

# Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results

Steven A. Greenstein, BA, Vinnie P. Shah, MD, Kristen L. Fry, OD, MS, Peter S. Hersh, MD

**PURPOSE:** To determine the changes in corneal thickness over time after corneal collagen crosslinking (CXL) for keratoconus and corneal ectasia.

**SETTING:** Cornea and refractive surgery subspecialty practice.

**DESIGN:** Prospective randomized controlled clinical trial.

**METHODS:** Corneal thickness at the apex, thinnest point, and pupil center were measured using Scheimpflug imaging (Pentacam) at baseline and 1, 3, 6, and 12 months after CXL. The treatment group was compared with both a sham-procedure control group and a fellow-eye control group. Associations with clinical outcomes (uncorrected and corrected distance visual acuities and maximum keratometry) were analyzed.

**RESULTS:** The study comprised 82 eyes, 54 with keratoconus and 28 with ectasia after laser in situ keratomileusis. The mean preoperative thinnest pachymetry was  $440.7 \mu\text{m} \pm 52.9$  (SD). After CXL, the cornea thinned at 1 month (mean change  $-23.8 \pm 28.7 \mu\text{m}$ ;  $P < .001$ ) and from 1 to 3 months (mean change  $-7.2 \pm 20.1 \mu\text{m}$ ,  $P = .002$ ), followed by a recovery of the corneal thickness between 3 months and 6 months (mean  $+20.5 \pm 20.4 \mu\text{m}$ ;  $P < .001$ ). At 1 year, apex and pupil-center thicknesses returned to baseline ( $P = .11$  and  $P = .06$ , respectively); however, the thinnest pachymetry remained slightly decreased from baseline to 12 months (mean change  $-6.6 \pm 22.4 \mu\text{m}$ ;  $P = .01$ ). The recovery of corneal thickness was more rapid in ectasia than in keratoconus. There was no association between the degree of corneal thinning at 3 months and clinical outcomes after CXL.

**CONCLUSIONS:** After CXL, the cornea thins and then recovers toward baseline thickness. The cause and implications of corneal thickness changes after CXL remain to be elucidated.

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Corneal collagen crosslinking (CXL) is a treatment to decrease the progression of keratoconus<sup>1</sup> in particular as well as other corneal thinning processes, such as ectasia after laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK).<sup>2</sup> Studies<sup>3–7</sup> suggest that CXL can also have beneficial visual and optical effects. For instance, in previous analyses of this cohort of patients, we reported improvement in corrected (CDVA) and uncorrected (UDVA) distance visual acuities, maximum and mean keratometry (K) values,<sup>7</sup> and 4 of 7 Pentacam (Oculus, Inc.) topographic indices.<sup>8</sup>

Anatomic and physiologic changes in the cornea after CXL remain to be thoroughly defined. In previous

work,<sup>9</sup> we looked at the natural history of CXL-associated corneal haze and found that haze was greatest 1 month postoperatively, plateaued at 3 months, and decreased between 3 months and 12 months. Other studies<sup>10–13</sup> have used confocal microscopy to evaluate the anatomic and cellular changes after CXL. Corneal thickness changes also have been noted after CXL.<sup>3–6,14–17</sup>

Because CXL is a new surgical procedure, it is important to characterize the time course of postoperative changes in the cornea that clinicians should anticipate, and assess any impact on clinical outcomes. Moreover, the ability to retreat and perform further procedures in these eyes may be affected by long-term

changes in corneal thickness after the initial CXL procedure. Thus, in this randomized controlled clinical trial, we evaluated the natural course of corneal thickness changes that occurred during 1 year after CXL.

## PATIENTS AND METHODS

Patients with progressive keratoconus and ectasia after LASIK were enrolled as part of a multicenter prospective randomized controlled clinical trial.<sup>A,B</sup> This study was approved and monitored by an investigational review board and complied with the U.S. Health Insurance Portability and Accountability Act. All patients provided informed consent.

The inclusion criteria were 14 years of age or older and axial topography consistent with keratoconus or corneal ectasia. Progressive keratoconus or ectasia was defined as 1 or more of the following changes over 24 months: an increase of 1.00 diopter (D) or more in the steepest K, 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. Exclusion criteria included a history of corneal surgery, chemical injury, delayed epithelial healing, and corneal pachymetry less than 300  $\mu\text{m}$ . All patients included in the ectasia group were post LASIK; no patient had previous PRK.

### Treatment Group

Patients were initially randomized into a treatment or sham control group. The treatment group received standard riboflavin 0.1%–ultraviolet A (UVA) CXL treatment according to the methodology described by Wollensak et al.<sup>1</sup> 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 T500 solution, Medio-Cross, Peschke Meditrade GmbH) was then administered topically every 2 minutes for 30 minutes. After riboflavin administration, riboflavin absorption throughout the corneal stroma and anterior chamber was confirmed on slitlamp examination. Ultrasonic pachymetry was performed; if the cornea was less than 400  $\mu\text{m}$ , 1 drop of hypotonic riboflavin 0.1% in sterile water (Medio-Cross

hypotonic, Peschke Meditrade GmbH) was administered every 10 seconds for 2-minute sessions, after which ultrasound pachymetry was performed to confirm that the stroma had swollen to 400  $\mu\text{m}$  or thicker. This was repeated until adequate corneal thickness was obtained.

