Control Group

In addition to the sham control group, a control group of fellow eyes of patients who did not have CXL treatment bilaterally was analyzed. The group comprised eyes with frank keratoconus or ectasia that did not have CXL, eyes with evidence of disease that did not meet the inclusion criteria of this study, and eyes with no evidence of disease. The topography index measurements were analyzed at baseline and 12 months and compared with the postoperative measurements in the treatment group at the same time points.

Postoperative Measurements

Topographic indices were obtained using the Pentacam topographer (Oculus, Inc.). To confirm that the Scheimpflug tracings actually followed the observed corneal surfaces, the edge pixel maps of the Scheimpflug images were viewed to ensure that they conformed to the edge of the image using the software interface of the topographer.

The topographer can calculate the following 7 indices: index of surface variance, a general measure of corneal surface irregularity; index of vertical asymmetry, a measure of the difference between superior curvature and inferior curvature in the cornea (similar to the commonly used I–S ratio[13–15]); keratoconus index; central keratoconus index; minimum radius of curvature, a measurement of the smallest radius of curvature of the cornea (ie, the maximum steepness of the cone); index of height asymmetry, a measurement similar to the index of vertical asymmetry but based on corneal elevation; and index of height decentration, calculated with Fourier analysis of corneal height to quantify the degree of vertical decentration. Table 1 shows the abnormal and pathological values. All data were measured preoperatively and 1, 3, 6, and 12 months postoperatively.

Statistical Analysis

Statistical analysis was performed using PASW Statistics software (version 18, SPSS, Inc.). A paired 2-tailed Student *t* test was performed to analyze the postoperative changes compared with baseline and to compare the postoperative changes over time. An independent *t* test was performed

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Table 1. Abnormal and pathological values for the topography indices (from topography device user's manual).

Index	Abnormal	Pathological
ISV	≥37	≥41
IVA	≥0.28	≥0.32
KI	≥1.07	≥1.07
CKI	≥1.03	≥1.03
R_{min}	<6.71	<6.71
IHA	≥19	>21
IHD	≥0.014	≥0.016

CKI = central keratoconus index; IHA = index of height asymmetry; IHD = index of height decentration; ISV = index of surface variance; IVA = index of vertical asymmetry; KI = keratoconus index; R_{min} = minimum radius of curvature

to compare the differences in postoperative changes between the treatment group and the individual control groups as well as between the keratoconus and ectasia subgroups. Pearson correlation coefficients (*r*) were used to analyze the possible correlation of postoperative topography measurements and postoperative visual acuity. A *P* value less than 0.05 was used to determine statistical significance.

RESULTS

Seventy-one eyes of 58 patients had CXL and were followed for 1 year. These eyes included 49 eyes with keratoconus and 22 with post-LASIK ectasia. The sham control group comprised 41 eyes of 41 patients (28 keratoconus and 13 ectasia), and the fellow-eye control group comprised 30 eyes of 30 patients (21 keratoconus and 9 ectasia).

Treatment Group

In the treatment group, there were statistically significant decreases in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature 1 year after CXL therapy. However, there were no significant changes in central keratoconus index, index of height asymmetry, and index of height decentration. Table 2 shows the complete data.

Index of Surface Variance One year postoperatively, the index of surface variance was significantly decreased from baseline (mean change −10.5 ± 18.2; $P<.001$). Initially, there was a significant increase (mean change 11.1 ± 13.7) in the index between baseline and 1 month ($P<.001$) followed by a significant decrease between 1 month and 3 months (mean change −11.3 ± 16.7; $P<.001$) and between 3 months and 6 months (mean change −7.58 ± 17.7; $P=.001$). Although the index decreased between 6 months and 12 months (mean change −2.72 ± 14.2), this change was not statistically significant ($P=.11$) (Figure 1, *A*).

Index of Vertical Asymmetry At 1 year, the index of vertical asymmetry was significantly decreased from baseline (mean change −0.11 ± 0.23; $P<.001$). Initially, there was a significant increase in the index between baseline and 1 month (mean change 0.11 ± 0.21; $P<.001$) followed by a significant decrease between 1 month and 3 months (mean change −0.11 ± 0.23; $P<.001$) and between 3 months and 6 months (mean change −0.08 ± 0.21; $P=.002$). There was no significant change in the index of vertical asymmetry between 6 months and 12 months (mean change −0.04 ± 0.21; $P=.14$) (Figure 1, *A*).

