Corneal Collagen Crosslinking Articles by Dr. Peter Hersh, M.D.

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

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PURPOSE: To evaluate 1-year outcomes of corneal collagen crosslinking (CXL) for treatment of keratoconus and corneal ectasia.

SETTING: Cornea and refractive surgery subspecialty practice.

DESIGN: Prospective randomized controlled clinical trial.

METHODS: Collagen crosslinking was performed in eyes with keratoconus or ectasia. The treatment group received standard CXL and the sham control group received riboflavin alone. Principal outcomes included uncorrected (UDVA) and corrected (CDVA) distance visual acuities, refraction, astigmatism, and topography-derived outcomes of maximum and average keratometry (K) value.

RESULTS: The UDVA improved significantly from 0.84 logMAR ± 0.34 (SD) (20/137) to 0.77 ± 0.37 logMAR (20/117) (P = .04) and the CDVA, from 0.35 ± 0.24 logMAR (20/45) to 0.23 ± 0.21 logMAR (20/34) (P<.001). Fifteen patients (21.1%) gained and 1 patient lost (1.4%) 2 or more Snellen lines of CDVA. The maximum K value decreased from baseline by 1.7 ± 3.9 diopters (D) (P<.001), 2.0 ± 4.4 D (P = .002), and 1.0 ± 2.5 D (P = .08) in the entire cohort, keratoconus subgroup, and ectasia subgroup, respectively. The maximum K value decreased by 2.0 D or more in 22 patients (31.0%) and increased by 2.0 D or more in 3 patients (4.2%).

CONCLUSIONS: Collagen crosslinking was effective in improving UDVA, CDVA, the maximum K value, and the average K value. Keratoconus patients had more improvement in topographic measurements than patients with ectasia. Both CDVA and maximum K value worsened between baseline and 1 month, followed by improvement between 1, 3, and 6 months and stabilization thereafter.

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Keratoconus and corneal ectasia occurring after laser in situ keratomileusis (LASIK) are noninflammatory processes in which the cornea deforms in association with thinning and biomechanical weakening. The incidence of keratoconus is approximately 1 in 2000, and the literature contains hundreds of cases of post-LASIK ectasia. Both diseases can result in irregular astigmatism, progressive myopia, or visual impairment secondary to stromal scarring. Because of optical aberrations caused by this progressive distortion and bowing of the cornea in keratoconus and ectasia, patients usually require rigid or complex curvature contact lenses to achieve good functional vision; spectacle correction frequently does not result in acceptable quality of vision. Furthermore, keratoconus tends to progress over the second to fifth decades of life and, ultimately, the need for corneal transplantation in 10% to 20% of cases. New treatments available to patients with keratoconus and ectasia include intrastromal corneal ring segment implantation, conductive keratoplasty, and corneal collagen cross-linking (CXL).

Collagen crosslinking has emerged as a promising technique to slow or stop the progression of keratoconus as well as post-LASIK ectasia. In this procedure, riboflavin (vitamin B2) is administered in conjunction with ultraviolet A (UVA, 365 nm). The interaction of riboflavin and UVA causes the formation of reactive oxygen species, leading to the formation of additional covalent bonds between collagen molecules, with consequent biomechanical stiffening of the cornea. In this study, we analyzed primary visual acuity, refractive, and topographic outcomes in
patients with keratoconus and post-LASIK ectasia over a 1-year postoperative period. In addition, we compared the treatment groups to sham and fellow-eye control groups.

PATIENTS AND METHODS

Patients were enrolled as part of multicenter prospective randomized controlled clinical trials performed under guidelines of the U.S. Food and Drug Administration and approved and monitored by an investigational review board. This study was compliant with the U.S. Health Insurance Portability and Accountability Act. All patients provided informed consent. Randomization was computer generated and, on the procedure day, a sealed envelope was opened revealing whether the eye would be in the sham or treatment group. Patients were aware of their randomly assigned group.

The inclusion criteria included patients 14 years of age or older, axial topography pattern consistent with keratoconus or corneal ectasia, an inferior–superior 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 (PRK)-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 0.50 D or more in manifest cylinder, an increase of 1.00 D or more in manifest refraction spherical equivalent (MRSE). Exclusion criteria included patients with a history of corneal surgery, corneal pachymetry less than 300 μm, history of chemical injury or delayed epithelial healing, pregnancy or lactation during the course of the study.

Treatment Group

Contact lens wearers were instructed to discontinue spherical soft lenses for a minimum of 3 days and soft toric rigid-gas permeable and hard lenses for a minimum of 2 weeks before the preoperative eye examination. Contact lens wearers required confirmation of a stable refraction at 2 examinations that were at least 7 days apart. A stable refraction was determined as one in which the MRSE and keratometry measurements at the first visit did not differ by more than 0.75 D from the respective measurements at the second visit.

Patients were initially randomized into a treatment or control group. The treatment group received standard UVA–riboflavin 0.1% CXL treatment. Corneal CXL was performed according to the methodology described by Wollensak et al.12 Initially, a topical anesthetic agent was administered and the central 9.0 mm epithelium removed by mechanical debridement. Riboflavin (0.1% in 20% dextran T500 solution) 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 (0.1% in sterile water) was administered, 1 drop every 10 seconds for 2-minute sessions, after which US pachymetry was performed to ascertain that the stroma had swollen to more than 400 μm. This was repeated until adequate corneal thickness was obtained. The cornea was aligned and exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm² (UV-X system, IROC AG). 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. Antibiotics and corticosteroid drops were continued 4 times daily for 1 week and 2 weeks, respectively. Patients were followed for 12 months postoperatively and had complete examinations at 1, 3, 6, and 12 months.

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, during which time 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 CXL treatment.

Fellow-Eye Control Group

In addition to the sham control group, a fellow-eye control group was analyzed. The fellow eyes of patients who did not have CXL treatment bilaterally were included in this group. 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 this study, and eyes with no evidence of disease. Visual acuity and topography measurements were analyzed at baseline and 12 months and compared with the postoperative measurements in the treatment group at the same time points.

Outcome Measures

Visual Acuity and Refraction The uncorrected distance visual acuity (UDVA) and CDVA were measured...
preoperatively and postoperatively at 1, 3, 6, and 12 months. Visual acuity measurements were obtained under controlled lighting conditions using a modified Lighthouse Early Treatment of Diabetic Retinopathy Study visual acuity test (2nd edition) with Sloan letters. Patients were tested 4 m from the visual acuity chart. If patients could not read any letters at 4 m, they were tested at 2 m. Visual acuity was recorded and analyzed as the logMAR value. Manifest refraction was performed preoperatively and 1, 3, 6, and 12 months postoperatively, and the MRSE and manifest astigmatism were analyzed. In the astigmatism analysis, vector analysis was performed as described by Holladay et al. In this study, the mean surgically induced astigmatism (SIA) and the vector magnitude of the SIA were analyzed using methodology similar to that in a previous analysis of PRK and LASIK. For a graphic representation of these results, data points were converted to Cartesian coordinates and the axis of cylinder values were doubled to give a doubled-angle plot. Thus, when plotted on an x–y graph, steepening toward 90 degrees (induced with the rule) is represented by points on the negative x-axis and steepening toward 180 degrees (induced against the rule) is represented by points on the positive x-axis. To better ascertain the directionality of the induced astigmatism change, right eyes and left eyes were assessed separately because the astigmatism axis between eyes in keratoconus may exhibit mirror-image symmetry.

Topography Topography measurements were obtained using a rotating Scheimpflug camera (Pentacam, Oculus, Inc.). The Scheimpflug system generates a 3-dimensional model of the cornea and anterior segment. Topographic data were obtained preoperatively and 1, 3, 6, and 12 months postoperatively. Maximum K values, average K values, flat K values, and steep K values as well as corneal astigmatism (simulated K) were recorded from the topography data generated by the Scheimpflug system.

Statistical Analysis Statistical analysis was performed using PASW Statistics software (version 18, SPSS, Inc.). Three groups were analyzed: the entire cohort, the individual keratoconus subgroup, and the ectasia subgroup. A paired 2-tailed Student t test was performed to analyze the postoperative outcome changes compared with baseline values and to analyze the postoperative outcome changes over time. An independent t test was performed to compare outcome data 12 months postoperatively between the keratoconus subgroup and ectasia subgroup and between the treatment group and control group. 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. Of the eyes, 49 were in the keratoconus subgroup and 22 in the post-LASIK ectasia subgroup. The sham control group comprised 41 eyes (28 keratoconus, 13 ectasia), and the fellow-eye control group comprised 30 eyes (21 keratoconus, 9 ectasia).

Visual Acuity Changes after Corneal Collagen Crosslinking

Uncorrected Distance Table 1 and Figure 1, top, show the UDVA over time. The changes in UDVA compared with baseline failed to reach statistical significance at 1 month, 3 months, or 6 months (P = .21, P = .47, and P = .35, respectively). At 12 months, the change in UDVA compared with baseline was statistically significant (P = .04). However, when the keratoconus and ectasia subgroups were analyzed individually, changes in UDVA compared with baseline were not statistically significant at any time point.

The UDVA improved by 2 or more Snellen lines in 18 eyes (25.4%); 6 eyes (8.5%) lost 2 or more Snellen lines of UDVA (Figure 1, bottom).

Corrected Distance Table 1 and Figure 2, top, show the CDVA over time. The mean CDVA remained unchanged at month 1 (mean change 0.02 ± 0.18 logMAR; P = .33). The mean CDVA improved significantly between 1 month and 3 months (mean change −0.07 ± 0.15 logMAR; P < .001) and between 3 months and 6 months (mean change −0.05 ± 0.12 logMAR; P < .001). There was no statistically significant change between 6 months and 12 months (mean change −0.02 ± 0.13, P = .27). At 12 months, the change in CDVA compared to baseline was statistically significant (P < .001).

Similar to the entire cohort, the mean CDVA improved significantly in the keratoconus subgroup (mean change −0.13 ± 0.21 logMAR; P < .001) and in the ectasia subgroup (mean change −0.07 ± 0.11 logMAR; P = .02) over 1 year. The mean CDVA in the keratoconus subgroup remained unchanged at 1 month (mean change 0.006 ± 0.18 logMAR; P = .81), improved between 1 month and 3 months (mean change −0.07 ± 0.14 logMAR; P = .001) and between 3 months and 6 months (mean change −0.06 ± 0.12 logMAR; P < .001), and plateaued between 6 months and 12 months postoperatively (mean change −0.01 ± 0.11 logMAR; P = .70). In contrast, in the ectasia subgroup, interval changes in CDVA failed to reach statistical significance (0 to 1 month, P = .20; 1 to 3 months, P = .08; 3 to 6 months, P = .32; 6 to 12 months, P = .21).

The CDVA improved by 2 or more Snellen lines in 15 eyes (21.1%); 1 eye (1.4%) in a patient with ectasia lost 2 Snellen lines of CDVA (Figure 2, bottom).

Refractive Changes after Corneal Collagen Crosslinking

Refraction There was a mean improvement of 0.86 D in the MRSE from preoperatively to 12 months postoperatively; however, the improvement was not statistically significant (P = .07). There was a statistically
significant improvement in MRSE between preoperatively and 1 month postoperatively (mean change $+0.76 \pm 2.13$ D; $P = .004$) but not between 1 month and 3 months (mean change $+0.38 \pm 2.73$ D; $P = .25$), between 3 months and 6 months (mean change $-0.26 \pm 1.58$; $P = .18$), or between 6 months and 12 months (mean change $-0.03 \pm 2.58$; $P = .92$) (Table 2 and Figure 3).

**Table 1.** Postoperative visual acuity in all eyes, the keratoconus subgroup, and the ectasia subgroup.

<table>
<thead>
<tr>
<th>Acuity/Group</th>
<th>Preop</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>$P$ Value (Keratoconus Vs Ectasia)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preop</td>
</tr>
<tr>
<td>UDVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>0.84 ± 0.34</td>
<td>0.87 ± 0.31</td>
<td>0.82 ± 0.37</td>
<td>0.81 ± 0.37</td>
<td>0.77 ± 0.37</td>
<td>.15</td>
</tr>
<tr>
<td>(20/137)</td>
<td>(20/148)</td>
<td>(20/131)</td>
<td>(20/129)</td>
<td>(20/117)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoconus</td>
<td>0.87 ± 0.35</td>
<td>0.91 ± 0.31</td>
<td>0.85 ± 0.37</td>
<td>0.86 ± 0.40</td>
<td>0.82 ± 0.39</td>
<td></td>
</tr>
<tr>
<td>(20/150)</td>
<td>(20/162)</td>
<td>(20/143)</td>
<td>(20/144)</td>
<td>(20/133)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectasia</td>
<td>0.75 ± 0.30</td>
<td>0.78 ± 0.30</td>
<td>0.74 ± 0.36</td>
<td>0.70 ± 0.29</td>
<td>0.65 ± 0.31</td>
<td></td>
</tr>
<tr>
<td>(20/112)</td>
<td>(20/120)</td>
<td>(20/109)</td>
<td>(20/101)</td>
<td>(20/89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>0.35 ± 0.24</td>
<td>0.37 ± 0.29</td>
<td>0.30 ± 0.22</td>
<td>0.25 ± 0.21</td>
<td>0.23 ± 0.21</td>
<td>.02</td>
</tr>
<tr>
<td>(20/45)</td>
<td>(20/47)</td>
<td>(20/40)</td>
<td>(20/35)</td>
<td>(20/34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoconus</td>
<td>0.39 ± 0.27</td>
<td>0.39 ± 0.30</td>
<td>0.32 ± 0.24</td>
<td>0.26 ± 0.23</td>
<td>0.25 ± 0.23</td>
<td></td>
</tr>
<tr>
<td>(20/49)</td>
<td>(20/50)</td>
<td>(20/42)</td>
<td>(20/36)</td>
<td>(20/36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectasia</td>
<td>0.26 ± 0.16</td>
<td>0.32 ± 0.25</td>
<td>0.25 ± 0.17</td>
<td>0.22 ± 0.17</td>
<td>0.19 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>(20/37)</td>
<td>(20/42)</td>
<td>(20/35)</td>
<td>(20/33)</td>
<td>(20/31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity

*Significant change compared with baseline measurements
†Significant change compared with previous visit measurement

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**Figure 1.** Top: Change in UDVA over time. Numbers reported are Snellen visual acuity ($20/\times$). Bottom: Change in UDVA Snellen lines between baseline and 12 months postoperatively (KC = keratoconus).

**Figure 2.** Top: Change in CDVA over time. Numbers reported are Snellen visual acuity ($20/\times$). Bottom: Change in CDVA Snellen lines between baseline and 12 months postoperatively.
Absolute  In the entire study cohort, all changes in the mean absolute manifest astigmatism between preoperatively and each postoperative visit failed to reach statistical significance (1 month, \( P = .39 \); 3 months, \( P = .24 \); 6 months, \( P = .97 \); 12 months, \( P = .84 \)). Similarly, absolute astigmatism in the keratoconus and ectasia subgroups remained unchanged at 1 year (Table 2). The manifest astigmatism improved by 1.00 D or more in 24 eyes (33.8%) (17 keratoconus, 7 ectasia), changed between −1.00 D and 1.00 D in 29 eyes (34.7%) (19 keratoconus, 10 ectasia), and worsened by 1.00 D or more in 18 eyes (25.4%) (13 keratoconus, 5 ectasia).