The cornea was exposed to UVA 365 nm light (UV-X system, IROC AG) for 30 minutes at an irradiance of 3.0 mW/cm<sup>2</sup>. During UVA exposure, isotonic riboflavin drops were continued every 2 minutes. Postoperatively, antibiotic and corticosteroid drops were administered and a therapeutic soft contact lens (Acuvue Oasys, Vistakon) was placed. The contact lens was removed after epithelial healing, typically 3 to 5 days postoperatively. Antibiotic drops were continued for 1 week and corticosteroid drops for 2 weeks.

### Control Groups

The sham control group received riboflavin ophthalmic solution 0.1% alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for 30 minutes. After the administration of riboflavin, the cornea was aligned with the UVA light; the 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.

In addition to the sham control group, a fellow-eye control group comprising fellow eyes of patients who did not have bilateral CXL treatment was analyzed. This group consisted of eyes with frank keratoconus or ectasia that did not have CXL, eyes with evidence of disease that did not meet the inclusion criteria of the study, and eyes with no evidence of disease. In this group, pachymetry measurements were analyzed at baseline and 12 months postoperatively.

### Pachymetry Measurements

Preoperative pachymetry measurements were obtained using a Pentacam Scheimpflug device and confirmed with ultrasound pachymetry (Sonogage, Inc.). To confirm that the Scheimpflug tracings followed the observed corneal surfaces, the software interface of the Scheimpflug system was used to view the edge pixel maps on the images to ensure they conformed to the edge of the image. One examiner (P.S.H.) measured the preoperative ultrasound thinnest pachymetry guided by individual topographic maps. No postoperative ultrasound measurements were analyzed in this study. The Scheimpflug pachymetry data were obtained from the corneal thickness map 1, 3, 6, and 12 months postoperatively. The following 3 pachymetry measurements were analyzed: location of thinnest pachymetry, pachymetry at the corneal apex, and pachymetry at the pupil center.

### Statistical Analysis

Statistical analysis was performed using PASW Statistics 18 (SPSS, Inc.). Three groups were analyzed: the entire cohort, the keratoconus subgroup, and the ectasia subgroup. A paired 2-tailed Student *t* test was used to analyze the postoperative changes compared with baseline and to analyze the changes in postoperative outcomes over time. An independent *t* test was used to compare measurement data between the keratoconus subgroup and the ectasia

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From the Cornea and Laser Eye Institute-Hersh Vision Group (Greenstein, Shah, Fry, Hersh), CLEI Center for Keratoconus, Teaneck, and the Department of Ophthalmology (Shah, Hersh), UMDNJ-New Jersey Medical School, Newark, New Jersey, USA.

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Corresponding author: Peter S. Hersh, MD, Cornea and Laser Eye Institute-Hersh Vision Group, CLEI Center for Keratoconus, 300 Frank W. Burr Boulevard, Teaneck, New Jersey 07666, USA. E-mail: phersh@vision-institute.com.

subgroup and between the treatment group and the control group. In addition, eyes that received hypotonic riboflavin were compared with those that did not require intraoperative stromal swelling.

To determine whether changes in pachymetry were related to clinical outcomes, the relationship between the change in pachymetry from baseline to 3 months and the 1-year changes in CDVA, UDVA, and maximum K were analyzed. The 3-month measurement was selected because it was the time of the largest pachymetry change. To determine whether there was a correlation between pachymetry changes and other CXL outcomes, Pearson correlation coefficients were used. A *P* value less than 0.05 was considered statistically significant.

## RESULTS

Eighty-two eyes (54 keratoconus, 28 post-LASIK ectasia) of 65 patients had CXL and were followed for 1 year. Fifty-six eyes (35 keratoconus, 21 ectasia) received hypotonic riboflavin before UVA light administration, and 26 eyes (19 keratoconus, 7 ectasia) received standard dextran riboflavin solution only. The sham control group comprised 41 eyes (28 keratoconus, 13 ectasia), and the fellow-eye control group comprised 39 eyes (25 keratoconus, 14 ectasia).

### Treatment Groups

Table 1 shows the Scheimpflug pupil, apex, and thinnest pachymetry measurements over time by group. Figure 1 shows the change in Scheimpflug pachymetry measurements over time in the keratoconus and corneal ectasia subgroups.

### Thinnest Pachymetry

The difference between the preoperative mean Scheimpflug thinnest pachymetry and the preoperative mean ultrasound thinnest pachymetry was not statistically significant (*P* = .3). There was a significant decrease in thinnest pachymetry between baseline and 1 month (mean change  $-23.8 \pm 28.7 \mu\text{m}$ ; *P* < .001) (Figure 1). There was further thinning between 1 month and 3 months (mean change  $-7.2 \pm 20.1 \mu\text{m}$ ; *P* = .002), followed by a significant increase between 3 months and 6 months (mean change  $+20.5 \pm 20.4 \mu\text{m}$ ; *P* < .001). The change in thinnest pachymetry between 6 months and 12 months (mean  $+3.9 \pm 22.9 \mu\text{m}$ ; *P* = .13) was not statistically significant. At 1 year, the mean thinnest pachymetry remained slightly decreased from baseline; the difference between the 2 time points was statistically significant (*P* = .01) (Table 1).

**Apical Pachymetry** There was a statistically significant decrease in apical pachymetry between baseline and 1 month (mean change  $-23.0 \pm 27.8 \mu\text{m}$ ; *P* < .001) and further thinning between 1 month and 3 months (mean change  $-7.2 \pm 20.8 \mu\text{m}$ ; *P* = .002) (Figure 1). This was followed by a significant increase in apical

pachymetry between 3 months and 6 months (mean change  $+19.6 \pm 21.8 \mu\text{m}$ ; *P* < .001) and between 6 months and 12 months (mean change  $+6.4 \pm 22.3 \mu\text{m}$ ; *P* = .01). The change in apical pachymetry from baseline to 12 months was not statistically significant (*P* = .06) (Table 1).