Keratoconus Index At 1 year, the keratoconus index was significantly decreased over baseline (mean change −0.04 ± 0.08; $P<.001$). There was a significant increase in the index between baseline and 1 month (mean change 0.03 ± 0.08; $P=.004$) followed by a significant decrease between 1 month and 3 months (mean change −0.03 ± 0.06; $P<.001$). There was no significant change in the index between 3 months and 6 months (mean change −0.03 ± 0.10, $P=.008$) or between 6 months and 12 months (mean change −0.003 ± 0.07, $P=.75$) (Figure 1, *A*).

Minimum Radius of Curvature At 1 year, the minimum radius of curvature was significantly increased (that is, the cornea was flattened) from baseline (mean change 0.16 ± 0.28; $P<.001$). Initially, there was a significant decrease in the radius of curvature between baseline and 1 month (mean change −0.14 ± 0.26; $P<.001$) followed by a significant increase between 1 month and 3 months (mean change 0.18 ± 0.24; $P<.001$) and between 3 months and 6 months (mean change 0.08 ± 0.23; $P=.007$). There was no significant change between 6 months and 12 months (0.04 ± 0.23; $P=.15$) (Figure 1, *B*).

Differences Between Keratoconus and Ectasia Subgroups There were no significant differences between the keratoconus subgroup and the ectasia subgroup in any postoperative corneal index between baseline and 1 year (index of surface variance, $P=.34$; index of vertical asymmetry, $P=.72$; keratoconus index, $P=.70$; central keratoconus index, $P=.62$; index of height asymmetry, $P=.11$; index of height decentration, $P=.36$; minimum radius of curvature, $P=.08$). Table 3 shows the complete data and analysis in the 2 subgroups.

Control Groups

Fellow Eye In the fellow-eye control group, there were no significant differences in any corneal index between baseline and 1 year postoperatively (index of surface variance, $P=.28$; index of vertical asymmetry, $P=.36$; keratoconus index, $P=.21$; central keratoconus index, $P=.69$; index of height asymmetry, $P=.68$;

Table 2. Postoperative topography indices (71 eyes).

Index	Mean ± SD					*P* Value		
		Postoperative						
	Baseline	1 Month	3 Months	6 Months	12 Months	KC Vs EC	Tx Vs Sham	Tx Vs FE
ISV	123.8 ± 56.6*	134.9 ± 55.9*†‡	123.6 ± 56.6*†‡	116.0 ± 53.7*‡	113.3 ± 56.7*†	.34*	.25*	<.001*
IVA	1.40 ± 0.69*	1.51 ± 0.68*†‡	1.40 ± 0.72*‡	1.32 ± 0.68*†‡	1.28 ± 0.75*†	.72*	.40*	.003*
KI	1.37 ± 0.23*	1.40 ± 0.25*†‡	1.36 ± 0.25*	1.33 ± 0.21*†‡	1.33 ± 0.23*†	.70*	.62*	<.001*
CKI	1.04 ± 0.13	1.07 ± 0.07†‡	1.05 ± 0.07‡	1.04 ± 0.07‡	1.04 ± 0.06	.62	.74	.52
IHA	31.0 ± 22.4	37.6 ± 31.4	34.1 ± 27.2	34.5 ± 27.1	29.1 ± 23.9	.11	.69	.36
IHD	0.12 ± 0.07	0.13 ± 0.07†‡	0.12 ± 0.08‡	0.11 ± 0.06†‡	0.11 ± 0.12	.36	.47	.52
R_{min}	5.88 ± 0.83*	5.75 ± 0.83*†‡	5.93 ± 0.86*‡	6.00 ± 0.80*†‡	6.04 ± 0.76*†	.08*	.15*	.20*

CKI = central keratoconus index; EC = ectasia subgroup; FE = fellow-eye control group; IHA = index of height asymmetry; IHD = index of height decentration; ISV = index of surface variance; IVA = index of vertical asymmetry; KC = keratoconus subgroup; KI = keratoconus index; R_{min} = minimum radius of curvature; Sham = sham control group; Tx = treatment group

*Statistically significant change from baseline to 1 year

†Statistically significant change compared with baseline measurements

‡Statistically significant change compared with previous measurement

index of height decentration, *P*=.85; minimum radius of curvature, *P*=.16). Similarly, there was no significant change in UDVA (mean change 0.04 ± 0.18 logMAR) or CDVA (0.04 ± 0.14 logMAR) between baseline and 1 year (both *P*=.2).