Vector Analysis of Surgically Induced Astigmatism  The mean SIA at 12 months was 0.61 D \( \times \) 73.4 degrees, 1.12 D \( \times \) 75.2 degrees, and 0.53 D \( \times \) 81.7 degrees in the entire cohort, the keratoconus subgroup, and the ectasia subgroup, respectively. In the entire cohort, the mean induced astigmatism was 0.99 D \( \times \) 88.8 degrees and 0.65 D \( \times \) 44.7 degrees in right eyes and left eyes, respectively (Figure 4). In the keratoconus subgroup, the mean induced astigmatism was 1.75 D \( \times \) 87.9 degrees and 1.01 D \( \times \) 49.8 degrees in the right eyes and left eyes, respectively. In the ectasia subgroup, the mean induced astigmatism was 0.65 \( \times \) 83.3 degrees and 0.42 \( \times \) 79.0 degrees in the right eyes and left eyes, respectively. Regarding the induced magnitude of astigmatism, the mean vectorial magnitude of SIA at 12 months was 2.99 \( \times \) 2.55 D, 3.16 \( \times \) 2.72 D, and 2.61 \( \times \) 2.15 D, in the entire cohort, the keratoconus subgroup, and the ectasia subgroup, respectively.

Postoperative Topography  Table 3 shows the postoperative topographic measurements.

Maximum Keratometry  There was a significant decrease in the mean maximum K value (−1.7 \( \pm \) 3.9 D) between preoperatively and 12 months postoperatively (\( P < .001 \)). There was a significant increase between baseline and 1 month (mean 1.39 \( \pm \) 2.80 D; \( P < .001 \)) and then a significant decrease between 1 month and 3 months (mean −1.69 \( \pm \) 2.55 D; \( P < .001 \)) and between 3 months and 6 months (mean −0.93 \( \pm \) 3.02; \( P = .01 \)). There was no significant change in maximum K between 6 months and 12 months (mean −0.48 \( \pm \) 3.20; \( P = .21 \)) (Figure 5, A).

In the keratoconus subgroup, there was a 2.00 D decrease in the mean maximum K value between preoperatively and 12 months postoperatively (\( P = .002 \)).
**Figure 4.** Double-angle plot of vector change in astigmatism 1 year after CXL. *Left:* Right eyes. *Right:* Left eyes.

**Table 3.** Postoperative topographic measurements by Scheimpflug imaging.

<table>
<thead>
<tr>
<th>Parameter/Group</th>
<th>Mean (D) ± SD</th>
<th>P Value (Keratoconus Vs Ectasia)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>1 Month</td>
</tr>
<tr>
<td>Maximum K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>58.6 ± 9.62</td>
<td>60.0 ± 9.80$^*$</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>60.4 ± 9.99</td>
<td>61.7 ± 10.2$^*$</td>
</tr>
<tr>
<td>Ectasia</td>
<td>54.7 ± 7.52</td>
<td>56.2 ± 7.78$^{+\dagger}$</td>
</tr>
<tr>
<td>Average K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>48.2 ± 6.97</td>
<td>48.8 ± 7.11$^{+\dagger}$</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>50.4 ± 7.06</td>
<td>50.8 ± 7.34</td>
</tr>
<tr>
<td>Ectasia</td>
<td>43.4 ± 3.54</td>
<td>44.3 ± 3.90$^{+\dagger}$</td>
</tr>
<tr>
<td>Flat K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>45.8 ± 6.42</td>
<td>46.3 ± 6.79</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>47.9 ± 6.35</td>
<td>48.2 ± 7.09</td>
</tr>
<tr>
<td>Ectasia</td>
<td>41.1 ± 3.32</td>
<td>42.0 ± 3.22</td>
</tr>
<tr>
<td>Steep K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>50.9 ± 7.33</td>
<td>51.7 ± 7.73$^{+\dagger}$</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>52.9 ± 7.45</td>
<td>53.8 ± 7.86$^{+\dagger}$</td>
</tr>
<tr>
<td>Ectasia</td>
<td>46.51 ± 4.73</td>
<td>47.0 ± 4.98</td>
</tr>
<tr>
<td>Astigmatism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All eyes</td>
<td>4.94 ± 2.45</td>
<td>5.46 ± 2.82</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>4.80 ± 2.42</td>
<td>5.64 ± 2.95$^{+\dagger}$</td>
</tr>
<tr>
<td>Ectasia</td>
<td>5.24 ± 2.55</td>
<td>5.06 ± 2.54</td>
</tr>
</tbody>
</table>

K = keratometry

$^*$Significant change compared with baseline measurements

$^{+\dagger}$Significant change compared with previous visit measurement
There was a significant increase between baseline and 1 month (mean change 1.33 ± 3.03 D; \( P = .003 \)) and a significant decrease between 1 month and 3 months (mean change −1.70 ± 2.66 D; \( P < .001 \)) and 3 months and 6 months (mean change −0.94 ± 3.22 D; \( P = .046 \)). There was no significant change between 6 months and 12 months (mean change −0.72 ± 3.58 D; \( P = .17 \)).

In the ectasia subgroup, there was a 1.00 D decrease in the mean maximum K value between preoperatively and 12 months postoperatively; however, this failed to reach statistical significance (\( P = .08 \)). There was a significant increase between baseline and 1 month (mean change 1.51 ± 2.27 D; \( P = .005 \)) and a significant decrease between 1 month and 3 months (mean change −1.66 ± 2.35 D; \( P = .003 \)). There were no significant changes between 3 months and 6 months (mean change −0.91 ± 2.60 D; \( P = .12 \)) or between 6 months and 12 months (mean change 0.05 ± 2.08 D; \( P = .91 \)).

The maximum K value decreased by 2.00 D or more in 22 eyes (31.0%) patients and remained unchanged in 28 eyes (39.4%) patients. It increased by 2.00 D or more in 3 eyes (4.2%) (Figure 5, B).

Figure 5. A: Change in maximum K over time. B: Change in maximum K between baseline and 12 months postoperatively. C: Change in average K over time (KC = keratoconus).
Average Keratometry In the entire cohort, there was a significant decrease in the mean average K value (−1.10 ± 2.39 D) between preoperatively and 12 months postoperatively (P < .001). There was a significant increase between baseline and 1 month (mean change 0.56 ± 1.87 D; P = .01) and significant decreases between 1 month and 3 months (mean change −1.11 ± 1.26 D; P < .001) and between 6 months and 12 months (mean change −0.41 ± 1.60 D; P = .03). There was no significant change between 3 months and 6 months mean change (−0.14 ± 1.99 D; P = .56) (Figure 5, C).

In the keratoconus subgroup, there was a 1.50 D decrease in the mean average K value between preoperatively and 12 months postoperatively (P < .001). There was a significant decrease between 1 month and 3 months (mean change −1.07 ± 1.38 D; P < .001) and between 6 months and 12 months (mean change −0.64 ± 1.79 D; P = .02). There were no significant changes in between baseline and 1 month (mean change 0.40 ± 2.07 D; P = .19) or between 3 months and 6 months (mean change −0.15 ± 2.27 D; P = .65).

In the ectasia subgroup, there was a 0.3 D decrease in the mean average K value between preoperatively and 12 months postoperatively; however, this failed to reach statistical significance (P = .22). There was a significant increase between baseline and 1 month (mean change 0.91 ± 1.28 D; P = .003) followed by a significant decrease between 1 month and 3 months (mean change −1.21 ± 0.99 D; P < .001). There were no significant changes between 3 months and 6 months (mean change −0.12 ± 1.16 D; P = .64) or between 6 months and 12 months (mean change 0.09 ± 0.92 D; P = .65).

Corneal Astigmatism (Simulated Keratometry) In the entire cohort and the ectasia subgroup, all changes in corneal astigmatism, measured by Scheimpflug simulated K, failed to reach significance at all time points. In the keratoconus subgroup, there were significant increases in corneal astigmatism compared with baseline at 1 month (P = .01) and 3 months (P = .02). However, the simulated K value returned to baseline at 6 months; there were no significant changes in corneal astigmatism compared with baseline at 6 months (P = .76) or 12 months (P = .87).

Comparison Between Groups Keratoconus Versus Ectasia The baseline CDVA, maximum K value, average K value, flat K value, and steep K value in the keratoconus subgroup were significantly different from the same baseline measurements in the ectasia subgroup (CDVA, P = .02; maximum K, P = .02; average K, P < .001; flat K value, P < .001; steep K, P < .001). However, there were no significant differences between the keratoconus subgroup and ectasia subgroup in changes in visual acuity (UDVA, CDVA), refraction (MRSE, manifest astigmatism), or topography (maximum K, average K, flat K, steep K, astigmatism) 12 months after CXL (Tables 1 to 3).

Control Groups Sham In the sham control group, there were no statistically significant changes in CDVA, manifest astigmatism, MRSE, maximum K value, average K value, steep K, or corneal astigmatism at the 1-month or 3-month follow-up visits. There was a statistically significant improvement in UDVA at 1 month (mean change −0.09 ± 0.26 logMAR; P = .03) and 3 months (mean change −0.08 ± 0.23 logMAR; P = .03) compared with baseline. There was also a statistically significant increase in flat K value from baseline to 3 months (mean change 0.54 ± 1.65 D; P = .04).

Fellow-Eye In the fellow-eye control group, there were no changes in UDVA, CDVA, maximum K, average K, flat K, steep K, MRSE, or corneal astigmatism over the 12-month study. The mean change in UDVA was −0.04 ± 0.18 logMAR (P = .19); in CDVA, −0.40 ± 0.14 logMAR (P = .17), in the maximum K value, +0.29 ± 1.19 D (P = .19); and in the average K value, +0.20 ± 0.79 D (P = .18). There was a statistically significant increase in manifest astigmatism (mean change 0.34 ± 0.82 D; P = .03) at 1 year.

Treatment Versus Control Groups At 3 months, there were no significant differences between the treatment and sham control group in changes from baseline in UDVA, CDVA, maximum K, or average K value (P = .13, P = .44, P = .25, and P = .89, respectively). At 1 year, all of the outcomes were significantly better in the treatment group than in the fellow-eye control group (P = .02, P < .001, P < .001, and P < .001, respectively) (Figure 6).

DISCUSSION Corneal collagen crosslinking is a promising new treatment for keratoconus and corneal ectasia. Crosslinking is thought to biomechanically strengthen the corneal stroma and, consequently, slow the progression of keratoconus and ectasia. In many cases, moreover, CXL improves the patient’s visual, refractive, and topographic outcomes with few reported complications. In this controlled clinical trial, visual acuity, refraction, and topography outcomes were analyzed in patients diagnosed with keratoconus and in those with post-LASIK corneal ectasia. This study represents one of the largest prospectively analyzed treatment groups to date. Unique to this investigation are
the comparisons of the treatment group with a sham control group and a fellow-eye control group, an analysis of the postoperative time course of CXL-mediated clinical changes, as well as an analysis of these patients as an entire cohort and individually within their respective keratoconus or ectasia subgroup. In our study, the mean UDVA was approximately 1 Snellen line better 12 months postoperatively. This improvement is somewhat less than previously reported. Vinciguerra et al.\textsuperscript{18} report a significant improvement in mean UDVA, from 0.77 logMAR preoperatively to 0.57 logMAR 12 months postoperatively. Caporossi et al.\textsuperscript{20} reported a significant improvement in mean UDVA of 2.41 Snellen lines.

In clinical practice, it is valuable to give the patient an idea of his or her possible outcomes as an individual, rather than as a population mean, to afford them proper expectations. Thus, it is helpful to look at the likelihood that an individual patient will improve or decline substantially. In this type of analysis, 18 eyes (25.4%) gained 2 or more lines of UDVA, and 6 eyes (8.5%) lost 2 or more lines of UDVA. The cause of UDVA loss in these patients is unclear and did not appear directly related to refractive error or change in corneal topography. Of the 6 eyes, 3 were in the keratoconus subgroup and 3 in the ectasia subgroup. The 3 keratoconus cases were stage I, stage III, and stage IV. The range of baseline UDVA in the 6 eyes was 20/40 to 20/100, and they lost between 2 lines and 4 lines of UDVA by 1 year postoperatively (Table 4).

Like UDVA, a significant improvement in postoperative CDVA has been reported in studies of CXL. In a study by Vinciguerra et al.\textsuperscript{18,21} in patients with stage III keratoconus, the mean CDVA improved from 0.28 logMAR to 0.14 logMAR 12 months postoperatively, and in patients with ectasia, the CDVA improved significantly, from 0.16 logMAR to 0.06 logMAR. Similarly, at 1-year follow-up, Caporossi et al.\textsuperscript{20} and Raiskup-Wolf et al.\textsuperscript{22} found significant improvements in CDVA (0.08 logMAR and 1.34 Snellen lines, respectively), with continued improvement after 1 year. Hafezi et al.\textsuperscript{13} report that CDVA improved in 4 of 10 eyes with post-LASIK ectasia.

In our study, there was also a significant improvement of more than 1 line of mean CDVA 1 year postoperatively (mean change 0.12 ± 0.19 logMAR). This was in contrast to the fellow-eye control group, in which CDVA did not change significantly. In the entire study cohort, 15 eyes (21.1%) gained 2 or more Snellen lines of CDVA and only 1 (1.4%) lost 2 lines of CDVA. The latter case had post-LASIK ectasia, and both the CDVA and UDVA decreased from 20/100 to 20/160 at 1 year; the cause was unclear. We are currently performing further analysis to determine preoperative predictors of patients in whom outcomes significantly improve or worsen after CXL treatment.

Looking at the time course of CDVA change in the entire study cohort, the significant changes in CDVA appeared to occur between 1 month and 3 months and between 3 months and 6 months, with a plateau

Table 4. Visual acuity in the 6 eyes that lost 2 or more Snellen lines of UDVA 1 year after CXL.

<table>
<thead>
<tr>
<th>Eye Subgroup</th>
<th>Stage of KC</th>
<th>UDVA (Snellen)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Mo Postop</td>
</tr>
<tr>
<td>1 Keratoconus</td>
<td>Stage I</td>
<td>20/80</td>
</tr>
<tr>
<td>2 Keratoconus</td>
<td>Stage III</td>
<td>20/80</td>
</tr>
<tr>
<td>3 Keratoconus</td>
<td>Stage IV</td>
<td>20/40</td>
</tr>
<tr>
<td>4 Ectasia</td>
<td>—</td>
<td>20/100</td>
</tr>
<tr>
<td>5 Ectasia</td>
<td>—</td>
<td>20/100</td>
</tr>
<tr>
<td>6 Ectasia</td>
<td>—</td>
<td>20/80</td>
</tr>
</tbody>
</table>

UDVA = uncorrected distance visual acuity
in improvement thereafter. In the keratoconus subgroup, the change in CDVA over time followed a pattern similar to that in the entire cohort. The ectasia subgroup did not have any significant changes between time points; however, there was a significant change in CDVA from baseline to 12 months postoperatively.

Previous studies report changes in the MRSE of 0.40 D, 1.43 D, and 2.20 D. In our study, the mean improvement in the MRSE at 12 months was 0.86 D. However, this change failed to reach statistical significance. Similarly, there were no significant changes in the MRSE in the keratoconus and ectasia subgroups. Poor reproducibility of subjective refraction in these patients with irregular corneal topographies might account for the lack of a significant difference in postoperative refraction after CXL.

Previous studies reported significant changes in manifest astigmatism of 0.93 D and 0.26 D respectively. In our study, the mean manifest astigmatism at 12 months was 0.40 D. However, this change failed to reach statistical significance. Similarly, there were no significant changes in the MRSE in the keratoconus and ectasia subgroups. Poor reproducibility of subjective refraction in these patients with irregular corneal topographies might account for the lack of a significant difference in postoperative refraction after CXL.

Previous studies reported significant changes in manifest astigmatism of 0.93 D and 0.26 D respectively. In our study, the mean manifest astigmatism at 12 months was 0.40 D. However, this change failed to reach statistical significance. Similarly, there were no significant changes in the MRSE in the keratoconus and ectasia subgroups. Poor reproducibility of subjective refraction in these patients with irregular corneal topographies might account for the lack of a significant difference in postoperative refraction after CXL.

The maximum K value is a key topographic indicator of the success of CXL because it measures, to some extent, the severity of the keratoconic cone. Previous studies report decreases in the K value of 2.01 D, 1.90 D, 1.46 D, and 1.42 D in keratoconic patients. Hafezi et al. report a decrease in maximum K value in patients with ectasia after LASIK. Our current study corroborates findings in these previous studies; we found a significant decrease in maximum K value of 1.70 D at 1 year, compared with no significant change in the fellow-eye control group. The largest change was in the keratoconus subgroup, which showed a 2.0 D flattening effect, whereas a smaller change of 1.0 D, which failed to reach statistical significance, was found in the ectasia subgroup.