**Pupil-Center Pachymetry** There was a significant decrease in pupil-center pachymetry between baseline and 1 month (mean change  $-24.6 \pm 24.1 \mu\text{m}$ ; *P* < .001) and further thinning between 1 month and 3 months (mean change  $-5.9 \pm 21.6 \mu\text{m}$ ; *P* = .02) (Figure 1). This was followed by a significant increase in pupil-center pachymetry between 3 months and 6 months (mean change  $+19.1 \pm 21.0 \mu\text{m}$ ; *P* < .001) and between 6 months and 12 months (mean change  $+8.0 \pm 20.4 \mu\text{m}$ ; *P* = .001). The mean change in pupil-center pachymetry from baseline to 12 months was not statistically significant (*P* = .10) (Table 1).

### Comparison Between Treatment Subgroups

**Keratoconus Versus Ectasia** In the keratoconus subgroup, the mean change in pupil-center pachymetry, pachymetry at the corneal apex, and thinnest pachymetry between baseline and 1 year was  $-6.4 \pm 20.3 \mu\text{m}$ ,  $-8.3 \pm 21.4 \mu\text{m}$ , and  $-12.1 \pm 23.4 \mu\text{m}$ , respectively. In the ectasia subgroup, the mean change in pupil-center pachymetry, pachymetry at the corneal apex, and thinnest pachymetry between baseline and 1 year was  $+2.3 \pm 14.9 \mu\text{m}$ ,  $+3.5 \pm 15.5 \mu\text{m}$ , and  $+4.1 \pm 16.0 \mu\text{m}$ , respectively. There were significant differences in the changes in thinnest pachymetry and pachymetry at the corneal apex between baseline and 12 months (difference between groups: *P* = .01 at corneal apex and *P* = .002 for thinnest pachymetry). The difference in the change in pupil-center pachymetry from baseline to 12 months between the keratoconus subgroup and ectasia subgroup was not statistically significant (*P* = .05). In general, the pachymetry thinned slightly in the keratoconus subgroup and thickened slightly in the ectasia subgroup (Figure 2).

**Dextran Versus Hypotonic Riboflavin** Table 2 shows the Scheimpflug pachymetry measurements over time in the dextran riboflavin group and hypotonic riboflavin group. In the group of patients who did not require hypotonic riboflavin for intraoperative stromal swelling, the pupil-center pachymetry (mean change  $-28.7 \pm 15.3 \mu\text{m}$ ; *P* < .001), pachymetry at the corneal apex (mean change  $-28.2 \pm 15.4 \mu\text{m}$ ; *P* < .001), and thinnest pachymetry (mean change  $-29.5 \pm 15.2 \mu\text{m}$ ; *P* < .001) became significantly thinner from baseline to 3 months. From 3 to 12 months, the pachymetry became significantly thicker (mean

**Table 1.** Scheimpflug pachymetry measurements over time in all eyes (N = 82), eyes with keratoconus (n = 54), and eyes with ectasia (n = 28 eyes).

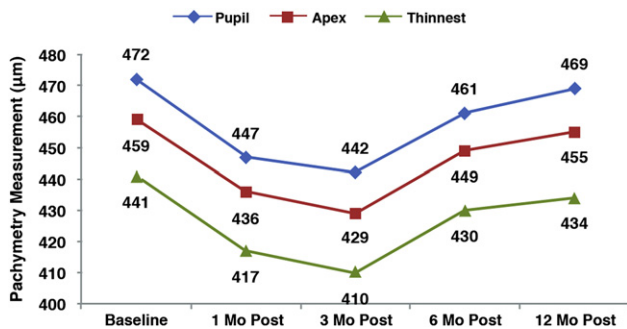
| Area/Group      | Mean Pachymetry (µm) ± SD |                            |                            |                            |                            |
|-----------------|---------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
|                 | Preop                     | 1 Mo                       | 3 Mo                       | 6 Mo                       | 12 Mo                      |
| <b>Pupil</b>    |                           |                            |                            |                            |                            |
| All eyes        | 472.0 ± 45.3              | 447.4 ± 48.7* <sup>†</sup> | 441.5 ± 47.7* <sup>†</sup> | 460.6 ± 44.9* <sup>†</sup> | 468.6 ± 44.4 <sup>†</sup>  |
| Keratoconus     | 472.1 ± 42.6              | 450.1 ± 44.3* <sup>†</sup> | 440.9 ± 47.4* <sup>†</sup> | 459.1 ± 42.8* <sup>†</sup> | 465.7 ± 42.9* <sup>†</sup> |
| Ectasia         | 471.9 ± 50.9              | 442.3 ± 56.7* <sup>†</sup> | 442.8 ± 49.3*              | 463.6 ± 49.4* <sup>†</sup> | 474.2 ± 47.5 <sup>†</sup>  |
| <b>Apex</b>     |                           |                            |                            |                            |                            |
| All eyes        | 459.4 ± 50.4              | 436.4 ± 52.2* <sup>†</sup> | 429.2 ± 53.2* <sup>†</sup> | 448.8 ± 48.0* <sup>†</sup> | 455.2 ± 51.0 <sup>†</sup>  |
| Keratoconus     | 458.2 ± 51.4              | 437.8 ± 51.3* <sup>†</sup> | 428.3 ± 55.1* <sup>†</sup> | 446.3 ± 48.2* <sup>†</sup> | 450.0 ± 52.5*              |
| Ectasia         | 461.7 ± 49.0              | 433.9 ± 54.7* <sup>†</sup> | 431.0 ± 50.0*              | 453.6 ± 48.1* <sup>†</sup> | 465.2 ± 47.4 <sup>†</sup>  |
| <b>Thinnest</b> |                           |                            |                            |                            |                            |
| All eyes        | 440.7 ± 52.9              | 416.9 ± 50.9* <sup>†</sup> | 409.7 ± 52.3* <sup>†</sup> | 430.3 ± 49.4* <sup>†</sup> | 434.1 ± 51.4 <sup>†</sup>  |
| Keratoconus     | 440.2 ± 55.4              | 418.1 ± 52.1* <sup>†</sup> | 408.8 ± 53.2* <sup>†</sup> | 429.0 ± 50.7* <sup>†</sup> | 428.1 ± 53.8*              |
| Ectasia         | 441.7 ± 48.7              | 414.5 ± 49.4* <sup>†</sup> | 411.5 ± 51.5*              | 432.7 ± 47.8* <sup>†</sup> | 445.8 ± 45.0 <sup>†</sup>  |