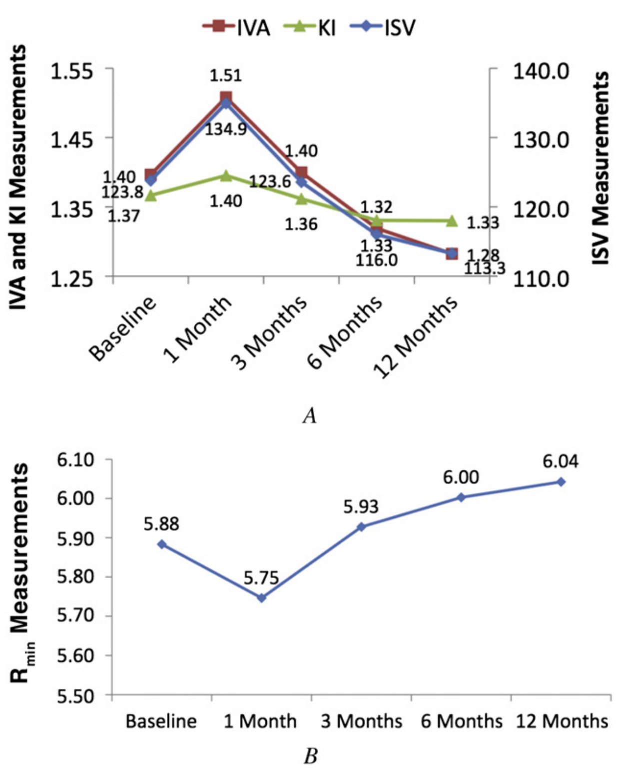

Figure 1. Change in postoperative topography indices over time in patients with keratectasia. *A*: Index of surface variance (ISV), index of vertical asymmetry (IVA), and keratoconus index (KI). *B*: minimum radius of curvature (R_{min}).

Sham Control Group In the sham control group, there were no significant changes in any corneal index between baseline and 3 months (index of surface variance, *P*=.20; index of vertical asymmetry, *P*=.29; keratoconus index, *P*=.83; central keratoconus index, *P*=.32; index of height asymmetry, *P*=.10; index of height decentration, *P*=.97; minimum radius of curvature, *P*=.71). The UDVA decreased significantly, from 0.93 ± 0.29 logMAR to 0.84 ± 0.32 logMAR (*P*=.03); however, there was no significant change in CDVA from baseline (0.40 ± 0.29 logMAR) to 1 year (0.38 ± 0.25 logMAR) (*P*=.3).

Treatment Versus Control Groups

The 1-year changes in the index of surface variance, index of vertical asymmetry, and keratoconus index were significantly better in the treatment group than in the fellow-eye control group (*P*<.001, *P*=.003, and *P*<.001, respectively) (Figure 2, *A* and *B*). However, there were no statistically significant differences in the 3 indices between the sham control group and the treatment group between baseline and 3 months (*P*=0.25, *P*=0.40, and *P*=0.62, respectively).

The change in the minimum radius of curvature (baseline to 12 months) in the fellow-eye control group was not significantly different from the change in the treatment group (*P*=.20). The change in the minimum radius of curvature from baseline to 3 months in the sham control group was not significantly different from the change in the treatment group during the same period (*P*=.15).

Correlation with Visual Acuity

In the entire cohort, there were significant improvements in UDVA (mean change −0.07 ± 0.26 logMAR;