In all groups, there was a significant increase in maximum K value at 1 month, followed by the largest decrease in maximum K value between 1 month and 3 months. In all groups, there was no significant change in the maximum K value between 6 months and 12 months. This contrasts with the findings of Caporossi et al. and Raiskup-Wolf et al., who report a continued decrease in maximum K values after the 1-year follow-up. Further follow-up is required to determine whether the maximum K value will continue to decrease after 12 months in patients with keratoconus or ectasia.

Individually, the maximum K value decreased by 2.0 D or more in 22 eyes (31.0%) (17 keratoconus, 5 ectasia) and increased by 2.0 D or more in 3 eyes (4.2%) (1 keratoconus, 2 ectasia). These latter 3 eyes would be considered treatment failures because cone progression was not stabilized. Similar to the results of Koller et al., the maximum K value increased by 1.00 D or more in 7 eyes (9.8%) (5 keratoconus, 2 ectasia). Curiously, none of the 7 eyes were among those that lost 2 or more lines of UDVA and CDVA.

Similar to maximum K value, the decrease in the average K value in the entire cohort at 12 months compared with baseline was significant. In the keratoconus subgroup, the average K value was significantly decreased at 12 months as well. However, in the ectasia subgroup, the average K value did not significantly change. Analogous to the maximum K value, all groups had the largest significant decrease in the average K value between 1 month and 3 months.

The flat K and steep K values showed improvements similar to those in the maximum K and average K values. It remains unclear whether the achieved flattening of the flat K value at 1 year is, in fact, a desirable outcome from the clinical viewpoint because it may militate irregularity of the corneal topography. Further study of corneal topography after CXL is needed to determine whether it is this general topographic flattening, or perhaps, more complex changes in the corneal optical contour, that result in the significant improvements in CDVA after CXL treatment.

In this study, there were significant differences between the baseline topographic measurements and CDVA in the keratoconus and ectasia subgroups. Therefore, it is difficult to accurately assess the differences in the changes in postoperative outcome measurements in these 2 groups. However, the data here and in previous studies suggest that there may be differences between the postoperative CXL outcomes in keratoconus patients and ectasia patients.

In the ectasia group, the only significant change in CDVA was when 1-year postoperative measurements were compared with baseline. In contrast to the keratoconus subgroup, the ectasia subgroup had no significant change in CDVA at any time interval between baseline and 12 months. This may suggest increased variability in the time course of CDVA changes in ectasia patients compared with changes in keratoconus patients.

Furthermore, although there was a trend toward improvement, there were no significant changes in maximum K, average K, or flat K in the ectasia subgroup; only steep K showed a statistically significant improvement at the 1-year follow-up. At baseline, the ectatic corneas in this study were flatter than those in the keratoconus subgroup and, therefore, the topographic
changes caused by CXL in these corneas may be subtler. Notwithstanding, our data suggest that ectatic corneas may not have as robust a response to CXL as keratoconus corneas. Similar to our findings, Vinciguerra et al. found no significant topographic changes (average K, flat K, steep K) in patients with post-LASIK ectasia.

The cause of a potential difference between keratoconic corneas and ectatic corneas is, as yet, unclear. Biomechanical differences caused by the LASIK flap; possible differences in the riboflavin diffusion rate in post-LASIK corneas, especially at the flap interface; and intrinsic pathophysiologic differences between keratoconus and ectasia may all contribute to the different responses to CXL between the 2 groups. Certainly, further study with a greater number of ectatic eyes is necessary to further elucidate differences in the response to CXL between eyes with keratoconus and eyes with ectasia.

Treatment patients were compared with a sham control group and a fellow-eye control group. In the study protocol, the sham control group received riboflavin alone and was placed under a UVA light that was turned off. Most notably, the epithelium was not removed in any of the control patients. Therefore, any contribution of deep epithelialization, rather than the UVA light treatment, to patient outcomes was not accounted for by this control group. In addition, these patients were only followed for 3 months, at which point they crossed over to the treatment group; therefore, our comparison with the treatment group was limited to 3 months.

These limitations of the sham control group suggested an additional comparison of the treatment group with a 12-month fellow-eye control group. Ideally, all fellow eyes would have been compared with treatment eyes. However, the protocol in this clinical trial allowed fellow-eye CXL 3 months after first-eye treatment. Therefore, in this study, the treatment group was compared only with the fellow eyes of patients who had unilateral treatment. Some fellow eyes in this study had no topographic or visual signs of keratoconus or ectasia. Thus, disease progression would be expected to be minimal.

The treatment group was compared with the 2 control groups. The changes in UDVA, CDVA, maximum K, and average K between baseline and 3 months in the sham control group were not significantly different than the changes in these measurements in the treatment group during the same 3-month period. However, treated eyes had significant improvement in UDVA, CDVA, maximum K, and average K compared with the fellow-eye controls. Thus, the efficacy of the CXL procedure in improving patient outcomes and stabilizing corneal ectatic progression over a 1-year period was clearly shown.

As seen, the basic clinical outcomes of CXL seem to follow a reproducible time course after treatment. In general, visual acuity and corneal steepness worsen somewhat at the 1-month time point. Resolution to baseline occurs by approximately 3 months, with improvement thereafter. This is similar to the clinical time course of CXL-associated corneal haze, which we reported elsewhere. In these cases, the haze is greatest at 1 month, plateaus at 3 months, and decreases significantly between 3 months and 12 months postoperatively. Thus, stromal and epithelial healing responses to CXL appear to continue over months, concomitant with the changes in clinical outcomes, which we report here.

REFERENCES


OTHER CITED MATERIAL


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Characteristics influencing outcomes of corneal collagen crosslinking for keratoconus and ectasia: Implications for patient selection

Steven A. Greenstein, MD, Peter S. Hersh, MD

**PURPOSE:** To determine preoperative patient characteristics that may predict topography and visual acuity outcomes of corneal collagen crosslinking (CXL).

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

**DESIGN:** Cohort study.

**METHODS:** Crosslinking was performed in eyes with keratoconus or corneal ectasia. Multiple regression and odds ratio analyses were performed to determine independent predictors of changes in topography-derived maximum keratometry (K) and corrected distance visual acuity (CDVA) 1 year postoperatively. Preoperative characteristics included sex, age, uncorrected distance visual acuity (UDVA), CDVA, maximum keratometry (K), corneal thickness, corneal haze, disease group, and cone location. Postoperative improvement in maximum K was defined as flattening of 2.0 diopters (D) or more and worsening as steepening of 1.0 D or more. Improvement in CDVA was defined as a gain of 2 lines or more and worsening as a loss of 1 line or more.

**RESULTS:** The study comprised 104 eyes (66 keratoconus; 38 corneal ectasia). Eyes with a preoperative CDVA of 20/40 or worse were 5.9 times (95% confidence interval [CI], 2.2-6.4) more likely to improve 2 Snellen lines or more. Eyes with a maximum K of 55.0 D or more were 5.4 times (95% CI, 2.1-14.0) more likely to have topographic flattening of 2.0 D or more. No preoperative characteristics significantly predicted worsening of visual acuity or corneal topography.

**CONCLUSIONS:** Patients with worse preoperative CDVA and higher K values, particularly with a CDVA of 20/40 or worse or a maximum K of 55.0 D or more, were most likely to have improvement after CXL. No preoperative characteristics were predictive of CXL failure.

**Financial Disclosure:** Dr. Hersh is a medical monitor for Avedro, Inc. Dr. Greenstein has no financial or proprietary interest in any material or method mentioned.

and visual acuity after CXL to begin to determine patients who are best treated with CXL and those who are poor candidates.

PATIENTS AND METHODS

Patients with progressive keratoconus or ectasia after laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) were enrolled as part of a multicenter prospective randomized controlled clinical trial. This study was approved and monitored by an investigational review board, was U.S. Health Insurance Portability and Accountability Act compliant, and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

The inclusion criteria included 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 a period of 24 months: an increase of 1.0 D or more in the steepest keratometry (K), an increase of 1.0 D or more in the manifest cylinder, or an increase of 0.5 D or more in the manifest refraction spherical equivalent. Exclusion criteria included a history of corneal surgery (except previous LASIK or PRK), chemical injury, delayed epithelial healing, and a corneal thickness less than 300 μm.

Surgical Technique

Crosslinking was performed according to the methodology described by Wöllensak et al. Topical anesthesia was administered, and the corneal epithelium was removed by mechanical debridement over the central 9.0 mm. Riboflavin (0.1% in 20.0% dextran T500 solution, Medio Cross, Peschke Meditrade GmbH) was then administered topically every 10 seconds for 2-minute sessions, after which ultrasonic pachymetry was performed to confirm that the stroma had swollen to more than 400 μm. This was repeated until adequate corneal thickness was obtained.

The cornea was exposed to ultraviolet-A (UV-A) 365 nm light (UV-X system, IROC Innocross AG) for 30 minutes at an irradiance of 3.0 mW/cm². During UV-A exposure, riboflavin drops were continued every 2 minutes.

Postoperatively, antibiotic and corticosteroid drops were administered and a therapeutic soft contact lens (Acuvue Oasys, Vistakon Pharmaceuticals, LLC) 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 were continued for 2 weeks.

Clinical Measurements

Visual Acuity The CDVA was measured preoperatively and 1 year postoperatively. High-contrast visual acuity measurements were obtained under controlled lighting conditions using a modified Lighthouse Early Treatment Diabetic Retinopathy Study visual acuity test (2nd edition) with Sloan letters. Patients were tested 4 m from the visual acuity chart. If patients could not read any letters at 4 m, they were tested at 2 m.

Maximum Keratometry and Topographic Cone Location Topography measurements were obtained using a Scheimpflug-based corneal topography instrument (Pentacam, Oculus Optikgeräte GmbH). Maximum K data were obtained preoperatively and 1 year postoperatively.

A previous study found that the magnitude of postoperative flattening after CXL was associated with preoperative cone location. Therefore, cone location was assessed as a preoperative characteristic in this study. The detailed methodology has been described. In brief, the preoperative cone location, defined by the Scheimpflug coordinates of maximum K, were divided into 2 groups as follows: eyes in which the maximum K was located in the central 3.0 mm optical zone (central cone) and eyes in which the maximum K was located outside the central 3.0 mm optical zone (peripheral cone).

Corneal Thickness (Pachymetry) Measurements Pachymetry measurements were obtained using the Scheimpflug instrument. The thinnest point on the corneal thickness map was obtained preoperatively and 1 year postoperatively.

Corneal Haze Measurements A complete description of the method used for measuring corneal haze using Scheimpflug densitometry has been described in detail. Briefly, images of all eyes were taken with the Scheimpflug instrument before the procedure and 1 year postoperatively. Using perimeter software included with the instrument, objective corneal densitometry (haze) was manually measured over the central 4.0 mm using the Scheimpflug image along 1 meridian on the axis nearest to the maximum K.

Statistical Analysis

Statistical analysis was performed using PASW software (version 18, IBM Inc.). First, a multiple regression analysis was performed to identify significant predictors of CDVA and maximum K 1 year postoperatively. Patients with severe keratoconus, as defined by McMahon et al., were excluded from analysis because the variability in their outcome measurements was too large for accurate analysis. Postoperative outcomes of maximum K and CDVA were chosen for analysis because they represent the most salient results of CXL.
in these disease processes. The topographic maximum K is an objective indicator of disease severity and progression, and the CDVA is the predominant visual function indicator. Preoperative characteristics assessed included patient age and sex, UDVA, CDVA, maximum K, thinnest pachymetry, corneal haze, disease (keratoconus versus ectasia), and topographic cone location. Multiple odds ratio (OR) analyses were performed for characteristics identified as significant on regression analysis.

An improvement in CDVA and maximum K was defined as an increase of more than 2 Snellen lines and flattening of more than 2.0 D, respectively, 1 year postoperatively. Because few patients in the study cohort had a loss of more than 2 Snellen lines of CDVA or a steepening of maximum K of more than 2.0 D, worsening of CDVA and maximum K were defined as a loss of 1 Snellen line or more and a steepening of 1.0 D or more, respectively. This was done to better identify patients who might do poorly with CXL. All patient outcomes that did not meet the above criteria were considered to be stable 1 year after CXL.

**RESULTS**

One hundred four eyes that had CXL for keratoconus (n = 66) or ectasia (n = 38) were analyzed. Overall, the mean CDVA improved and the mean maximum K flattened from preoperatively to 1 year after CXL; both changes were statistically significant (P < .001). Table 1 shows the preoperative and 1-year postoperative CXL measurements.

**Corrected Distance Visual Acuity**

**Multiple Regression Analysis** Table 2 shows the individual characteristics assessed and the regression coefficients included in the analysis. In the multivariate regression analysis, the CDVA and maximum K value were the only significant predictors of the 1-year postoperative CDVA.

**Odds Ratio Analysis** Eyes with a preoperative CDVA of 20/40 or worse were 5.4 times more likely to improve by 2 Snellen lines or more 1 year after CXL (95% confidence interval [CI], 2.1-14.0). Specifically, 22 (43.1%) of 51 eyes with a CDVA of 20/40 or worse had worsening of 1 Snellen line or more compared with 4 (7.8%) of 51 eyes with a CDVA of 20/40 or worse. However, the difference was not statistically significant (OR, 0.5; 95% CI, 0.14-1.70).

Although the multiple regression analysis identified an association between the preoperative maximum K value and the postoperative CDVA, all OR analyses failed to reach statistical significance.

**Maximum Keratometry**

**Multiple Regression Analysis** Table 5 shows the individual characteristics assessed and regression coefficients included in the analysis. In this multivariate regression analysis, preoperative maximum K was the only significant predictor of the 1-year postoperative maximum K.

**Odds Ratio Analysis** Eyes with a maximum K value of 55.0 D or more were 5.4 times more likely than eyes with a maximum K value of less than 55.0 D to have flattening of 2.0 D or more 1 year after CXL (CI, 2.1-14.0). Specifically, 20 (45.4%) of 44 eyes with a maximum K value of 55.0 D or more flattened by 2.0 D or more compared with 8 (13.3%) of 60 eyes with a preoperative maximum K of less than 55.0 D.

<table>
<thead>
<tr>
<th>Table 1. Preoperative and 1-year postoperative CXL measurements.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Mean UDVA, logMAR (Snellen)</td>
</tr>
<tr>
<td>Mean CDVA, logMAR (Snellen)</td>
</tr>
<tr>
<td>Mean maximum K (D)</td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity

*P < .05 indicates significant change.

<table>
<thead>
<tr>
<th>Table 2. Preoperative characteristics included in the multiple regression analysis for the outcome of CDVA.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preop Variable</strong></td>
</tr>
<tr>
<td>(Constant)</td>
</tr>
<tr>
<td>KC vs EC</td>
</tr>
<tr>
<td>Cone location</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>UDVA</td>
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<td>CDVA</td>
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<tr>
<td>MRSE</td>
</tr>
<tr>
<td>Maximum K</td>
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<tr>
<td>Thinnest pachymetry</td>
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<tr>
<td>Haze</td>
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</tbody>
</table>

CDVA = corrected distance visual acuity; EC = ectasia; K = keratometry; KC = keratoconus; MRSE = manifest refraction spherical equivalent; UDVA = uncorrected distance visual acuity

*Coefficients were considered significant if P < .05.*
Table 6 shows the complete list of postoperative maximum K OR analyses.

Two eyes (1.9%) steepened 2.0 D or more 1 year after CXL. Regarding eyes that continued to have topographic progression at the more subtle 1.0 D level, there was no difference between groups; 4 (10.0%) of 44 eyes with a maximum K value of 55.0 D or more had 1.0 D or more of steepening of the maximum K value 1 year after CXL compared with 5 (8.3%) of 60 eyes with a maximum K value less than 55.0 D. Moreover, eyes with a maximum K value of 55.0 D or more, or less than 55.0 D, were equally likely to remain topographically stable (±1.0 D) 1 year after CXL (OR, 0.9; CI, 0.24-3.40).