CDVA = corrected distance visual acuity; EC = ectasia; FE = fellow eye KC = keratoconus; K<sub>max</sub> = maximum keratometry; Sham = sham control; Tx = treatment; UDVA = uncorrected distance visual acuity  
 \*Significant change compared with baseline measurement (P < .05)  
<sup>†</sup>Significant change compared with previous visit measurement (P < .05)  
<sup>‡</sup>Pearson correlation coefficient significant (P < .05)

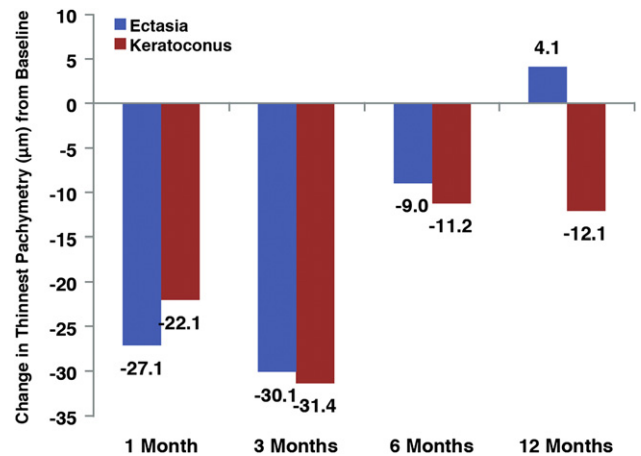
change +19.9 ± 18.1 µm, +18.9 ± 17.8 µm, and +15.2 ± 20.3 µm, respectively; P=.001) (Table 2). At 1 year, the pupil-center pachymetry (mean change -8.9 ± 17.4 µm; P=.01), pachymetry at the corneal apex (mean change -9.3 ± 17.3 µm; P=.01), and thinnest pachymetry (mean change -14.3 ± 18.6 µm; P=.001), were significantly thinner than preoperatively.

In the hypotonic riboflavin solution group, the mean ultrasound thinnest pachymetry was 337.3 ± 39.8 µm after the initial 30-minute administration of the dextran riboflavin solution. The mean number of

hypotonic riboflavin cycles required to swell the cornea to 400 µm or more was 5.8 ± 3.8. After hypotonic riboflavin administration and at the initiation of UVA light exposure, the mean ultrasound thinnest pachymetry was 413.8 ± 11.4 µm. Between baseline and 3 months, the pupil-center pachymetry (mean change -31.3 ± 20.9 µm; P < .001), pachymetry at the corneal apex (mean change -31.2 ± 21.6 µm; P < .001), and thinnest pachymetry (mean change ±31.7 ± 23.6 µm; P < .001) became significantly thinner than preoperatively. From 3 to 12 months, the pachymetry became significantly thicker (mean change +30.6 ±



**Figure 1.** Change in Scheimpflug pachymetry measurements over time in patients with keratoconus and corneal ectasia.



**Figure 2.** Change in Scheimpflug thinnest pachymetry measurements over time in patients with keratoconus versus patients with ectasia after LASIK.

**Table 1.** (Cont.)

| Baseline to 12 Mo<br>(KC vs EC) | P Value for Change              |                                  |  | Pearson Correlation Coefficient |              |                    |
|---------------------------------|---------------------------------|----------------------------------|--|---------------------------------|--------------|--------------------|
|                                 | Baseline to 12 Mo<br>(Tx vs FE) | Baseline to 3 Mo<br>(Tx vs Sham) |  | With<br>UDVA                    | With<br>CDVA | With $K_{max}$     |
| .05                             | .4                              | <.001                            |  | -0.09                           | 0.04         | 0.01               |
|                                 | .03                             | <.001                            |  | -0.15                           | 0.19         | -0.09              |
|                                 | .2                              | <.001                            |  | -0.05                           | -0.29        | 0.31               |
| .01                             | .5                              | <.001                            |  | -0.07                           | -0.02        | -0.14              |
|                                 | .06                             | <.001                            |  | -0.06                           | 0.09         | -0.25              |
|                                 | .1                              | <.001                            |  | -0.10                           | -0.32        | 0.25               |
| .002                            | .2                              | <.001                            |  | -0.14                           | -0.07        | -0.37 <sup>‡</sup> |
|                                 | .02                             | <.001                            |  | -0.17                           | -0.03        | -0.50 <sup>‡</sup> |
|                                 | .1                              | <.001                            |  | -0.04                           | -0.18        | 0.11               |

21.9  $\mu\text{m}$ ,  $+29.3 \pm 25.1 \mu\text{m}$ , and  $+28.7 \pm 24.1 \mu\text{m}$ , respectively; all  $P < .001$ ). At 1 year, the pupil-center pachymetry (mean change  $-0.7 \pm 19.3 \mu\text{m}$ ;  $P = .8$ ), pachymetry at the corneal apex (mean change  $-1.9 \pm 21.3 \mu\text{m}$ ;  $P = .5$ ), and thinnest pachymetry (mean change  $-3.0 \pm 23.3 \mu\text{m}$ ;  $P = .3$ ) measurements were not significantly changed from preoperatively.