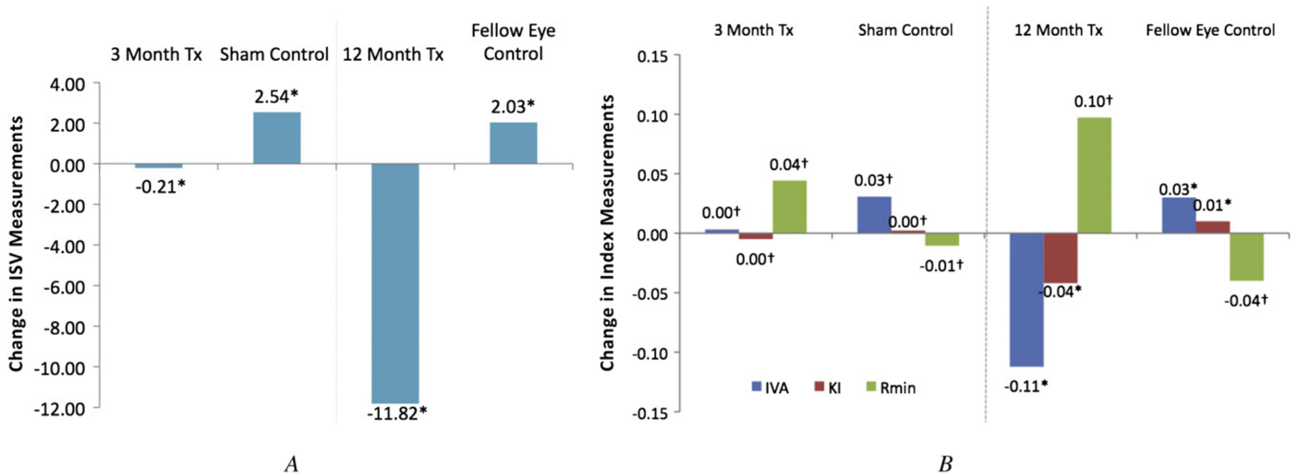

Figure 2. *A*: Comparison of the index of surface variance (ISV) between baseline and 3 months in the treatment group versus the sham control group. *B*: Comparison of the change in the postoperative index of vertical asymmetry (IVA), keratoconus index (KI), and radii minimum (R_{min}) in the treatment group versus fellow-eye control group (* = significant difference between groups; † = no significant difference between groups; Tx = treatment group).

P = .04) and CDVA (mean change −0.12 ± 0.19 logMAR; P < .001) from baseline to 1 year after CXL. The improvement in UDVA was slightly correlated with the improvement in the index of surface variance (mean change −10.5 ± 18.2; P < .001) from baseline to 12 months (r = 0.25, P = .04). However, the 1-year improvements in UDVA and CDVA were not correlated with the improvements in the minimum radius of

Table 3. Postoperative topographic indices (49 keratoconus eyes, 22 ectasia eyes).

	Mean ± SD				
		Postoperative			
Subgroup/Index	Baseline	1 Month	3 Months	6 Months	12 Months
Keratoconus	—	—	—	—	—
ISV	122.2 ± 48.2*	133.3 ± 49.4*[†‡]	121.9 ± 45.7*[‡]	114.3 ± 44.0*[†‡]	110.3 ± 44.9*[†‡]
IVA	1.29 ± 0.47*	1.39 ± 0.48*[†‡]	1.29 ± 0.46*[‡]	1.22 ± 0.45*[†‡]	1.17 ± 0.51*[†]
KI	1.37 ± 0.20*	1.39 ± 0.20*[†‡]	1.36 ± 0.19*[‡]	1.33 ± 0.17*[†]	1.33 ± 0.18*[†]
CKI	1.05 ± 0.16	1.08 ± 0.07	1.07 ± 0.07[‡]	1.06 ± 0.07	1.05 ± 0.06
IHA	35.2 ± 23.5	41.9 ± 33.6	39.2 ± 28.6	38.9 ± 28.6	31.0 ± 26.7
IHD	0.12 ± 0.06	0.13 ± 0.07[†‡]	0.12 ± 0.07[‡]	0.11 ± 0.06	0.12 ± 0.13
R_{min}	5.71 ± 0.82*	5.59 ± 0.82*[†‡]	5.75 ± 0.84*[‡]	5.82 ± 0.78*[†‡]	5.89 ± 0.75*[†]
Ectasia	—	—	—	—	—
ISV	127.3 ± 73.2	138.6 ± 69.4[†‡]	127.3 ± 76.6[‡]	119.9 ± 71.9	119.9 ± 77.7
IVA	1.63 ± 1.00	1.78 ± 0.95[†‡]	1.64 ± 1.09[‡]	1.54 ± 1.01	1.53 ± 1.07
KI	1.37 ± 0.31	1.40 ± 0.34	1.37 ± 0.35[‡]	1.32 ± 0.29[‡†]	1.33 ± 0.33
CKI	1.01 ± 0.06	1.03 ± 0.06[‡†]	1.01 ± 0.05[‡]	0.99 ± 0.04[‡†]	1.0 ± 0.05
IHA	21.8 ± 16.7	28.0 ± 23.8	22.9 ± 20.3	24.7 ± 21.0	25.0 ± 16.0
IHD	0.11 ± 0.09	0.13 ± 0.08[†‡]	0.12 ± 0.10	0.09 ± 0.07[†‡]	0.10 ± 0.07
R_{min}	6.26 ± 0.75	6.10 ± 0.74[†‡]	6.31 ± 0.80[‡]	6.40 ± 0.70[†]	6.37 ± 0.70