**DISCUSSION**

In our previous studies of 1-year outcomes of corneal collagen crosslinking, we found improvements in the mean CDVA, UDVA, maximum K value, quantitative indices of corneal topography, higher-order wavefront aberrations, and subjective visual function after CXL. However, although CXL appears generally promising for eyes with keratoconus and corneal ectasia, from a clinical perspective it would be helpful to identify the characteristics of eyes that do well after the procedure and those that do poorly. This would facilitate proper patient selection and identify possible exclusion criteria. For example, although in our past studies the mean CDVA improved from 20/45 to 20/34, individually 21.1% of eyes improved by more than 2 Snellen lines and 1 eye (1.4%) lost 2 Snellen lines. Similarly, although the mean maximum K value flattened from baseline by a mean of 1.7 D, individually the mean maximum K value flattened by more than 2.0 D in 31.0% of eyes and increased by more than 2.0 D or more in 4.2%.

**Table 3.** Odds ratios performed at multiple preoperative CDVA stratifications.

<table>
<thead>
<tr>
<th>Preop CDVA Stratification</th>
<th>Improvement of ≥ 2 Snellen Lines, n (%)</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In Eyes with Preop CDVA Better than</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>CDVA in Column 1</td>
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<td></td>
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<tr>
<td></td>
<td>In Eyes with Preop CDVA Equal to or</td>
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<td></td>
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<tr>
<td></td>
<td>Worse than CDVA in Column 1</td>
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<td></td>
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<tr>
<td>20/25</td>
<td>0/5</td>
<td>28/99 (28)</td>
<td>1.4x</td>
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<tr>
<td>20/32</td>
<td>0/23</td>
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<td>6/53 (11)</td>
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<td>20/50</td>
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<td>20/80</td>
<td>20/95 (20)</td>
<td>8/9 (89)</td>
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</tbody>
</table>

CDVA = corrected distance visual acuity; CI = confidence interval; OR = odds ratio
*Relative likelihood that an eye with preoperative CDVA worse than or equal to the preoperative CDVA in the first column will improve by ≥ 2 Snellen lines compared with an eye with better than the CDVA stratification

**Table 4.** Characteristics of 3 patients who lost 2 or more Snellen lines of CDVA 1 year after CXL.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Right</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Group</td>
<td>KC</td>
<td>EC</td>
<td>EC</td>
</tr>
<tr>
<td>Age (y)</td>
<td>22</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
<td>Indian</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Preop CDVA (logMAR)</td>
<td>0.8</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>SE (D)</td>
<td>−9.6</td>
<td>−4.1</td>
<td>−1.0</td>
</tr>
<tr>
<td>Maximum K (D)</td>
<td>67.3</td>
<td>43.5</td>
<td>50.9</td>
</tr>
<tr>
<td>Thinnest pachymetry (µm)</td>
<td>373</td>
<td>439</td>
<td>420</td>
</tr>
<tr>
<td>Haze (densitometry)</td>
<td>15.7</td>
<td>15.7</td>
<td>14.5</td>
</tr>
<tr>
<td>Snellen lines lost</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; EC = ectasia; K = keratometry; KC = keratoconus; SE = spherical equivalent

**Table 5.** Preoperative characteristics included in the multiple regression analysis for maximum K.

<table>
<thead>
<tr>
<th>Preop Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>2.0</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>KC vs EC</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Cone location</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Age</td>
<td>−0.02</td>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.7</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>UDVA</td>
<td>−0.2</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>CDVA</td>
<td>0.1</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Maximum K</td>
<td>0.9</td>
<td>0.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thinnest pachymetry</td>
<td>0.2</td>
<td>0.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Haze</td>
<td>2.0</td>
<td>3.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; EC = ectasia; K = keratometry; KC = keratoconus; UDVA = uncorrected distance visual acuity
*Coefficients were considered significant if P < .05
Thus, identifying predictors of these individual good results and bad results would have substantial clinical significance.

As yet, such specific predictors of positive and negative CXL outcomes have not been clearly elucidated. In this effort, 2 studies by Koller et al.19,20 deserve attention. In the first study of 105 eyes, 3 eyes lost 2 Snellen lines of CDVA at 1 year.19 Two characteristics—age over 35 years and CDVA better than 20/25—were identified as risk factors for this loss of vision (OR, 13.14 for age and 18.18 for CDVA). Eight eyes (7.6%) showed continued progression of keratoconus 1 year after CXL; progression was defined as an increase in the maximum K value of more than 1.0 D, similar to the definition in our study. Two preoperative characteristics—maximum K over 58.0 D and female sex—were identified as risk factors for continued disease progression (OR, 5.32 for K and 3.11 for sex). In a second study by Koller et al.,20 a preoperative K value of more than 54.0 D was associated with a greater likelihood of postoperative flattening of more than 1.0 D, a finding corroborated by our study. With regard to clinical decision-making, the latter study conflicts somewhat with the earlier conclusion that a K value of more than 58.0 D was associated with a greater risk for continued disease progression. However, this highlights the importance of defining the clinical goals in an individual CXL patient, as we will discuss shortly.

In our analysis, the only independent predictor of a change in the postoperative CDVA after CXL was the preoperative CDVA. Eyes with worse preoperative CDVA were more likely to have an improvement of 2 Snellen lines or more. Specifically, eyes with a preoperative Snellen visual acuity of 20/40 or worse were 5.9 times more likely to improve by 2 lines or more; 43.1% of eyes with a CDVA of 20/40 or worse had an improvement of 2 lines or more compared with only 11.0% of eyes that had a CDVA of better than 20/40. With regard to eyes that lost vision from the procedure, the most salient indicator of an unwanted outcome, there was no independent preoperative indicator. Of the 3 eyes losing 2 lines or more, there were no consistent causes. When analyzed at the more sensitive endpoint of only 1 line loss, there was a suggestion that eyes with a CDVA of better than 20/40 preoperatively had a greater propensity to lose 1 line (15.1%) than eyes with a worse preoperative CDVA (7.8%). However, this difference was not statistically significant; this could be a result of the small number of eyes that lost vision after the procedure. A larger study might identify good vision as a risk factor, as was found in Koller et al.’s study.19

To summarize from the viewpoint of clinical decision-making, from our current knowledge it might be reasonable to conclude that with regard to CDVA, eyes with worse vision initially would expect the greatest chance of actual improvement, all eyes are equally likely to remain stable within 2 lines of CDVA, and eyes with initially good CDVA (better than 20/40) may be somewhat more susceptible to a loss of 1 line.

In our analysis, the only independent predictor of the 1-year postoperative maximum K value was the preoperative maximum K value. Specifically, eyes with a maximum K of 55.0 D or more were 5.4 times more likely to have topographic flattening of 2.0 D or more after CXL than eyes with flatter corneas. However, with regard to eyes in which corneal topography continued to steepen—that is, those in which the crosslinking procedure failed to stabilize the disease—there were no independent predictors of continued topographic steepening even at the more refined level of more than 1.0 D. All eyes were equivalently likely to be stabilized by the CXL procedure. Specifically, in the subgroup with an initial maximum K value of 55.0 D or more, 40 (90%) of 44 eyes had less than 1.0 D of progression 1 year after

<table>
<thead>
<tr>
<th>Preop Maximum K (D) Stratification</th>
<th>Flattening of ≥2.0 D, n (%)</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Eyes with Preop Maximum K</td>
<td>In Eyes with Preop Maximum K Equal to or Steeper Than K in Column 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatter Than K in Column 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.0</td>
<td>1/19 (5)</td>
<td>29/85 (34)</td>
<td>8.4x</td>
</tr>
<tr>
<td>55.0</td>
<td>8/60 (13)</td>
<td>20/44 (45)</td>
<td>5.4x</td>
</tr>
<tr>
<td>60.0</td>
<td>13/81 (16)</td>
<td>15/23 (65)</td>
<td>9.8x</td>
</tr>
<tr>
<td>65.0</td>
<td>19/94 (20)</td>
<td>9/10 (90)</td>
<td>35.5x</td>
</tr>
</tbody>
</table>

CI = confidence interval; K = keratometry; OR = odds ratio

*Relative likelihood that an eye with preoperative maximum K greater than or equal to the preoperative maximum K in the first column will flatten by ≥2.0 D compared with an eye with maximum K flatter than the maximum K stratification.
CXL. Similarly, in the subgroup with an initial maximum K value of less than 55.0 D, 55 (92%) of 60 eyes were stable.

We will now discuss the implications for patient selection. The essential goal of CXL is to stabilize the progression of ectatic corneal disorders, such as keratoconus and ectasia. Indeed, documented disease progression was an entry criterion in our study. With regard to disease stabilization, CXL indeed appears efficacious; 98.1% of eyes showed less than 2.0 D and 91.6% showed less than 1.0 D of topographic progression over the 1-year follow-up. However, in addition to stabilization of the disease process, this study elucidates other potential benefits of CXL. In particular, the CDVA and maximum K values both improved to a clinically significant extent in a subset of eyes. Twenty-eight (26.9%) of 104 eyes had an improvement in CDVA by 2 Snellen lines or more and 28 (26.9%) of 104 eyes had an improvement in maximum K by 2.0 D or more. Such improvements could aid patients in their spectacle use or contact lens tolerance.

Therefore, knowing the characteristics associated with CXL outcomes and in reviewing previous literature regarding the natural progression of keratoconus and ectasia, we may be able to start selecting eyes for CXL based on preoperative measurements (Figure 1). As shown here, the 2 most important predictors of vision and topography improvement after CXL are preoperative CDVA and maximum K, respectively. Because we found no independent predictors of failure of CXL to stabilize disease progression, it is reasonable that all eyes with progressive keratoconus or corneal ectasia should be considered for CXL treatment with the goal of diminishing disease progression. However, the clinician may still want to take the preoperative CDVA into account before suggesting treatment. Although there were no independent predictors of CDVA loss at the 2 Snellen line or 1 Snellen line level, there was a suggestion that eyes with better than 20/40 CDVA preoperatively had a greater propensity to lose 1 line. Thus, eyes with good visual acuity and progressive disease are generally stabilized (and would likely ultimately lose CDVA as the disease continues to progress without treatment) but may have a somewhat greater chance of losing a line of CDVA as a result of the procedure. The ophthalmologist should be aware of this and the patient properly counseled.

Our study did not include eyes with stable keratoconus, which was defined in our protocol as stability over a 2-year period before entry into the clinical trial. However, previous literature suggests that many eyes with ostensibly stable keratoconus are likely to progress slowly over time. Gordon et al.21 found that all keratoconus eyes with visual acuity worse than 20/40 ultimately were more likely to require penetrating keratoplasty. Furthermore, on average, eyes diagnosed with keratoconus can expect to lose 2 letters of high-contrast CDVA and 4 letters of low-contrast CDVA and have 1.6 D of steepening of the flattest K value over 7 to 8 years.22,23 Independent predictors of a loss of 10 letters or more (2 lines) of high- or low-contrast CDVA over 7 years were race other than non-Hispanic white, a steeper first definite apical clearance lens, and a CDVA greater than 35 low-contrast letters and 49 high-contrast letters, respectively.22 In addition, young age, nonwhite racial status, poorer CDVA, and a steeper cornea (flat K) were predictors of 3.0 D or more steepening of the flattest K over an 8-year period. Thus, when taken in light of the published literature on the natural history of keratoconus, our findings may suggest that eyes with worse CDVA, specifically 20/40 or less, and more advanced keratoconus, specifically maximum K of 55.0 D or more, may benefit from CXL despite having “stable” keratoconus. The goal in such cases would not be to diminish disease progression per se but to prevent or postpone keratoplasty by potentially improving spectacle or contact lens tolerance by improving CDVA or diminishing topography irregularity. It is also reasonable for the ophthalmologist to monitor these eyes closely and defer CXL treatment until there is evidence of frank topographic or visual signs of disease progression. Further study is underway to determine the effect of CXL treatment on stable keratoconus and corneal ectasia.

Figure 1. Treatment algorithm for CXL patient selection (CDVA = corrected distance visual acuity; CXL = collagen crosslinking).
For patients with progressive keratoconus and corneal ectasia, our study shows that eyes with worse CDVA and higher K readings, in general, are more likely to have an improvement after CXL. These findings suggest that all eyes with progressive keratoconus and corneal ectasia should be considered for treatment with CXL with the goal of stabilizing the disease progression. Patients and physicians should be aware of the risk for loss of visual acuity, particularly in eyes with a preoperative CDVA better than 20/40.

**WHAT WAS KNOWN**
- Previous CXL studies report that in addition to stabilizing the cornea, there is, on average, improvement in topographic and visual acuity outcomes.

**WHAT THIS PAPER ADDS**
- Eyes with worse preoperative CDVA and higher maximum K values, particularly with a CDVA of 20/40 or worse or a maximum K of 55.0 D or more, were more likely to have improvement after CXL.
- No preoperative characteristics were independently predictive of CXL failure.
- An algorithm is presented to begin to determine patients who are best treated with CXL and those who are poor candidates.

**REFERENCES**
22. Davis LJ, Schechtman KB, Wilson BS, Rosenstiel CE, Riley CH, Libassi DP, Gundel RE, Rosenberg L, Gordon MO, Zadnik K, the


OTHER CITED MATERIAL


Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia

Nneka O. Brooks, MD, Steven Greenstein, MD, Kristen Fry, OD, MS, Peter S. Hersh, MD

PURPOSE: To assess subjective visual function after corneal collagen crosslinking (CXL).

SETTING: Cornea and refractive surgery subspecialty practice.

DESIGN: Prospective randomized controlled clinical trial.

METHODS: Patients completed a subjective questionnaire regarding visual symptoms administered preoperatively and 1 year after CXL. Patients ranked self-reported symptoms of photophobia, difficulty night driving, difficulty reading, diplopia, fluctuations in vision, glare, halo, starburst, dryness, pain, and foreign-body sensation on a scale from 1 to 5. Possible associations of symptoms with changes in corrected distance visual acuity (CDVA) and maximum keratometry were also analyzed.

RESULTS: One hundred seven eyes of 76 patients had CXL for keratoconus (n = 71) or ectasia (n = 36). The mean preoperative to 1-year postoperative changes in night driving (3.2 ± 1.5 [SD] to 2.8 ± 1.5), difficulty reading (3.1 ± 1.5 to 2.9 ± 1.3), diplopia (2.5 ± 1.3 to 2.1 ± 1.2), glare (3.1 ± 1.4 to 2.7 ± 1.2), halo (2.9 ± 1.4 to 2.5 ± 1.3), starbursts (2.6 ± 1.5 to 2.4 ± 1.4), and foreign-body sensation (1.8 ± 1.1 to 1.6 ± 0.9) were statistically significant. There were no associations between the change in any symptom and changes in CDVA. There was a weak association between the change in night driving, pain, and foreign-body sensations and the change in maximum keratometry.

CONCLUSIONS: After CXL, patients noted subjective improvement in visual symptoms, specifically night driving, difficulty reading, diplopia, glare, halo, starbursts, and foreign-body sensation. These subjective outcomes corroborate quantitative clinical improvements seen after CXL.

Financial Disclosure: Dr. Hersh is medical monitor for Avedro, Inc. No author has a financial or proprietary interest in any material or method mentioned.


Keratoconus and corneal ectasia after laser in situ keratomileusis (LASIK) are noninflammatory processes in which the corneal architecture deforms in association with biomechanical weakening. In an effort to mitigate the progression of these ectatic corneal disorders, corneal collagen crosslinking (CXL) was recently introduced. In addition to stabilizing the corneal architecture, results in clinical studies suggest that CXL can have beneficial effects on corneal optics and vision, with few reported complications. In our previous reports of 1-year CXL outcomes, patients had an improvement in corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), maximum and average keratometry (K) values, several corneal topography indices, and corneal and optical higher-order aberrations (HOAs).