At 3 months, the changes between groups in pupil-center pachymetry, pachymetry at the corneal apex, and thinnest pachymetry were not significantly different from each other (pupil-center,  $P = .4$ ; corneal apex,  $P = .5$ ; thinnest,  $P = .7$ ). However, the recovery

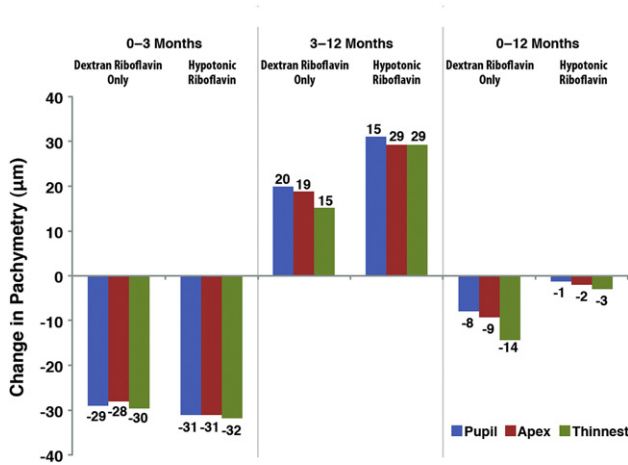
of all 3 measurements between 3 months and 12 months was significantly different, with the corneal thickness in the hypotonic riboflavin group recovering more substantially (pupil-center,  $P = .04$ ; corneal apex,  $P = .06$ ; thinnest pachymetry,  $P = .02$ ). Overall, the changes in pupil-center pachymetry and pachymetry at the corneal apex from baseline to 1 year were not significantly different between patients who received and those who did not receive hypotonic riboflavin (both  $P = .1$ ); however, the group that did not require hypotonic riboflavin for intraoperative corneal swelling showed more thinning at

**Table 2.** Scheimpflug pachymetry measurements over time in the dextran riboflavin group (56 eyes) and hypotonic riboflavin group (26 eyes).

| Group/Area           | Mean Pachymetry ( $\mu\text{m}$ ) $\pm$ SD |                                |                                |                                |                               |
|----------------------|--|--------------------------------|--------------------------------|--------------------------------|-------------------------------|
|                      | Preop                                      | 1 Mo Postop                    | 3 Mo Postop                    | 6 Mo Postop                    | 12 Mo Postop                  |
| Dextran riboflavin   |  |                                |                                |                                |                               |
| Pupil                | 491.4 $\pm$ 45.7                           | 462.3 $\pm$ 41.7 <sup>*†</sup> | 462.7 $\pm$ 46.0 <sup>*</sup>  | 477.7 $\pm$ 44.9 <sup>*†</sup> | 482.6 $\pm$ 49.9 <sup>*</sup> |
| Apex                 | 486.6 $\pm$ 46.8                           | 457.6 $\pm$ 42.7 <sup>*†</sup> | 458.4 $\pm$ 44.9 <sup>*</sup>  | 473.5 $\pm$ 43.3 <sup>*†</sup> | 477.3 $\pm$ 49.8 <sup>*</sup> |
| Thinnest             | 472.5 $\pm$ 45.4                           | 443.4 $\pm$ 44.1 <sup>*†</sup> | 443.0 $\pm$ 44.8 <sup>*</sup>  | 459.6 $\pm$ 42.3 <sup>*†</sup> | 458.2 $\pm$ 47.3 <sup>*</sup> |
| Hypotonic riboflavin |  |                                |                                |                                |                               |
| Pupil                | 462.5 $\pm$ 42.4                           | 440.1 $\pm$ 50.5 <sup>*†</sup> | 431.1 $\pm$ 45.4 <sup>*†</sup> | 452.2 $\pm$ 42.9 <sup>*†</sup> | 461.7 $\pm$ 40.2 <sup>†</sup> |
| Apex                 | 446.8 $\pm$ 47.2                           | 426.6 $\pm$ 53.6 <sup>*†</sup> | 415.6 $\pm$ 51.5 <sup>*†</sup> | 437.3 $\pm$ 46.0 <sup>*†</sup> | 444.9 $\pm$ 48.7 <sup>†</sup> |
| Thinnest             | 425.9 $\pm$ 49.8                           | 404.6 $\pm$ 49.5 <sup>*†</sup> | 394.3 $\pm$ 48.5 <sup>*†</sup> | 416.7 $\pm$ 46.8 <sup>*†</sup> | 423.0 $\pm$ 49.7              |

<sup>\*</sup>Significant change compared with baseline measurements ( $P < .05$ )

<sup>†</sup>Significant change compared with previous visit measurement ( $P < .05$ )



**Figure 3.** Comparison of the change in Scheimpflug pachymetry measurements in eyes requiring hypotonic riboflavin and those that did not receive intraoperative swelling.

one year than those who received hypotonic riboflavin ( $P=.03$ ) (Figure 3).