CDVA = corrected distance visual acuity; CKI = central keratoconus index; IHA = index of height asymmetry; IHD = index of height decentration; ISV = index of surface variance; IVA = index of vertical asymmetry; KI = keratoconus index; R_{min} = minimum radius of curvature; UDVA = uncorrected distance visual acuity

*Statistically significant change from baseline to 1 year

[†]Statistically significant change compared with baseline measurements

[‡]Statistically significant change compared with previous measurement

[§]Statistically significant Pearson correlation coefficient curvature, index of vertical asymmetry, or keratoconus index measurements. Tables 3 and 4 show detailed correlation and visual acuity data.

DISCUSSION

Corneal collagen crosslinking is a new treatment for patients with keratoconus[1] and LASIK-induced ectasia.[2] In past work in this prospective randomized controlled clinical trial, we looked at general clinical outcomes,[6] CXL-associated corneal haze,[16] and corneal thickness changes after CXL.[17] In this study, we evaluated the postoperative changes in 7 Pentacam topography indices and looked for associations with 1-year visual acuity outcomes. Changes in these measurements provide a more comprehensive analysis of the potential improvement in the shape and optical properties of the cornea after crosslinking.

In general, all the topography indices were elevated over normal in patients with keratectasia (except for minimum radius of curvature, which is the inverse of corneal steepness and therefore is expected to decrease). Thus, a significant decrease in any of the postoperative measurements after CXL may indicate improvement in the contour of the cornea. Because CDVA in keratectasia is decreased, for the most part by corneal optical irregularity, improved visual acuity after CXL might be expected to result from improved topography regularity. This study attempted to address these issues and quantitate topography changes.

A previous study of patients with progressive keratectasia by Koller et al.[18] found significant improvement in 4 of 7 Pentacam topography indices (central keratoconus index, keratoconus index, index of height asymmetry, minimum radius of curvature) 1 year after CXL. In this study, we also found improvement in 4 of the indices, including the keratoconus index and minimum radius of curvature, as in the Koller study. However, we also found improvement in the index of surface variance and index of vertical asymmetry. Thus, although the 2 studies found improvement in topography after CXL, it is unclear why some of the improvements were in different topography indices.

The improvements in the minimum radius of curvature in our study are consistent with the decreases in the maximum K value after CXL in several studies,[7–10] including our previous analysis of this patient cohort.[6] Significant improvements were also found in the index of surface variance, indicating a decrease in the curvature variation compared with the mean curvature of the cornea, and in the index of vertical asymmetry, a measurement of the difference between

Table 3. (Cont.)

LogMAR UDVA (Snellen)		LogMAR CDVA (Snellen)		Pearson Correlation	
Baseline	12 Months	Baseline	12 Months	With UDVA	With CDVA
0.87 ± 0.35 (20/148)	0.82 ± 0.39 (20/132)	0.39± 0.27 (20/49)	0.25 ± 0.23† (20/36)		
—	—	—	—	0.26	0.09
—	—	—	—	0.19	0.10
—	—	—	—	0.14	0.01
—	—	—	—	−0.10	−0.32§
—	—	—	—	0.18	0.32§
—	—	—	—	−0.10	−0.26
—	—	—	—	0.31§	−0.03
0.75 ± 0.30 (20/112)	0.65 ± 0.31 (20/89)	0.26 ± 0.16 (20/36)	0.19 ± 0.14† (20/31)		
—	—	—	—	0.26	0.07
—	—	—	—	0.32	0.00
—	—	—	—	0.27	−0.18
—	—	—	—	−0.09	−0.05
—	—	—	—	−0.26	0.43§
—	—	—	—	−0.09	−0.06
—	—	—	—	0.03	0.07

Table 4. Visual acuity results (71 eyes).