Although objective improvements after CXL are well documented in the literature, to date subjective patient findings have yet to be explored. The importance of incorporating the patient’s perspective on the outcomes of medical and surgical interventions is widely recognized. Specifically, questionnaires that examine patient-reported assessments of symptoms and visual function in a standardized way have been shown to capture information not detected by traditional clinical measures. Therefore, in this study we analyzed patient-reported subjective visual function outcomes 1 year after collagen crosslinking.
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. The trial was approved and monitored by an investigational review board, and all patients provided informed consent. All work in this study was compliant with the U.S. Health Insurance Portability and Accountability Act. Two patient cohorts were treated, 1 with progressive keratoconus and 1 with corneal ectasia after LASIK.

The inclusion criteria included age 14 years or older, axial topography consistent with keratoconus or corneal ectasia, an inferior–superior ratio greater than 1.5 on topography mapping, CDVA worse than 20/20, removal of contact lenses for a specified period of time depending on the type of lens, and a diagnosis of progressive keratoconus or LASIK-induced ectasia. Progressive keratoconus 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 the manifest refraction spherical equivalent. Exclusion criteria included a history of corneal surgery, corneal pachymetry less than 300 μm, a history of chemical injury or delayed epithelial healing, and pregnancy or lactation during the course of the study.

Crosslinking Treatment

Collagen crosslinking was performed according to the methodology described by Wollensak et al. Topical anesthesia was administered and the corneal epithelium removed by mechanical debridement over the central 9.0 mm. 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 and if the cornea was less than 400 μm, hypotonic riboflavin (0.1% in sterile water; Medio Cross hypotonic, Peschke Meditrade GmbH) was administered, 1 drop every 10 seconds for 2 minute sessions, after which ultrasonic pachymetry was performed to confirm that the stroma had swollen to 400 μm or more. This was repeated until adequate corneal thickness was obtained.

The cornea was exposed to ultraviolet-A (UVA) 365 nm light (UV-X system, IROC AG) for 30 minutes at an irradiance of 3.0 mW/cm². During UVA exposure, 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. In the case of delayed epithelialization, the contact lens was retained or the ocular surface managed at the discretion of the surgeon. Antibiotic drops were continued for 1 week, and corticosteroid drops were continued for 2 weeks.

Patient Questionnaire

Patients were asked to fill out a questionnaire that scored various subjective vision function parameters (Figure 1). In this study, subjective outcomes of photophobia, difficulty in night driving, difficulty reading, diplopia, fluctuations in vision, glare, halo, starburst, dryness, pain, and foreign-body sensation were analyzed. The parameters were scored on a scale of 1 (none) through 5 (severe). The questionnaire were filled out preoperatively and 1 year postoperatively.

Statistical Analysis

The data are presented as the mean subjective visual score for each of the 11 parameters queried. Analysis was performed using PASW software (version 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 change in scoring for all 11 parameters from baseline. An

Figure 1. Sample patient questionnaire.
independent t test was used to compare scores in the keratoconus subgroup and the ectasia subgroup. Pearson correlation coefficients were used to analyze possible associations between each of the 11 criteria and the objective parameters of CDVA and maximum K value. A $P$ value less than 0.05 was used to determine statistical significance. Visual acuity measurements were calculated as logMAR and converted to Snellen visual acuity for presentation.

RESULTS

One hundred seven eyes of 76 patients with CXL completed the questionnaire and were followed for 1 year. Of the total cohort, 71 eyes were in the keratoconus group and 36 eyes were in the post-LASIK ectasia group.

All 11 parameters analyzed in the study showed improvement after 12 months, with 7 reaching statistical significance. Figure 2 and Table 1 show the results of all preoperative and postoperative symptoms analyzed. Parameters found to be statistically significant in the entire study group were night driving ($P < .01$), difficulty reading ($P = .01$), diplopia ($P < .01$), glare ($P < .01$), halo ($P < .01$), starbursts ($P = .02$), and foreign-body sensation ($P = .01$) (Figure 2). Parameters that showed slight, but not statistically significant improvement were photophobia ($P = .18$), visual fluctuation ($P = .07$), dryness ($P = .43$), and pain ($P = .90$).

Subgroup Analysis

Table 2 and Table 3 show the results in the keratoconus subgroup and ectasia subgroup, respectively. The keratoconus subgroup had statistically significant improvements in reading ($P = .02$), diplopia ($P < .01$), halo ($P = .02$), and foreign-body sensation ($P = .02$). The ectasia subgroup had statistically significant improvements in driving ($P < .01$), glare ($P < .01$), and starburst ($P = .02$).

Relationship to Objective Outcomes

In analyzing the relationship between objective results and the 11 subjective parameters, no

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**Table 1.** Patient self-assessed mean subjective ratings preoperatively and 1 year after CXL in all patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preop</th>
<th>1 Y Postop</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photophobia</td>
<td>2.66</td>
<td>2.50</td>
<td>.18</td>
</tr>
<tr>
<td>Driving</td>
<td>3.24</td>
<td>2.81</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Reading</td>
<td>3.14</td>
<td>2.85</td>
<td>.01*</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2.53</td>
<td>2.14</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Fluctuation in vision</td>
<td>2.63</td>
<td>2.43</td>
<td>.07</td>
</tr>
<tr>
<td>Glare</td>
<td>3.05</td>
<td>2.74</td>
<td>.01*</td>
</tr>
<tr>
<td>Halo</td>
<td>2.88</td>
<td>2.54</td>
<td>.01*</td>
</tr>
<tr>
<td>Starburst</td>
<td>2.64</td>
<td>2.41</td>
<td>.02*</td>
</tr>
<tr>
<td>Dryness</td>
<td>2.10</td>
<td>2.03</td>
<td>.43</td>
</tr>
<tr>
<td>Pain</td>
<td>1.56</td>
<td>1.55</td>
<td>.90</td>
</tr>
<tr>
<td>Foreign body</td>
<td>1.83</td>
<td>1.59</td>
<td>.01*</td>
</tr>
</tbody>
</table>

*Statistically significant ($P < .05$)

---

**Table 2.** Patient self-assessed mean subjective ratings preoperatively and 1 year after CXL in the keratoconus subgroup.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preop</th>
<th>1 Y Postop</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photophobia</td>
<td>2.70</td>
<td>2.55</td>
<td>.31</td>
</tr>
<tr>
<td>Driving</td>
<td>2.93</td>
<td>2.61</td>
<td>.06</td>
</tr>
<tr>
<td>Reading</td>
<td>2.87</td>
<td>2.54</td>
<td>.02*</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2.31</td>
<td>1.92</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Fluctuation in vision</td>
<td>2.37</td>
<td>2.25</td>
<td>.39</td>
</tr>
<tr>
<td>Glare</td>
<td>2.87</td>
<td>2.66</td>
<td>.16</td>
</tr>
<tr>
<td>Halo</td>
<td>2.70</td>
<td>2.35</td>
<td>.02*</td>
</tr>
<tr>
<td>Starburst</td>
<td>2.35</td>
<td>2.20</td>
<td>.22</td>
</tr>
<tr>
<td>Dryness</td>
<td>1.96</td>
<td>1.93</td>
<td>.81</td>
</tr>
<tr>
<td>Pain</td>
<td>1.51</td>
<td>1.52</td>
<td>.88</td>
</tr>
<tr>
<td>Foreign body</td>
<td>1.85</td>
<td>1.61</td>
<td>.05*</td>
</tr>
</tbody>
</table>

*Statistically significant ($P < .05$)

---

**Table 3.** Patient self-assessed mean subjective ratings preoperatively and at 1 year after CXL in the ectasia subgroup.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preop</th>
<th>1 Y Postop</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photophobia</td>
<td>2.58</td>
<td>2.42</td>
<td>.37</td>
</tr>
<tr>
<td>Driving</td>
<td>3.86</td>
<td>3.22</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Reading</td>
<td>3.67</td>
<td>3.47</td>
<td>.27</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2.97</td>
<td>2.58</td>
<td>.08</td>
</tr>
<tr>
<td>Fluctuation in vision</td>
<td>3.14</td>
<td>2.78</td>
<td>.07</td>
</tr>
<tr>
<td>Glare</td>
<td>3.39</td>
<td>2.89</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Halo</td>
<td>3.17</td>
<td>2.92</td>
<td>.17</td>
</tr>
<tr>
<td>Starburst</td>
<td>3.19</td>
<td>2.83</td>
<td>.02*</td>
</tr>
<tr>
<td>Dryness</td>
<td>2.39</td>
<td>2.22</td>
<td>.32</td>
</tr>
<tr>
<td>Pain</td>
<td>1.67</td>
<td>1.61</td>
<td>.70</td>
</tr>
<tr>
<td>Foreign body</td>
<td>1.81</td>
<td>1.56</td>
<td>.10</td>
</tr>
</tbody>
</table>

*Statistically significant ($P < .05$)
parameters analyzed had a correlation with the CDVA. Night driving ($P = .01$), pain ($P = .04$), and foreign-body sensation ($P < .001$) had weak but significant correlations to maximum K. The Pearson correlation was 0.252, 0.204, and 0.345, respectively.

**DISCUSSION**

Collagen crosslinking, although developed primarily to mitigate progression of ectatic corneal processes, has also been found to improve visual acuity and corneal topography characteristics in some patients.\(^3\)–\(^7\),\(^10\)–\(^12\) These effects are likely secondary to changes in the cornea’s optical architecture, a result of the direct cross-linking effects and the consequent wound-healing processes.\(^14\)–\(^16\)

In previous reports, we presented extensive analyses of the objective clinical outcomes from the clinical trial presented in this paper. A review of these results should help to place the subjective patient outcomes reported here in clearer clinical perspective.

At 1 year, the mean UDVA improved significantly, from $0.84 \log MAR \pm 0.34$ (SD) (20/137) to $0.77 \pm 0.37 \log MAR (20/117)$ ($P = .04$), and the mean CDVA improved from $0.35 \pm 0.24 \log MAR (20/45)$ to $0.23 \pm 0.21 \log MAR (20/34)$ ($P < .001$).\(^10\) When stratified by individual eyes, the UDVA improved by 2 or more Snellen lines in 25.4% of eyes and 8.5% of eyes lost 2 or more Snellen lines. The CDVA improved by 2 or more Snellen lines in 21.1% of eyes, and 1 patient (1.4%) lost 2 Snellen lines.

The mean maximum keratometric value derived from corneal topography (Pentacam, Oculus, Inc.) decreased from baseline by 1.7 ± 3.9 D ($P < .001$) 1 year after CXL.\(^10\),\(^11\) The mean maximum K value decreased by 2.0 D or more in 31.0% of patients and increased by 2.0 D or more in 4.2%. In addition, analyses of topographic indices found significant improvements in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature compared with baseline (all $P < .001$).

We also analyzed changes in corneal (Pentacam) and total ocular aberrations (LadarWave, Alcon Laboratories, Inc.) after CXL.\(^12\) The mean preoperative total anterior corneal HOAs, total coma, 3rd-order coma, and vertical coma were $4.68 \pm 2.33 \mu m$, $4.40 \pm 2.32 \mu m$, $4.36 \pm 2.30 \mu m$, and $4.04 \pm 2.27 \mu m$, respectively. At 1 year, these anterior corneal HOAs significantly decreased to $4.27 \pm 2.25 \mu m$, $4.01 \pm 2.29 \mu m$, $3.96 \pm 2.27 \mu m$, and $3.66 \pm 2.22 \mu m$, respectively (all $P < .001$). There were no significant changes in posterior corneal HOAs. The mean preoperative total ocular HOAs, total coma, 3rd-order coma, and trefoil were $2.80 \pm 1.0 \mu m$, $2.60 \pm 1.03 \mu m$, $2.57 \pm 1.03 \mu m$, and $0.98 \pm 0.46 \mu m$, respectively. At 1 year, these ocular HOAs significantly decreased to $2.59 \pm 1.06 \mu m$, $2.42 \pm 1.07 \mu m$, $2.39 \pm 1.07 \mu m$, and $0.88 \pm 0.49 \mu m$, respectively (all $P = .01$).

Collagen crosslinking–associated corneal haze was measured both by Scheimpflug image densitometry and slitlamp biomicroscopy.\(^14\) Haze was greatest at 1 month, plateaued at 3 months, and significantly decreased between 3 months and 12 months. Specifically, the mean preoperative corneal densitometry was $14.9 \pm 1.93$ (Pentacam Scheimpflug densitometry units). Densitometry peaked at 1 month (mean $23.4 \pm 4.40$; $P < .001$), with little change at 3 months (mean $22.4 \pm 4.79$; $P = .06$), and decreased between 3 months and 6 months ($19.4 \pm 4.48$; $P < .001$) and between 6 months and 12 months. By 12 months, densitometry continued to improve but had not completely returned to baseline (mean $17.0 \pm 3.82$; $P < .001$). The postoperative course of slitlamp haze was similar to objective densitometry measurements.

Corneal thickness was measured before and after CXL using Scheimpflug imaging.\(^14\) The mean preoperative thinnest pachymetry was $440.7 \pm 52.9 \mu m$. During treatment and after debridement of the epithelium, 32% of eyes required stromal swelling with hypotonic riboflavin before UVA administration. Postoperatively, we found that the cornea initially thinned and then recovered toward baseline. After CXL, the cornea thinned at 1 month (mean change = $-23.8 \pm 28.7 \mu m$, $P < .001$) and from 1 to 3 months (mean change = $-7.2 \pm 20.1 \mu m$, $P = .002$), followed by a recovery of the corneal thickness between 3 months and 6 months (mean change = $+20.5 \pm 20.4 \mu m$, $P < .001$). At 1 year, corneal thickness remained slightly decreased from baseline to 12 months (mean change $-6.6 \pm 22.4 \mu m$, $P = .01$).

These analyses give a broad overview of the clinical course after crosslinking. In an effort to expand this objective assessment of the efficacy of the CXL procedure and elucidate the expected clinical response, the analysis of self-reported patient optical symptoms and visual function perception is instructive. In this study, patients generally noted subjective improvement in visual symptoms. Specifically, night driving, difficulty reading, diplopia, glare, halo, starbursts, and foreign-body sensation were improved 1 year after CXL. This corroborates the objective findings of improved quantitative visual, optical, and topographic metrics after CXL. It also speaks to patient satisfaction with the procedure.

Curiously, none of the measured parameters showed a correlation to the CDVA. Despite significant improvements in vision, topography, and wavefront measurements after CXL, there remains high variability in objective measurements in the keratoconus and ectasia patient cohorts. Subjective improvement, although not
specifically statistically correlated to objective improvement, may lend further credence to the efficacy of CXL in improving visual function in these corneal disease processes.

REFERENCES


OTHER CITED MATERIAL

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

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

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 \( P < 0.001 \)). 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.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned. Additional disclosure is found in the footnotes.


Corneal collagen crosslinking (CXL) is a promising new treatment to strengthen and stabilize the cornea in cases of keratoconus and ectasia after laser in situ keratomileusis (LASIK). The increase in biomechanical strength 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 and in other studies, 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. 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.
As stated in the previous study, 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 pre-treatment pachymetry measurement between 300 μm and 400 μm received hypotonic riboflavin for stromal swelling12), 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. 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/cm². 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 ratio13–15); 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...
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 $-10.5 \pm 18.2$; $P < .001$). Initially, there was a significant increase (mean change $11.1 \pm 13.7$) in the index between baseline and 1 month ($P < .001$) followed by a significant decrease between 1 month and 3 months (mean change $-11.3 \pm 16.7$; $P < .001$) and between 3 months and 6 months (mean change $-7.58 \pm 17.7$; $P = .001$). Although the index decreased between 6 months and 12 months (mean change $-2.72 \pm 14.2$), 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 $-0.11 \pm 0.23$; $P < .001$). Initially, there was a significant increase in the index between baseline and 1 month (mean change $0.11 \pm 0.21$; $P < .001$) followed by a significant decrease between 1 month and 3 months (mean change $-0.11 \pm 0.23$; $P < .001$) and between 3 months and 6 months (mean change $-0.08 \pm 0.21$; $P = .002$). There was no significant change in the index of vertical asymmetry between 6 months and 12 months (mean change $-0.04 \pm 0.21$; $P = .14$) (Figure 1, A).