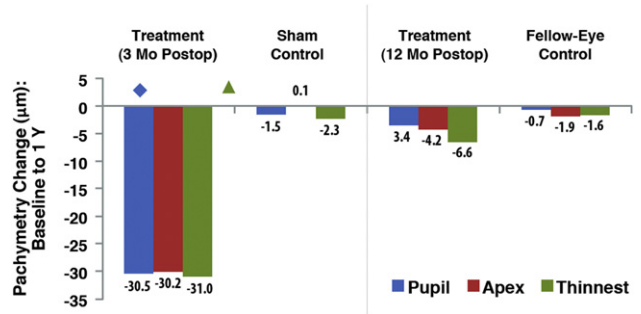
**Control Groups**

**Sham Control** In the sham control group, there were no statistically significant changes in any study measurement between baseline and 3 months. The mean change in thinnest pachymetry, pachymetry at the corneal apex, and pupil-center pachymetry was  $-1.5 \pm 18.4 \mu\text{m}$  ( $P=.6$ ),  $+0.07 \pm 21.2 \mu\text{m}$  ( $P=.98$ ), and  $-2.3 \pm 23.9 \mu\text{m}$ , ( $P=.6$ ), respectively.

**Fellow-Eye Control** As in the sham control group, in the fellow-eye control group there were no statistically significant changes in any study measurement between baseline and 12 months. The mean change in thinnest pachymetry, pachymetry at the corneal apex, and pupil-center pachymetry was  $-0.67 \pm 13.9 \mu\text{m}$  ( $P=.8$ ),  $-1.9 \pm 15.9 \mu\text{m}$  ( $P=.5$ ), and  $-1.6 \pm 19.2 \mu\text{m}$  ( $P=.6$ ), respectively.

**Treatment Versus Control Group**

The changes in all pachymetry measurements between baseline and 3 months in the sham control group were significantly different from the changes in the treatment group (all  $P<.001$ ) (Figure 4). The treated corneas thinned significantly compared with the control corneas. There was no statistically significant difference in changes from baseline to 1 year between the fellow-eye control group and the treatment group the changes in pupil-center pachymetry ( $P=.4$ ), apex pachymetry ( $P=.5$ ), or thinnest pachymetry ( $P=.2$ ).

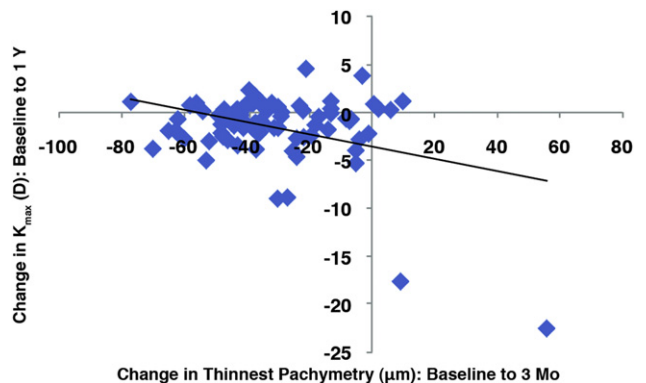


**Figure 4.** Comparison of the change in Scheimpflug pachymetry measurements between baseline and 3 months in the treatment group versus the sham control group and between baseline and 12 months in the treatment group versus the fellow-eye control group.

**Clinical Correlation with Visual Acuity and Keratometry**

The correlation between the change in pachymetry between baseline and 3 months (the time of maximum corneal thickness change) and the 1-year changes in CDVA, UDVA, and maximum K were analyzed. In the entire cohort, the change in all 3 pachymetry measurements between baseline and 3 months were not significantly associated with improvement in 1-year CDVA or UDVA (Table 1).

There was a negative correlation between the change in thinnest pachymetry between baseline and 3 months and the 1-year change in maximum K ( $r = -0.37$ ,  $P=.001$ ); that is, the less corneal thinning occurring between baseline and 3 months, the greater the flattening of the cone at 1 year (Figure 5). However, the changes in pachymetry



**Figure 5.** Scatterplot showing the correlation between the change in thinnest pachymetry between baseline and 3 months versus the change in maximum K between baseline and 1 year ( $K_{\text{max}}$  = maximum keratometry).

at the corneal apex ( $P = .21$ ) and pupil-center pachymetry ( $P = .92$ ) between baseline and 3 months were not correlated with flattening of the maximum K value.

## DISCUSSION

Corneal collagen crosslinking is a promising new modality to stabilize the cornea in keratoconus<sup>1</sup> and ectasia.<sup>2,15</sup> The increase in biomechanical stiffness<sup>18,19</sup> after CXL slows the progression of keratoconus and ectasia and, in many cases, improves the patient's visual and topographic outcomes.<sup>3-6,14</sup> In this study, the postoperative changes in corneal thickness after corneal CXL were analyzed over time. Evaluating these changes is important because it will improve the physician's understanding of the natural clinical course to expect after CXL, further elucidate the possible mechanisms of corneal changes after CXL, and allow evaluation of the possible relationship between the changes and the procedure's safety and efficacy.<sup>20-22</sup>

Corneal thinning is generally concomitant with the early CXL postoperative course. A previous study<sup>17</sup> found that intraoperative ultrasound pachymetry decreased after the initial 30 minutes of riboflavin administration, and several others<sup>3-6,14-17</sup> report corneal thickness changes after CXL. In the current study, the pupil-center pachymetry and pachymetry at the corneal apex at 1 year appeared to be the same as the preoperative measurements; however, the thinnest pachymetry remained slightly, although statistically significantly, thinner than preoperatively. This is similar to the results in previous studies.<sup>5,14,16</sup> In contrast to our results, Vinciguerra et al.<sup>6</sup> found a decrease in pupil-center pachymetry and no change in thinnest pachymetry in eyes with keratoconus and a significant decrease in pupil-center pachymetry and thinnest pachymetry in eyes with ectasia 1 year after CXL.