	Mean ± SD					
	LogMAR UDVA (Snellen)		LogMAR CDVA (Snellen)		Pearson Correlation	
Parameter	Baseline	12 Months	Baseline	12 Months	With UDVA	With CDVA
Acuity	0.84 ± 0.34 (20/138)	0.77 ± 0.37* (20/118)	0.35 ± 0.24 (20/45)	0.23 ± 0.21* (20/34)	—	—
ISV	—	—	—	—	0.2†	0.1
IVA	—	—	—	—	0.2	0.1
KI	—	—	—	—	0.2	−0.05
CKI	—	—	—	—	−0.1	−0.02
IHA	—	—	—	—	0.1	0.3†
IHD	—	—	—	—	−0.1	−0.03
R_{min}	—	—	—	—	−0.1	−0.02

CDVA = corrected distance visual acuity; CKI = central keratoconus index; IHA = index of height asymmetry; IHD = index of height decentration; ISV = index of surface variance; IVA = index of vertical asymmetry; KI = keratoconus index; R_{min} = minimum radius of curvature; UDVA = uncorrected distance visual acuity
*Statistically significant change compared with baseline measurements
†Statistically significant Pearson correlation coefficient

the superior curvature and inferior curvature of the cornea. The decrease in the index of vertical asymmetry may be analogous to an improvement in the more commonly used I–S ratio.[13–15] Finally, there was significant improvement in the keratoconus index, indicating normalization of the keratoconic topographic appearance postoperatively (Figure 3). The overall improvements in these 4 indices suggest, in general, that the cone was flattening and that the post-CXL cornea was becoming more optically regular and symmetric.

In this study, there was no significant difference in the change in any topography index from baseline to 1 year postoperatively between keratoconus patients and ectasia patients. Therefore, all patients with keratoconus and ectasia were reported as 1 cohort. However, in an individual analysis of these 2 subgroups, the improvement in the index of surface variance, index of vertical asymmetry, keratoconus, and minimum radius of curvature appeared to be statistically significant in the keratoconus group only. In our previous study of post-CXL maximum and average K values,[6] we similarly noted a more robust clinical response in keratoconus eyes than in ectasia eyes. It is unclear whether these findings suggest that ectatic corneas have less response to CXL than keratoconic

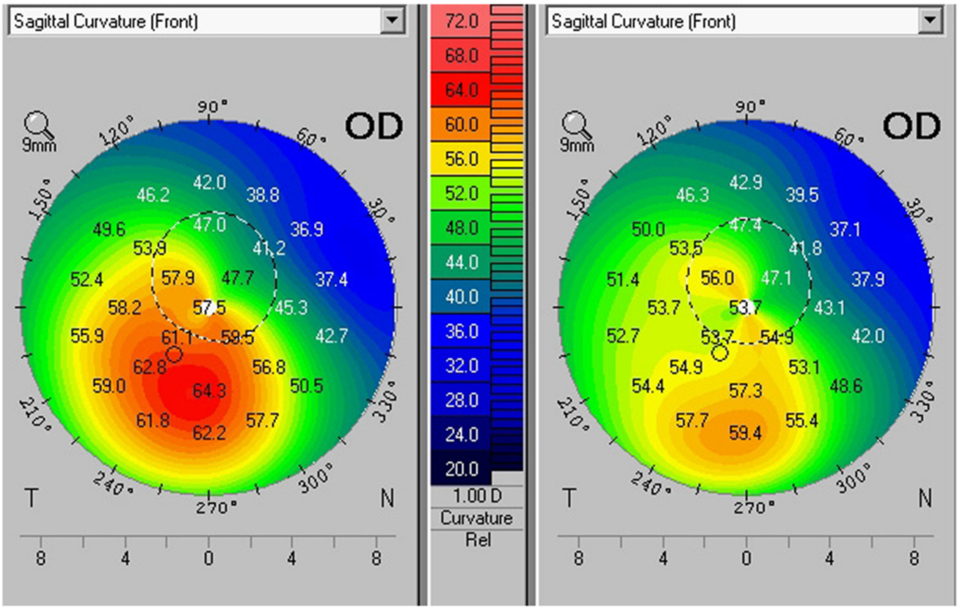

Figure 3. *Left*: Preoperative sagittal curvature map. *Right*: Twelve-month postoperative sagittal curvature map showing improvement in the keratoconus index.

corneas or whether the smaller number of ectasia patients in this study did not have the statistical power to clearly show such changes. More broadly, it remains unclear whether ectasia and keratoconus are similar disease entities or whether they have inherent pathophysiologic differences that ultimately might suggest different criteria for their management.