Keratoconus Index
At 1 year, the keratoconus index was significantly decreased over baseline (mean change $-0.04 \pm 0.08$; $P < .001$). There was a significant increase in the index between baseline and 1 month (mean change $0.03 \pm 0.08$; $P = .004$) followed by a significant decrease between 1 month and 3 months (mean change $-0.03 \pm 0.06$; $P < .001$). There was no significant change in the index between 3 months and 6 months (mean change $0.03 \pm 0.10$; $P = .008$) or between 6 months and 12 months (mean change $-0.003 \pm 0.07$; $P = .75$) (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 $0.16 \pm 0.28$; $P < .001$). Initially, there was a significant decrease in the radius of curvature between baseline and 1 month (mean change $-0.14 \pm 0.26$; $P < .001$) followed by a significant increase between 1 month and 3 months (mean change $0.18 \pm 0.24$; $P < .001$) and between 3 months and 6 months (mean change $0.08 \pm 0.23$; $P = .007$). There was no significant change between 6 months and 12 months ($0.04 \pm 0.23$; $P = .15$) (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, $P = .68$;
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 \( P = .2 \)).

**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 (\( P = .25 \), \( P = .40 \), and \( P = .62 \), 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;
P = .04) and CDVA (mean change $-0.12 \pm 0.19$ log-MAR; $P < .001$) 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 $-10.5 \pm 18.2$; $P < .001$) 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 curvature.

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

<table>
<thead>
<tr>
<th>Subgroup/Index</th>
<th>Mean ± SD</th>
<th>Baseline</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratoconus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ISV</td>
<td></td>
<td>122.2 ± 48.2*</td>
<td>133.3 ± 49.4**</td>
<td>121.9 ± 45.7***</td>
<td>114.3 ± 44.0****</td>
<td>110.3 ± 44.9*****</td>
</tr>
<tr>
<td>IVA</td>
<td></td>
<td>1.29 ± 0.47*</td>
<td>1.39 ± 0.48**</td>
<td>1.29 ± 0.46***</td>
<td>1.22 ± 0.45****</td>
<td>1.17 ± 0.51*****</td>
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<tr>
<td>KI</td>
<td></td>
<td>1.37 ± 0.20*</td>
<td>1.39 ± 0.20**</td>
<td>1.36 ± 0.19***</td>
<td>1.33 ± 0.17****</td>
<td>1.33 ± 0.18*****</td>
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<tr>
<td>CKI</td>
<td></td>
<td>1.05 ± 0.16</td>
<td>1.08 ± 0.07</td>
<td>1.07 ± 0.07*</td>
<td>1.06 ± 0.07*</td>
<td>1.05 ± 0.06</td>
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<tr>
<td>IHA</td>
<td></td>
<td>35.2 ± 23.5</td>
<td>41.9 ± 33.6</td>
<td>39.2 ± 28.6</td>
<td>38.9 ± 28.6</td>
<td>31.0 ± 26.7</td>
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<tr>
<td>IHD</td>
<td></td>
<td>0.12 ± 0.06</td>
<td>0.13 ± 0.07**</td>
<td>0.12 ± 0.07*</td>
<td>0.11 ± 0.06</td>
<td>0.12 ± 0.13</td>
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<tr>
<td>Rmin</td>
<td></td>
<td>5.71 ± 0.82*</td>
<td>5.59 ± 0.82**</td>
<td>5.75 ± 0.84*</td>
<td>5.82 ± 0.78***</td>
<td>5.89 ± 0.75****</td>
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<tr>
<td>Ectasia</td>
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<tr>
<td>ISV</td>
<td></td>
<td>127.3 ± 73.2</td>
<td>138.6 ± 69.4**</td>
<td>127.3 ± 76.6***</td>
<td>119.9 ± 71.9*</td>
<td>119.9 ± 77.7*</td>
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<tr>
<td>IVA</td>
<td></td>
<td>1.63 ± 1.00</td>
<td>1.78 ± 0.95**</td>
<td>1.64 ± 1.09*</td>
<td>1.54 ± 1.01*</td>
<td>1.53 ± 1.07*</td>
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<tr>
<td>KI</td>
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<td>1.37 ± 0.31</td>
<td>1.40 ± 0.34</td>
<td>1.37 ± 0.35*</td>
<td>1.32 ± 0.29***</td>
<td>1.33 ± 0.33*</td>
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<tr>
<td>CKI</td>
<td></td>
<td>1.01 ± 0.06</td>
<td>1.03 ± 0.06**</td>
<td>1.01 ± 0.05**</td>
<td>0.99 ± 0.04***</td>
<td>1.0 ± 0.05</td>
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<tr>
<td>IHA</td>
<td></td>
<td>21.8 ± 16.7</td>
<td>28.0 ± 23.8</td>
<td>22.9 ± 20.3</td>
<td>24.7 ± 21.0</td>
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<tr>
<td>IHD</td>
<td></td>
<td>0.11 ± 0.09</td>
<td>0.13 ± 0.08**</td>
<td>0.12 ± 0.10</td>
<td>0.09 ± 0.07***</td>
<td>0.10 ± 0.07</td>
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<tr>
<td>Rmin</td>
<td></td>
<td>6.26 ± 0.75</td>
<td>6.10 ± 0.74**</td>
<td>6.31 ± 0.80*</td>
<td>6.40 ± 0.70*</td>
<td>6.37 ± 0.70*</td>
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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; Rmin = 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 and LASIK-induced ectasia. In past work in this prospective randomized controlled clinical trial, we looked at general clinical outcomes, CXL-associated corneal haze, and corneal thickness changes after CXL. 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 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. 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, including our previous analysis of this patient cohort. 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

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<th>Table 3. (Cont.)</th>
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</table>
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

Table 4. Visual acuity results (71 eyes).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LogMAR UDVA (Snellen)</th>
<th>LogMAR CDVA (Snellen)</th>
<th>Pearson Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Months</td>
<td>Baseline</td>
</tr>
<tr>
<td>Acuity</td>
<td>0.84 ± 0.34 (20/138)</td>
<td>0.77 ± 0.37* (20/118)</td>
<td>0.35 ± 0.24 (20/45)</td>
</tr>
<tr>
<td>ISV</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IVA</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>KI</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>CKI</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IHA</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IHD</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rmin</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

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; Rmin = minimum radius of curvature; UDVA = uncorrected distance visual acuity

*Statistically significant change compared with baseline measurements
†Statistically significant Pearson correlation coefficient

![Figure 3. Left: Preoperative sagittal curvature map. Right: Twelve-month postoperative sagittal curvature map showing improvement in the keratoconus index.](image-url)
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 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 and CXL-associated corneal haze 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. 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.

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, 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. 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, 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.

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.

REFERENCES

2. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced...

OTHER CITED MATERIAL

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Cornea and Laser Eye Institute-Hersh Vision Group, CLEI Center for Keratoconus, Teaneck, New Jersey, USA
Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia

Steven A. Greenstein, MD, Kristen L. Fry, OD, MS, Matthew J. Hersh, Peter S. Hersh, MD

PURPOSE: To determine changes in higher-order aberrations (HOAs) after corneal collagen crosslinking (CXL).

SETTING: Cornea and refractive surgery practice.

DESIGN: Prospective randomized controlled clinical trial.

METHODS: Corneal and ocular HOAs were measured and analyzed using the Pentacam device and Ladarwave aberrometer, respectively, at baseline and 12 months after CXL.

RESULTS: Ninety-six eyes (64 keratoconus, 32 ectasia) of 73 patients had CXL. A fellow-eye control group comprised 42 eyes. The mean preoperative total anterior corneal HOAs, total coma, 3rd-order coma, and vertical coma were 4.68 mG2.33 (SD), 4.40 mG2.32 mG, 4.36 mG2.30 mG, and 4.04 mG2.27 mG, respectively. At 1 year, the mean values decreased significantly to 4.27 mG2.25 mG, 4.01 mG2.29 mG, 3.96 mG2.27 mG, and 3.66 mG2.22 mG, respectively (all P<.001). There were no significant changes in posterior corneal HOAs. The mean preoperative total ocular HOAs, total coma, 3rd-order coma, trefoil, and spherical aberration were 2.80 mG1.0 mG, 2.60 mG1.03 mG, 2.57 mG1.03 mG, 0.98 mG0.46 mG, and 0.90 mG0.42 mG, respectively. At 1 year, the mean values decreased significantly to 2.59 mG1.06 mG, 2.42 mG1.07 mG, 2.39 mG1.07 mG, 0.88 mG0.49 mG, and 0.83 mG0.38 mG, respectively (all P<.01). After CXL, HOAs were significantly improved compared with the control group. Changes in HOAs were not statistically associated with an improvement in visual acuity or most subjective visual symptoms, however.

CONCLUSION: Corneal and ocular HOAs decreased after CXL, suggesting an improvement in corneal shape.

Financial Disclosure: Dr. Hersh is medical monitor for Avedro, Inc. No author has a financial or proprietary interest in any material or method mentioned.


Keratoconus and corneal ectasia after laser in situ keratomileusis (LASIK) are noninflammatory processes in which the corneal architecture deforms in association with thinning.1 The progressive distortion of the cornea results in irregular astigmatism, progressive myopia, and increased higher-order aberrations (HOAs),2-6 with consequent loss of visual function.

Recently, corneal collagen crosslinking (CXL) was introduced as a new therapy to mitigate the progression of these ectatic corneal disorders.7,8 Findings in recent studies suggest that CXL can also have beneficial visual and optical effects,9-14 with few reported complications.15-17 In our previous reports of 1-year CXL outcomes,11,18 patients had an improvement in corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), maximum and average keratometry (K) values, and several quantitative indices of corneal topography.

In this study, to further assess optical quality after CXL, we evaluated the effect of CXL on HOAs by analyzing changes in anterior corneal HOAs, posterior corneal HOAs, and total ocular HOAs 1 year after treatment. In addition, changes in HOAs were correlated with changes in visual acuity (UDVA and CDVA) and patient-reported visual symptoms.

PATIENTS AND METHODS

Patients with progressive keratoconus and ectasia after LASIK, were enrolled as part of a multicenter prospective randomized controlled clinical trial.3,4 This study was approved and monitored by an investigational review board and complied with the U.S. Health Insurance Portability and Accountability Act. Informed consent was obtained from all patients.

The inclusion criteria included 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 value, 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 (except previous intrastromal corneal ring segment removal), chemical injury, delayed epithelial healing, and a corneal pachymetry less than 300 μm.

**Treatment Group**

Collagen crosslinking was performed according to the methodology described by Wollensak et al.1 Topical anesthesia was administered, and the corneal epithelium was removed by mechanical debridement over the central 9.0 mm. 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. Ultrasound (US) pachymetry was performed and if the cornea was less than 400 μm, hypotonic riboflavin (0.1% in sterile water, Medio-Cross hypotonic) 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 more than 400 μm. This was repeated until adequate corneal thickness was obtained.

The cornea was exposed to ultraviolet-A (UVA) 365 nm light (UV-X system, IROC AG) for 30 minutes at an irradiance of 3.0 mW/cm². During UV exposure, riboflavin drops were continued every 2 minutes.

Postoperatively, antibiotic and corticosteroid drops were administered and a therapeutic soft contact lens (Accuvue 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 Group**

In this study, a fellow-eye control group was analyzed. This group comprised the fellow eyes of patients who did not have CXL bilaterally and included eyes with frank keratoconus or ectasia that did not have CXL, eyes with evidence of disease that did not meet the study’s inclusion criteria, and eyes with no evidence of disease. Anterior and posterior corneal HOAs were measured and analyzed at baseline and 12 months. Unlike the treated eyes, fellow eyes were not dilated at the 12-month follow-up examination. Therefore, ocular HOA data were not available for the control group.

**Higher-Order Aberrations Measurements**

Anterior and posterior corneal aberrations over the central 6.5 mm were measured preoperatively and at 12 months postoperatively using the Pentacam device (Oculus Inc.). The device extrapolates anterior corneal HOA and posterior corneal HOA Zernike coefficients from corneal elevation data obtained by Scheimpflug imagery.

Ocular HOAs were measured through a 6.5 mm pupil using a Ladarwave wavefront aberrometer (Alcon Laboratories, Inc.). This Shack-Hartmann aberrometer measures total ocular HOAs. Measurements were performed after the eyes were dilated preoperatively and 12 months postoperatively. If ocular HOAs could not be measured after multiple attempts (usually on the basis of a markedly distorted cornea), the patient was removed from the ocular HOA analysis.

For corneal and ocular HOAs, the changes in total HOAs (3rd to 6th order), total coma (3rd and 5th order), 3rd-order coma, vertical coma, horizontal coma, spherical aberration (4th and 6th), and trefoil aberrations were analyzed.

**Visual Acuity and Symptoms**

The UDVA and CDVA were measured preoperatively and 1 year postoperatively. High-contrast visual acuity measurements were obtained under controlled lighting conditions using a modified Lighthouse Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity test (2nd edition) with Sloan letters. Patients were tested 4 m from the visual acuity chart. If patients could not read any letters at 4 m, they were tested at 2 m.

To further ascertain changes in visual function that occur after CXL, patients completed a subjective questionnaire on their visual symptoms. The questionnaire was administered preoperatively and at 1 year. Patients ranked symptoms on a scale from 1 to 5 (1 = none; 2 = mild; 3 = moderate; 4 = marked; 5 = severe). In this study, the visual symptoms analyzed included difficulty driving at night, glare, halos, and starbursts (Figure 1).

**Statistical Analysis**

Statistical analysis was performed using PASW software (version 18, SPSS, Inc.). The change in the root-mean-square (RMS) wavefront error was analyzed in 3 groups: the entire cohort and subgroups stratified to a diagnosis of keratoconus or ectasia. A paired 2-tailed Student t test was used to analyze the postoperative changes compared with baseline values. An independent t test was used to compare measurement data 12 months postoperatively between the keratoconus subgroup and ectasia subgroup and between the treatment group and the control group.

To determine whether changes in HOAs were related to visual acuity outcomes, the relationship between the change in these aberrations between baseline and 12 months and the 1-year changes in CDVA and the UDVA were analyzed. Similarly, to determine whether changes in HOAs were related to visual symptoms, the relationship between the change...
in these aberrations between baseline and 12 months and the 1-year changes in reported visual symptoms were also analyzed using Pearson correlation coefficients. A $P$ value less than 0.05 was used to determine statistical significance.

**RESULTS**

Ninety-six eyes (64 in keratoconus subgroup; 32 in ectasia subgroup) of 73 patients had CXL and were followed for 1 year. Anterior corneal HOAs and posterior corneal HOAs were measured in all 96 eyes. Ocular HOAs were measured in 48 eyes (31 keratoconus, 17 ectasia). The fellow-eye control group comprised 42 eyes (26 keratoconus, 16 ectasia).

**Anterior Corneal Aberrations**

The mean preoperative and 1-year postoperative anterior corneal HOAs are shown in Table 1 and Figure 2, top. The total anterior corneal HOAs improved by more than 1.0 μm in 14 eyes (9 keratoconus, 5 ectasia) and by 0.0 to 1.0 μm in 57 eyes (40 keratoconus, 17 ectasia). The total anterior corneal HOAs worsened by 0.0 to 1.0 μm in 24 eyes (15 keratoconus,
ectasia) and by more than 1.0 μm in 1 eye (with ectasia) (Figure 2, bottom).

The mean changes in total HOAs, total coma (combined 3rd and 5th order), 3rd-order coma, and vertical coma were statistically significant, but the changes in horizontal coma, trefoil, and spherical aberration were not.