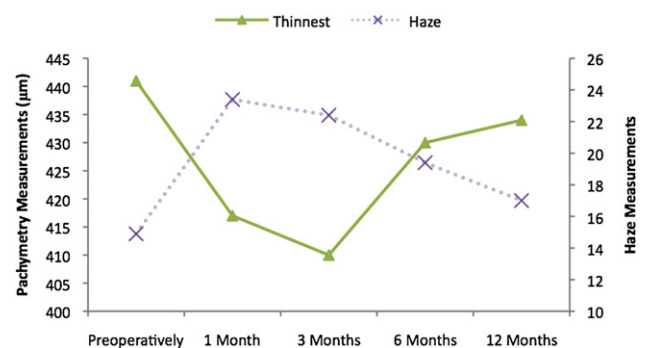
In our analysis of the change in corneal thickness over time, all pachymetry measurements thinned 1 month and 3 months postoperatively and appeared to increase between 3 months and 12 months. The physiology of this initial thinning and subsequent rethickening is, as yet, unclear. Epithelial remodeling is a possible early factor in corneal-thickness changes. Although reepithelialization after CXL is generally complete 4 to 5 days after surgery,<sup>13</sup> continued epithelial remodeling could influence the total corneal thickness over time. However, the continued decrease in corneal thickness from 1 to 3 months suggests other causes of the changes in corneal thickness. Anatomic and structural changes in corneal collagen fibrils, such as compression of collagen fibrils (especially the more transverse-oriented anterior fibrils),<sup>10,23</sup> changes in corneal hydration<sup>24</sup> and edema,<sup>25,26</sup> keratocyte

apoptosis,<sup>13,27,28</sup> and changes in glycosaminoglycans<sup>29</sup> might be implicated.

In a previous study,<sup>9</sup> we defined the natural history of CXL-associated corneal haze. Haze after CXL is different in clinical character from haze after other procedures, such as excimer laser PRK. The former is a dust-like change in the corneal stroma or a midstromal demarcation line,<sup>23</sup> whereas the latter has a more reticulated subepithelial appearance. Corneal thinning and stromal haze may result, similarly, from the complex structural and physiologic wound-healing changes in the cornea after CXL.<sup>30</sup> Thus, thinning and haze may be distinct clinical components of the basic CXL healing process. Alternatively, it is possible that the thinning of the cornea is the essential cause of the clinical stromal haze that we see. Corneal thinning per se might change the orientation and separation of the collagen lamellae, causing light scatter and leading to the clinical appearance of corneal haze.<sup>31,32</sup> As the cornea rethickens, the lamellar array may normalize with a concomitant decrease in observable stromal haze. This is supported by the finding that the time course of CXL-associated corneal haze and corneal thinning and rethickening is similar; the corneal haze seems to maximize when the cornea has most thinned and clears as the cornea thickens (Figure 6).<sup>9</sup>

From a clinical and physiologic viewpoint, the implications of corneal rethickening with time after CXL remain unclear. Whether it represents a response to normal wound healing and physiologic mechanisms or is an actual regression of the CXL effect requires further investigation and longer term follow-up. Studies that have followed CXL patients for several years suggest, however, that corneal stability is maintained over the longer time frame.<sup>4,5</sup>

In our previous work,<sup>7</sup> we found differences in CXL outcomes between keratoconus and ectasia. Recent



**Figure 6.** Change in Scheimpflug thinnest pachymetry measurements over time after CXL. The chart represents the change in CXL-associated corneal haze over time (measured by Scheimpflug densitometry) in a similar group of patients with keratectasia (from previously published data<sup>9</sup>).

studies, as well as our previous analysis, found that ectatic corneas appear to have a less robust response to CXL than keratoconic corneas.<sup>7,15</sup> Similarly, in the current study, there was a significant difference in the change in all pachymetry measurements between keratoconus patients and ectasia patients 1 year after CXL. In ectasia patients, all three 1-year pachymetry measurements were slightly above preoperative measurements, whereas in the keratoconus patients the same pachymetry measurements were slightly below preoperative measurements. This difference was most evident in thinnest pachymetry. One-year postoperative measurements were significantly decreased from baseline in keratoconus patients but were not significantly different from baseline in ectasia patients. There appears to be similar thinning of ectatic corneas and keratoconic corneas between baseline and 3 months; however, ectatic corneas appear to recover (ie, rethicken) faster than keratoconic corneas. In support of our early findings, therefore, it is possible that CXL does not have as robust or long-lasting biomechanical effect in the ectasia cornea as in the keratoconus cornea, a difference that could also affect clinical outcomes. However, this remains speculative and any differences in CXL outcomes between keratoconus eyes and ectasia eyes must be further defined and elucidated.