Our previous analyses[6,16,17] showed that clinical outcomes after CXL are time dependent. Similarly, corneal topography appears to change over time during the first year after surgery. In general, the topography indices were worse at 1 month than at baseline. This worsening was similar to the initial worsening in postoperative visual acuity[6] and CXL-associated corneal haze[16] in the early period after CXL. After the first month, there was progressive improvement in the index of surface variance, index of vertical asymmetry, minimum radius of curvature, and keratoconus index between 1 month and 6 months. Although the pathophysiology–wound healing etiology of this natural history after CXL is unclear, the early clinical worsening coincides with the reepithelialization process and with postoperative keratocyte apoptosis and repopulation, as noted in studies using confocal microscopy.[19] Therefore, this ongoing wound-healing process likely militates months-long changes in the topography of the cornea after CXL.

In this study, a sham control group was used for comparison with the treatment group. The protocol for this trial required the sham control group to be followed for 3 months, at which point the patients crossed over to the treatment group. In addition, the epithelium was not removed in the control patients, so there can be no definitive conclusion about whether the relative outcomes were a result of the UVA light treatment itself or simply of the removal of the epithelium, which allows better absorption of the riboflavin.[20]

Recognizing the limitations of the sham control group, a 12-month fellow-eye control group of patients who did not have bilateral CXL therapy was also compared with the treatment group. Ideally, the same number of fellow eyes and treatment eyes would have been compared. However, the protocol for this trial allowed bilateral CXL treatment in patients who met the study criteria in both eyes. Thus, fellow eyes that had CXL before the 1-year examination were lost from this control group.

In both control groups, all postoperative indices remained the same. When looking at the significant changes in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature in the treatment group compared with the sham control group, there were no significant differences between the postoperative changes in these groups 3 months postoperatively. However, when the treatment group was compared with the fellow-eye control group at 1 year, there were significant differences in the changes in the index of vertical asymmetry, index of surface variance, and keratoconus index between the groups, indicating that the eyes in the treatment group improved after CXL while the fellow eyes remained the same or worsened.

An improvement in the Pentacam corneal indices suggests that the cornea is assuming a more regular shape. Indeed, because the loss of spectacle-correctable visual acuity in keratoconus and ectasia is predominantly from perturbations in the corneal optics, improvements in visual acuity after CXL would be expected to derive from improvements in definable measures of corneal topographic regularity. However, to date, it has been difficult to capture the correlation between the clinical and topographic changes of the cornea and improvements in visual acuity.[16,17] In this study, there did not appear to be a meaningful correlation between the changes in any corneal index and the changes in postoperative visual acuity. Further study is underway to determine baseline characteristics and outcome measures that are potential predictors of improvement in visual acuity after CXL.

All index measurements were done using Scheimpflug imagery reconstructed by the Pentacam software. Because there is a typical postoperative corneal haze and/or demarcation line after CXL,[16,21–24] the reconstruction of the Scheimpflug image, and thus ultimate topography analysis, may be artifactually affected. However, our observations of proper edge pixel placement by the software in postoperative corneas suggest this was not the case. Moreover, Pentacam topography measurements have been validated in many studies.[18,25,26]

In conclusion, the clinical and optical outcomes of CXL for the treatment of keratoconus and corneal ectasia continue to be elucidated. Keratectasia patients appear to have improvements in corneal topography after CXL, including the general curvature variation of the cornea, the difference between the superior and inferior curvature of the cornea, the keratoconus index, and the minimum radius of curvature, suggesting an overall improvement in the optical contour of the cornea. Further study is underway to identify and elucidate additional characteristics that may be associated with topography and visual acuity outcomes after CXL.

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