**Posterior Corneal Aberrations**

The mean preoperative and 1-year postoperative posterior corneal HOAs are shown in Table 1 and Figure 3. All but one decreased, but no change was statistically significant.

**Total Ocular Aberrations**

The mean preoperative and 1-year postoperative ocular HOAs are shown in Table 1 and Figure 4, top. The total ocular HOAs improved by more than 1.0 μm in 5 patients (all keratoconus) and by 0.0 to 1.0 μm in 28 patients (18 keratoconus, 10 ectasia). The total ocular HOAs worsened by 0.0 to 1.0 μm in 15 patients (8 keratoconus, 7 ectasia) and by more than 1.0 μm in no patient (Figure 4, bottom).

**Table 1.** Anterior and posterior corneal HOAs in the treatment group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total HOAs</th>
<th>Total Coma</th>
<th>3rd-Order Coma</th>
<th>Vertical Coma</th>
<th>Horizontal Coma</th>
<th>Trefoil</th>
<th>Spherical Aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior corneal HOAs (n = 96)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>4.68 ± 2.33</td>
<td>4.40 ± 2.32</td>
<td>4.36 ± 2.30</td>
<td>4.04 ± 2.27</td>
<td>1.26 ± 0.99</td>
<td>0.37 ± 0.36</td>
<td>1.40 ± 0.76</td>
</tr>
<tr>
<td>1 year postop</td>
<td>4.27 ± 2.25</td>
<td>4.01 ± 2.29</td>
<td>3.96 ± 2.22</td>
<td>3.66 ± 2.22</td>
<td>1.14 ± 0.95</td>
<td>0.42 ± 0.41</td>
<td>1.29 ± 0.60</td>
</tr>
<tr>
<td><strong>Posterior corneal HOAs (n = 96)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>8.87 ± 5.05</td>
<td>8.15 ± 4.76</td>
<td>7.98 ± 4.67</td>
<td>7.24 ± 4.37</td>
<td>2.60 ± 2.37</td>
<td>1.00 ± 0.75</td>
<td>3.19 ± 2.24</td>
</tr>
<tr>
<td>1 year postop</td>
<td>8.70 ± 4.68</td>
<td>8.06 ± 4.52</td>
<td>7.92 ± 4.45</td>
<td>7.23 ± 4.20</td>
<td>2.54 ± 2.12</td>
<td>1.02 ± 0.82</td>
<td>2.99 ± 1.77</td>
</tr>
<tr>
<td><strong>Ocular HOAs (N = 48)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>2.80 ± 1.00</td>
<td>2.60 ± 1.03</td>
<td>2.57 ± 1.03</td>
<td>2.17 ± 2.23</td>
<td>0.57 ± 0.94</td>
<td>0.98 ± 0.46</td>
<td>0.90 ± 0.42</td>
</tr>
<tr>
<td>1 year postop</td>
<td>2.59 ± 1.06</td>
<td>2.42 ± 1.07</td>
<td>2.39 ± 1.07</td>
<td>2.05 ± 2.11</td>
<td>0.56 ± 0.98</td>
<td>0.88 ± 0.49</td>
<td>0.83 ± 0.38</td>
</tr>
</tbody>
</table>

HOAs = higher-order aberrations
*Combined 3rd and 5th orders
†Statistically significant change

Figure 2. A: Anterior corneal HOAs (RMS wavefront error) preoperatively and at 1 year after CXL. Error bars represent 2 standard deviations from the mean. Asterisks indicate a significant change compared with preoperative measurements (P < .05). B: Individual changes in anterior corneal HOA wavefront error between baseline and 1 year postoperatively (n = 96 eyes) (HOA = higher-order aberration; RMS = root mean square).

Figure 3. Posterior corneal HOAs (RMS wavefront error) preoperatively and at 1 year. Error bars represent 2 standard deviations from the mean () (HOA = higher-order aberration; RMS = root mean square).
The mean changes in total HOAs, total coma, 3rd-order coma, trefoil, and spherical aberration were statistically significant, but the changes in vertical coma and horizontal coma were not.

Keratoconus Subgroup Versus Ectasia Subgroup

Table 2 shows the individual anterior corneal, posterior corneal, and ocular HOA data in the keratoconus subgroup and the ectasia subgroup. In general, there were larger mean changes in anterior corneal HOAs and ocular HOAs in the keratoconus subgroup than in the ectasia subgroup (Figure 5). However, there was no statistically significant difference in the CXL-mediated changes in HOAs between the keratoconus subgroup and the ectasia subgroup.

Clinical Correlation with Visual Acuity and Subjective Visual Function Symptoms

Analysis of all 96 eyes in the study showed significant improvement in logMAR UDVA and logMAR CDVA at 1 year (mean change $-0.09 \pm 0.25$ lines and $-0.10 \pm 0.18$ lines, respectively; both $P=.001$). Similarly, there was a significant improvement in the mean UDVA and CDVA in the 48 eyes included in the analysis of ocular HOAs (mean change $-0.13 \pm 0.22$ lines and $-0.12 \pm 0.19$ lines, respectively; both $P<.001$). However, neither the improvement in UDVA nor the improvement in CDVA was significantly correlated with the improvement in ocular HOAs or anterior corneal HOAs after CXL (Table 3).

To further elucidate possible associations of post-CXL HOA changes with UDVA and CDVA, eyes were stratified to 2 groups; that is, those that had an improvement in HOAs and those in which HOAs worsened after CXL. Table 4 shows the preoperative and postoperative UDVA and CDVA measurements in these 2 groups. There were no significant between-group differences in anterior corneal HOAs (UDVA: $P=.86$; CDVA: $P=.15$) or ocular HOAs (UDVA: $P=.62$; CDVA: $P=.13$).

On the subjective symptom questionnaire, the mean preoperative rating (96 eyes) was 3.1 $\pm$ 1.3 for difficulty driving at night, 3.1 $\pm$ 1.2 for the presence of glare, 2.9 $\pm$ 1.4 for the presence of halos, and 2.6 $\pm$ 1.4 for the presence of starbursts (Figure 6). At 1 year, there was a significant decrease in reported glare (2.8 $\pm$ 1.2; $P=.004$). There was a mean decrease in reported difficulty with night driving (2.9 $\pm$ 1.3), the presence of halos (2.7 $\pm$ 1.3), and the presence of starbursts (2.5 $\pm$ 1.4); however, these changes failed to reach statistical significance ($P=.8$, $P=.07$, and $P=.6$, respectively). In the 48 eyes included in the ocular HOA analysis, the mean preoperative rating was 3.1 $\pm$ 1.4 for difficulty driving at night, 2.8 $\pm$ 1.3 for the presence of glare, 2.7 $\pm$ 1.4 for the presence of halos, and 2.3 $\pm$ 1.4 for the presence of starbursts. At 1 year, there was a mean decrease in reported difficulty with night driving (3.1 $\pm$ 1.4), the presence of glare (2.6 $\pm$ 1.2), the presence of halos (2.6 $\pm$ 1.3), and the presence of starbursts (2.5 $\pm$ 1.4); however, these changes failed to reach statistical significance ($P=.8$, $P=.03$, $P=.6$, and $P=.2$, respectively).

As with the visual acuity analysis, there was no correlation between an improvement in any HOA and an improvement in subjective visual function symptoms of night driving, glare, and halos after CXL (Table 5). However, there was a statistically significant correlation between the change in total ocular HOAs and the change in reported starbursts 1 year after CXL ($r = 0.5$, $P<.001$).

Control Group

Anterior Corneal Aberrations

The mean preoperative and 1-year postoperative anterior corneal HOAs are shown in Table 6. There was a mean increase in...
the mean increases in total posterior corneal HOAs, total coma, and 3rd-order coma were shown in Table 6. The mean increases in total posterior corneal HOAs, total coma, and 3rd-order coma are statistically significant, but the mean increases in vertical coma, horizontal coma, trefoil, and spherical aberration were not.

### Posterior Corneal Aberrations

The mean preoperative and 1-year postoperative posterior corneal HOAs are shown in Table 6. The mean increases in total posterior corneal HOAs, total coma, and 3rd-order coma were statistically significant, but the mean increases in vertical coma, horizontal coma, trefoil, and spherical aberration were not.

#### Treatment Versus Control Groups

**Anterior Corneal Aberrations**

Preoperatively, all anterior corneal HOAs were significantly higher in the treatment group than in the control group (all $P < .001$, except spherical, which was $P = .009$). At 1 year, all anterior corneal HOAs remained significantly higher in the treatment group than in the control group (all $P < .001$, except spherical, which was $P = .004$). At 1 year, however, there was a mean decrease in anterior corneal HOAs in the treatment group and a mean increase in anterior corneal HOAs in the control group. The differences in anterior corneal HOA changes between the treatment group and the control group were statistically significant over time (all $P < .001$ except coma and spherical, which were both $P = .04$). There was no statistically significant difference in the change in trefoil from baseline to 1 year between the treatment group and the control group ($P = .2$).

**Posterior Corneal Aberrations**

Preoperatively, all posterior corneal HOAs in the treatment group were significantly higher than in the control group (all $P < .001$). At 1 year, all posterior corneal HOAs

### Table 2. Higher-order aberrations in the keratoconus subgroup and ectasia subgroup.

<table>
<thead>
<tr>
<th>Group/Parameter</th>
<th>Total HOA</th>
<th>Spherical Aberrations</th>
<th>Total Coma*</th>
<th>Primary Coma</th>
<th>Vertical Coma</th>
<th>Horizontal Coma</th>
<th>Trefoil Coma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Keratoconus</strong></td>
<td></td>
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<tr>
<td>Anterior corneal HOAs (n = 64)</td>
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</tr>
<tr>
<td>Preop</td>
<td>4.57 ± 2.09</td>
<td>1.34 ± 0.85</td>
<td>4.32 ± 2.01</td>
<td>4.28 ± 2.00</td>
<td>3.95 ± 1.96</td>
<td>1.26 ± 1.02</td>
<td>0.36 ± 0.35</td>
</tr>
<tr>
<td>1 year postop</td>
<td>4.11 ± 1.92</td>
<td>1.18 ± 0.61</td>
<td>3.88 ± 1.93</td>
<td>3.84 ± 1.91</td>
<td>3.53 ± 1.85</td>
<td>1.10 ± 0.94</td>
<td>0.45 ± 0.46</td>
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<td>Posterior corneal HOAs (n = 64)</td>
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</tr>
<tr>
<td>Preop</td>
<td>8.83 ± 4.87</td>
<td>3.17 ± 2.25</td>
<td>8.13 ± 4.54</td>
<td>7.94 ± 4.45</td>
<td>7.17 ± 4.02</td>
<td>2.66 ± 2.59</td>
<td>0.98 ± 0.81</td>
</tr>
<tr>
<td>1 year postop</td>
<td>8.85 ± 4.45</td>
<td>3.00 ± 1.82</td>
<td>8.22 ± 4.27</td>
<td>8.07 ± 4.20</td>
<td>7.34 ± 3.90</td>
<td>2.65 ± 2.17</td>
<td>1.10 ± 0.86</td>
</tr>
<tr>
<td>Ocular HOAs (n = 31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>2.83 ± 1.08</td>
<td>0.80 ± 0.40</td>
<td>2.69 ± 1.07</td>
<td>2.65 ± 1.07</td>
<td>2.34 ± 1.13</td>
<td>0.47 ± 0.37</td>
<td>0.93 ± 0.46</td>
</tr>
<tr>
<td>1 year postop</td>
<td>2.55 ± 1.17</td>
<td>0.73 ± 0.33</td>
<td>2.43 ± 1.16</td>
<td>2.39 ± 1.15</td>
<td>2.13 ± 1.14</td>
<td>0.40 ± 0.34</td>
<td>0.83 ± 0.52</td>
</tr>
<tr>
<td><strong>Ectasia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs (n = 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>4.89 ± 2.78</td>
<td>1.51 ± 0.57</td>
<td>4.57 ± 2.86</td>
<td>4.53 ± 2.85</td>
<td>4.22 ± 2.82</td>
<td>1.27 ± 0.95</td>
<td>0.40 ± 0.38</td>
</tr>
<tr>
<td>1 year postop</td>
<td>4.61 ± 2.79</td>
<td>1.50 ± 0.52</td>
<td>4.27 ± 2.89</td>
<td>4.21 ± 2.90</td>
<td>3.93 ± 2.84</td>
<td>1.21 ± 0.99</td>
<td>0.36 ± 0.26</td>
</tr>
<tr>
<td>Posterior corneal HOAs (n = 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>8.95 ± 5.17</td>
<td>3.22 ± 2.27</td>
<td>8.19 ± 5.24</td>
<td>8.05 ± 5.16</td>
<td>7.39 ± 5.06</td>
<td>2.48 ± 1.96</td>
<td>1.01 ± 0.63</td>
</tr>
<tr>
<td>1 year postop</td>
<td>8.38 ± 5.17</td>
<td>2.98 ± 1.70</td>
<td>7.74 ± 5.03</td>
<td>7.62 ± 4.98</td>
<td>7.02 ± 4.79</td>
<td>2.32 ± 2.04</td>
<td>0.86 ± 0.73</td>
</tr>
<tr>
<td>Ocular HOAs (n = 17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>2.74 ± 0.87</td>
<td>1.09 ± 0.41</td>
<td>2.45 ± 0.97</td>
<td>2.42 ± 0.97</td>
<td>1.86 ± 1.04</td>
<td>0.77 ± 0.57</td>
<td>1.07 ± 0.46</td>
</tr>
<tr>
<td>1 year postop</td>
<td>2.67 ± 0.85</td>
<td>1.00 ± 0.42</td>
<td>2.41 ± 0.94</td>
<td>2.39 ± 0.94</td>
<td>1.91 ± 0.90</td>
<td>0.84 ± 0.61</td>
<td>0.97 ± 0.42</td>
</tr>
</tbody>
</table>

HOAs = higher-order aberrations
*Combined 3rd and 5th orders
†Statistically significant change compared with preoperative measurements ($P < .05$)
remained significantly higher in the treatment group than in the control group (all \( P < .001 \)). At 1 year, there was a mean decrease in posterior corneal HOAs in the treatment group and a mean increase in posterior corneal HOAs in the control group. However, these differences between groups failed to reach statistical significance (total: \( P = .07 \); total coma: \( P = .1 \); 3rd-order coma: \( P = .1 \); vertical coma: \( P = .2 \); horizontal coma: \( P = .4 \); trefoil: \( P = .09 \); spherical: \( P = .08 \)).

**DISCUSSION**

Increased anterior corneal HOAs, posterior corneal HOAs, and ocular HOAs are optical sequelae of keratoconus and corneal ectasia that contribute to the diminished visual function in eyes with these corneal disease processes.\(^2,3,19,20\) Collagen crosslinking, although developed primarily to mitigate progression of ectatic corneal processes, has also been found to improve visual acuity and corneal topography characteristics in some patients with keratoconus and ectasia.\(^9-13,16,21\) These effects are likely secondary to changes in the cornea’s optical architecture, a result of the direct CXL effects and the consequent wound-healing processes.\(^22\) For example, in our previous report of 1-year CXL outcomes,\(^11\) patients had an improvement in CDVA (from 20/45 to 20/34) and in UDVA (from 20/137 to 20/117). Moreover, the topography-derived maximum K value flattened by 1.7 D. As further evidence of CXL-mediated corneal architectural changes, we found that several corneal topography quantitative indices also improved after treatment.\(^18\) Because optical aberrations are the predominant cause of vision dysfunction in keratoconus and ectasia, this study was designed to further elucidate the optical changes that occur after CXL.