The use of hypotonic riboflavin to swell the corneal stroma before UV application in those corneas, which have less than the 400  $\mu\text{m}$  thickness, has been suggested in CXL treatment.<sup>33</sup> Because intraoperative pachymetry could relate to postoperative pachymetry changes,<sup>17</sup> we analyzed eyes with regard to whether they required intraoperative swelling with hypotonic riboflavin. Similar to the entire cohort, in eyes that required hypotonic riboflavin before UVA light exposure, pupil-center pachymetry and pachymetry at the corneal apex appeared the same at 1 year as preoperatively. In contrast to the entire cohort, the thinnest pachymetry in the hypotonic riboflavin group rethickened to preoperative measurements as well. Interestingly, despite a similar postoperative course, the thinnest pachymetry, pachymetry at the corneal apex, and pupil-center pachymetry all remained thinner than preoperative measurements in the standard dextran riboflavin group. This may be a statistical anomaly resulting from the thicker preoperative pachymetry in the dextran riboflavin group. However, a more detailed comparison of the postoperative pachymetry course showed similar thinning between baseline and 3 months in both the hypotonic and dextran riboflavin groups and significantly more rethickening in the hypotonic riboflavin group. The reason for the more rapid thickening remains unclear. Further studies of the use of different riboflavin preparations

should help elucidate potential differences in outcomes between them.

In this study, a fellow-eye and a sham control group were used for comparison with the treatment groups. The sham control group was followed for 3 months, at which point, per the study protocol, the patients crossed over to the treatment group. The epithelium was not removed in these control patients, so there can be no definitive conclusion about whether the outcomes were a result of the UVA light treatment or simply the removal of the epithelium, which allows better absorption of the riboflavin.<sup>34</sup>

With these limitations of the sham control group, a 12-month fellow-eye control group of patients who did not have bilateral CXL therapy was compared with the treatment group. Ideally, all fellow eyes would have been compared with treatment eyes. However, bilateral CXL treatment was performed in both eyes of many patients who met the study criteria; per the study protocol, treatment was not withheld in eyes with progressive keratoconus or ectasia in this control group.

In sham and fellow-eye control groups, postoperative pachymetry measurements remained the same at 3 months and 12 months, respectively. There were significant differences in postoperative pachymetry changes between the treatment group and the sham control group at the 3-month follow-up. There was significant corneal thinning in the treatment group, whereas the corneal thickness remained unchanged in the sham control group. However, when the treatment group was compared with the fellow-eye control group, there were no significant differences in corneal thickness changes at the 1-year follow-up. This appears to indicate that corneal thickness recovers 1 year after CXL therapy.

In this study, we evaluated the association between 3-month pachymetry changes and clinical outcomes because that was the time point of greatest thinning. Thus, if corneal thickness changes were associated with clinical outcomes or served as a proxy for CXL-mediated physiologic or anatomic effects that could affect clinical outcomes, the change in pachymetry at 3 months would seem appropriate to consider. In general, corneal thinning between baseline and 3 months was not associated with visual acuity improvement after CXL. We did find, however, that less thinning of thinnest pachymetry between baseline and 3 months was weakly correlated with an improvement in maximum K value at 1 year ( $r = -0.37$ ,  $P = .001$ ). In an individual group analysis, this correlation between thinnest pachymetry and maximum K was only significant in keratoconus patients ( $r = -0.50$ ,  $P < .001$ ). However, 2 keratoconus patients had thickening between baseline and 3 months and substantial flattening of the cone at 1



year. When these outliers were removed from the data, there was no significant correlation between the change in thinnest pachymetry from baseline to 3 months and the change in maximum K from baseline to 1 year ( $r = 0.06, P = .59$ ). Therefore, it is unclear whether there is clinical significance to the correlation between the change in thinnest pachymetry at 3 months and the change in maximum K at 1 year.

Regarding the methodology for assessing the results in this study, most measurements were taken using Scheimpflug imaging obtained with the Pentacam device. In the literature, the relationship of ultrasound and Pentacam pachymetry measurements is generally good.<sup>35–38</sup> Furthermore, in keratoconic corneas, Pentacam central corneal thickness measurements were found to be more reproducible and repeatable than measurements with ultrasound pachymetry.<sup>39</sup> However, the decrease in pachymetry found in this study could be an artifact of inaccurate measurement by the Pentacam system as a result of the postoperative corneal haze,<sup>39,40</sup> typically seen clinically after CXL.<sup>4,5,9,13,28</sup> Indeed, difficulty measuring post-CXL pachymetry has been reported using the Orbscan scanning-slit topography device (Bausch & Lomb).<sup>4</sup> However, in contrast to postoperative Orbscan measurements, Pentacam and ultrasound pachymetry measurements are found to be similar after PRK, despite the corneal haze inherent in that procedure.<sup>37</sup> In the present study, moreover, the edge pixel maps of the Scheimpflug images were confirmed by the investigators and it did not appear as though postoperative corneal haze affected proper edge pixel placement by the Pentacam software. Pentacam pachymetry measurements have been validated in other studies,<sup>39,41–43</sup> and the consistency of our findings in the present study suggests that, in general, Pentacam optical pachymetry is correct.

In conclusion, the physiology of corneal healing, time course of clinical changes, and ultimate clinical outcomes of CXL for the treatment of keratoconus and ectasia continue to be elucidated. In this study, we found that, after CXL, corneas initially thinned and then recovered toward baseline over the first postoperative year. Additional study of the anatomic and physiologic sequelae of CXL should aid in further describing the mechanisms and impact of changes in corneal thickness after the procedure.

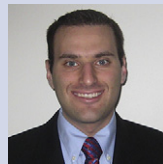
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First author:

Steven A. Greenstein, BA

*Cornea and Laser Eye Institute-Hersh Vision Group, CLEI Center for Keratoconus, Teaneck, New Jersey, USA*