In this study, a detailed analysis of HOAs showed significant improvements in ocular HOAs and

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**Table 3. Correlation between HOAs and visual acuity measurements at 1 year.**

<table>
<thead>
<tr>
<th>Group/Parameter</th>
<th>Pearson Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total HOA</td>
</tr>
<tr>
<td>Entire cohort</td>
<td></td>
</tr>
<tr>
<td>UDVA</td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs</td>
<td>0.6</td>
</tr>
<tr>
<td>Posterior corneal HOAs</td>
<td>0.1</td>
</tr>
<tr>
<td>Ocular HOAs (n = 48)</td>
<td>−0.2</td>
</tr>
<tr>
<td>CDVA</td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs</td>
<td>0.03</td>
</tr>
<tr>
<td>Posterior corneal HOAs</td>
<td>0.03</td>
</tr>
<tr>
<td>Ocular HOAs (n = 48)</td>
<td>0.04</td>
</tr>
<tr>
<td>Keratoconus</td>
<td></td>
</tr>
<tr>
<td>UDVA</td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs</td>
<td>0.1</td>
</tr>
<tr>
<td>Posterior corneal HOAs</td>
<td>−0.02</td>
</tr>
<tr>
<td>Ocular HOAs (n = 31)</td>
<td>−0.2</td>
</tr>
<tr>
<td>CDVA</td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs</td>
<td>0.1</td>
</tr>
<tr>
<td>Posterior corneal HOAs</td>
<td>0.1</td>
</tr>
<tr>
<td>Ocular HOAs (n = 31)</td>
<td>−0.01</td>
</tr>
<tr>
<td>Ectasia</td>
<td></td>
</tr>
<tr>
<td>UDVA</td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs</td>
<td>0.06</td>
</tr>
<tr>
<td>Posterior corneal HOAs</td>
<td>0.01</td>
</tr>
<tr>
<td>Ocular HOAs (n = 17)</td>
<td>0.01</td>
</tr>
<tr>
<td>CDVA</td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs</td>
<td>−0.2</td>
</tr>
<tr>
<td>Posterior corneal HOAs</td>
<td>−0.06</td>
</tr>
<tr>
<td>Ocular HOAs (n = 17)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

\(^2\)CDVA = corrected distance visual acuity; HOAs = higher-order aberrations; UDVA = uncorrected distance visual acuity

\(^1\)Statistically significant \((P < .05)\)
anterior corneal HOAs 1 year after CXL. These findings corroborate results in previous studies, which found general improvements in HOAs after CXL. In particular, we found that total HOAs and coma significantly improved after CXL when derived from the cornea alone and when measured as total ocular aberrations. Total anterior corneal HOAs improved in 74% of eyes, and ocular HOAs improved in 69% of eyes. In no case did ocular HOAs worsen by more than 1.0 μm, and anterior corneal HOAs worsened by greater than 1.0 μm in only 1 ectasia patient. Despite the worsening of anterior corneal HOAs in this patient, the UDVA remained stable (20/400) and the CDVA improved from 20/50 to 20/40; the patient reported subjective improvement in night driving, glare, halos, and starburst symptoms.

Although in general, visual acuity appears to improve after CXL, the mitigating factor of this improvement remains unclear. For instance, analyses of topography, pachymetry, corneal haze, and corneal biomechanics after CXL have failed to identify clinical characteristics that correlate with post-CXL visual acuity changes. As the proximate cause of most visual impairment in keratoconus and ectasia, HOAs might be expected to predict improvement in vision after CXL. However, in this study, improvements in corneal aberrations and in total ocular aberrations after CXL did not appear to be associated with the improvements in UDVA or CDVA.

Aside from compromised visual acuity per se, increased HOAs also clinically manifest as subjective visual symptoms of glare, halos, and starbursts. However, as with visual acuity outcomes, there did not appear to be any clinically relevant associations between the improvement in HOAs and the improvement in any of these visual symptoms after CXL, except an association of decreased total ocular HOAs with an improvement in reported starbursts. Additional study is required to further elucidate the effect of changing HOAs on visual function after CXL, perhaps also exploring possible associations with contrast sensitivity and low-contrast visual acuity.

To better ascertain differences in response to CXL, HOAs in a keratoconus subgroup and an ectasia subgroup were compared. In this analysis, there was no significant difference between the subgroups 1 year after CXL. Notwithstanding this finding, different trends observed in the 2 subgroups may be clinically enlightening. There was more improvement in anterior corneal HOAs and ocular HOAs in the keratoconus subgroup, a finding consistent with our previously reported CXL topography results. It is unclear whether these findings suggest that ectatic corneas respond less to CXL than keratoconic corneas, whether differences in the preoperative topographic cone location in keratoconus corneas and ectatic corneas (unpublished data) contribute to this difference, or whether these findings are simply the statistical result of the smaller number of ectatic corneas in our study cohort. Further studies should be performed to elucidate differences in outcomes between eyes with keratoconus and eyes with ectasia after CXL.

Finally, the treatment group was compared with a fellow-eye control group. Ideally, the same number of
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 the control group. Furthermore, because the fellow eye was not dilated at the 1-year follow-up examination, ocular HOA data in the control eyes were not available for comparison in this study. Notwithstanding this potential shortcoming, corneal HOAs generally worsened between baseline and 1 year in the control group. Moreover, the improvements in anterior corneal HOAs, total coma, 3rd-order coma, and vertical coma in the CXL-treatment group were significantly different from the fellow-eye control group at 1 year.

In assessing the results in this study, it should be noted that the corneal aberration measurements were performed using Scheimpflug imagery of the Pentacam device. Topographic and pachymetric Pentacam measurements have been validated in other studies26–29; however, the accuracy and repeatability of Pentacam corneal wavefront measurements remain unclear. Muftuoglu et al.30 report good repeatability of Pentacam Zernike coefficients in patients who had penetrating keratoplasty and Descemet-stripping automated endothelial keratoplasty; however,

Table 5. Correlation between HOAs and subjective visual symptoms ratings at 1 year.

<table>
<thead>
<tr>
<th>HOA</th>
<th>Driving at night</th>
<th>Glare</th>
<th>Halos</th>
<th>Starbursts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior corneal HOAs (n = 96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior corneal HOAs (n = 96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular HOAs (n = 48)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation Coefficient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total HOAs</td>
<td>Spherical Aberrations</td>
<td>Total Coma*</td>
<td>Primary Coma</td>
<td>Vertical Coma</td>
</tr>
<tr>
<td>Driving at night</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs (n = 96)</td>
<td>−0.002</td>
<td>0.02</td>
<td>−0.02</td>
<td>−0.01</td>
</tr>
<tr>
<td>Posterior corneal HOAs (n = 96)</td>
<td>0.01</td>
<td>−0.05</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Ocular HOAs (n = 48)</td>
<td>0.04</td>
<td>−0.09</td>
<td>0.06</td>
<td>0.2</td>
</tr>
<tr>
<td>Glare</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs (n = 96)</td>
<td>0.03</td>
<td>0.08</td>
<td>−0.001</td>
<td>−0.004</td>
</tr>
<tr>
<td>Posterior corneal HOAs (n = 96)</td>
<td>−0.01</td>
<td>0.03</td>
<td>−0.03</td>
<td>−0.05</td>
</tr>
<tr>
<td>Ocular HOAs (n = 48)</td>
<td>0.04</td>
<td>−0.09</td>
<td>0.06</td>
<td>0.2</td>
</tr>
<tr>
<td>Halos</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior corneal HOAs (n = 96)</td>
<td>0.04</td>
<td>0.05</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Posterior corneal HOAs (n = 96)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ocular HOAs (n = 48)</td>
<td>0.07</td>
<td>−0.08</td>
<td>0.1</td>
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<tr>
<td>Starbursts</td>
<td></td>
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<tr>
<td>Anterior corneal HOAs (n = 96)</td>
<td>0.2*</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Posterior corneal HOAs (n = 96)</td>
<td>0.03</td>
<td>0.06</td>
<td>−0.01</td>
<td>−0.02</td>
</tr>
<tr>
<td>Ocular HOAs (n = 48)</td>
<td>0.5*</td>
<td>0.4</td>
<td>0.5*</td>
<td>0.5*</td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; HOAs = higher-order aberrations; UDVA = uncorrected distance visual acuity

*Combined 3rd and 5th orders
†Statistically significant (P < .05)

Table 6. Anterior and posterior corneal HOAs in the control group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total HOAs</th>
<th>Total Coma*</th>
<th>3rd-Order Coma</th>
<th>Vertical Coma</th>
<th>Horizontal Coma</th>
<th>Trefoil</th>
<th>Spherical Aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior corneal HOAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>1.80 ± 1.01</td>
<td>1.37 ± 1.12</td>
<td>1.34 ± 1.12</td>
<td>1.11 ± 1.00</td>
<td>0.55 ± 0.66</td>
<td>0.21 ± 0.20</td>
<td>1.00 ± 0.42</td>
</tr>
<tr>
<td>1 year postop</td>
<td>1.93 ± 1.10</td>
<td>1.50 ± 1.21</td>
<td>1.47 ± 1.20</td>
<td>1.25 ± 1.10</td>
<td>0.58 ± 0.66</td>
<td>0.19 ± 0.20</td>
<td>1.02 ± 0.45</td>
</tr>
<tr>
<td>Posterior corneal HOAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>3.22 ± 2.15</td>
<td>2.46 ± 2.39</td>
<td>2.37 ± 2.37</td>
<td>1.85 ± 1.96</td>
<td>0.89 ± 1.58</td>
<td>0.52 ± 0.63</td>
<td>1.74 ± 0.49</td>
</tr>
<tr>
<td>1 year postop</td>
<td>3.48 ± 2.19†</td>
<td>2.75 ± 2.40†</td>
<td>2.67 ± 2.38†</td>
<td>2.20 ± 2.05</td>
<td>0.92 ± 1.58</td>
<td>0.54 ± 0.45</td>
<td>1.81 ± 0.61</td>
</tr>
</tbody>
</table>

HOAs = higher-order aberrations
*Combined 3rd and 5th orders
†Statistically significant change
data were available for analysis in this study. Previous
letters. Therefore, only high-contrast visual acuity
ETDRS visual acuity test (2nd edition) with Sloan
acuity to be measured with a modified Lighthouse
cam device uses elevation data to extrapolate the
in some eyes exceeded the instrument’s dynamic
range. Unlike the Ladarwave aberrometer, the Pentacam
device uses elevation data to extrapolate the
Zernike coefficients; therefore, anterior corneal HOA
and posterior corneal HOA data were available for
all patients.

A second limitation of this study was the incomplete
ocular HOA data available for analysis. The Ladarwave
aberrometer could not measure ocular HOAs in all patients. This is likely because of the extreme
magnitude of HOAs in this patient population, which
in some eyes exceeded the instrument’s dynamic
range. Unlike the Ladarwave aberrometer, the Pentacam
device uses elevation data to extrapolate the
Zernike coefficients; therefore, anterior corneal HOA
and posterior corneal HOA data were available for
all patients.

Finally, the protocol for this study required visual
acuity to be measured with a modified Lighthouse
ETDRS visual acuity test (2nd edition) with Sloan
letters. Therefore, only high-contrast visual acuity
data were available for analysis in this study. Previous
studies report that low-contrast visual acuity testing
may be more sensitive when measuring the effect
of HOAs on visual acuity. Further studies are required
to determine the effect of HOAs on low-contrast visual
acuity after CXL.

In conclusion, the clinical outcomes of CXL for the
treatment of keratoconus and ectasia continue to be
elucidated. In this study, we found that anterior
corneal HOAs and ocular HOAs, in particular coma,
improved after corneal CXL.

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Cornea and Laser Eye Institute–Hersh Vision Group, CLEI Center for Keratoconus, Teaneck, New Jersey, USA
In Vivo Biomechanical Changes After Corneal Collagen Cross-linking for Keratoconus and Corneal Ectasia: 1-Year Analysis of a Randomized, Controlled, Clinical Trial

Steven A. Greenstein, MD, Kristen L. Fry, OD, MS, and Peter S. Hersh, MD

Purpose: To investigate the in vivo, corneal, biomechanical changes after corneal collagen cross-linking (CXL) using the Ocular Response Analyzer (ORA) in patients with keratoconus and post-laser in situ keratomileusis (LASIK) ectasia.

Methods: Single-center, prospective, randomized, controlled, clinical trial. After CXL (69 eyes, 46 keratoconus and 23 post-LASIK), corneal hysteresis (CH) and corneal resistance factor (CRF) were measured using the ORA and analyzed in a treatment, sham control, and fellow eye control group at baseline and 1, 3, 6, and 12 months.

Results: There were no significant changes in CH (change = 0.05 ± 1.5; P = 0.78) or CRF (change = 1.4; P = 0.1) at 1 year compared to preoperative values. Changes in CH and CRF were not correlated with changes in clinical outcomes of uncorrected visual acuity, best spectacle-corrected visual acuity, and maximum keratometry. There were no significant changes in CH in the sham or fellow eye control groups (P sham = 0.7, P TN = 0.3) or CRF (P sham = 0.6, P TN = 0.72).

Conclusions: Despite an increase in CRF at one month, there were no statistically significant changes in CH and CRF measurements 1 year after CXL. Development of other in vivo biomechanical metrics would aid in evaluating the corneal response to CXL.

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Keratoconus and post-laser in situ keratomileusis (LASIK) ectasia are disease processes in which the cornea deforms in association with thinning and biomechanical weakening. An understanding of corneal biomechanics may help to elucidate the cause and natural history of these ectatic processes. The cornea is a viscoelastic structure with both viscous and elastic components. In response to stress, there is an immediate elastic response of the cornea followed by a prolonged, time-dependent, viscoelastic response. Early studies measured a decrease in elasticity in corneas with keratoconus. Although the pathogenesis of keratoconus and ectasia currently remains unclear, it seems that a primary event leads to the loss and/or slippage of collagen fibrils and changes to the extracellular matrix in the corneal stroma. These changes are thought to cause biomechanical instability of the corneal stroma with consequent changes in both the cornea's anatomical and topographic architecture.

UVA/riboflavin–mediated collagen cross-linking (CXL) for the treatment of keratoconus and post-LASIK ectasia is thought to increase the biomechanical strength of the cornea. Wolensak et al reports that immediate stress measurements increased by 71.9% and 328.9% in porcine and human corneas, respectively, after CXL. In rabbit corneas, these increases in stress measurements were maintained between 69.7% and 106% at 6 months postoperatively. Such postoperative increases in Young modulus were further demonstrated with collagen hydrogels exposed to UVA/riboflavin therapy.

We reported encouraging results of CXL in a previous randomized, controlled, clinical trial. In that study of 1-year CXL outcomes, patients experienced an improvement in both best spectacle-corrected visual acuity (BSCVA) and uncorrected visual acuity (UCVA), and maximum keratometry (Kmax) and average keratometry. Despite laboratory and clinical findings, however, to date it has been difficult to quantify the actual biomechanical changes effected by CXL in vivo.

The Ocular Response Analyzer (ORA; Reichert, Inc, Buffalo, NY) is a commercially available device designed to obtain in vivo measurements of corneal biomechanical properties. Two core metrics are used to describe the biomechanical strength of the cornea: corneal hysteresis (CH) and corneal resistance factor (CRF). CH is a measurement of the viscous dampening in corneal tissue, and CRF is a measurement of the entire viscoelastic response of the cornea, both in response to a graded and time-dependentplanation pressure applied by the ORA. To measure CH and CRF, a tube is automatically aligned with the patient's eye and an air puff is released of a specific time and pressure gradient. Concomitant with the air pulse, the ORA measures 2

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applanation pressures: the first pressure is measured when the cornea is moving inward, and the second pressure is measured as the cornea recoils to its native position. In addition, a waveform of this temporal corneal deformation is captured. Measurements derived from the waveform signal such as peak amplitudes, timing of peaks, width of peaks, and others have been used to characterize the biomechanical properties of individual corneas.\textsuperscript{16-19}

In this study, in an effort to elucidate corneal biomechanical changes in vivo after CXL, ORA measurements of CH and CRF were analyzed over a 1-year period after the CXL procedure and also were correlated with visual acuity and topographic outcomes after CXL.

MATERIALS AND METHODS

Patients with progressive keratoconus and ectasia were enrolled as part of a multicenter, prospective, randomized, controlled, clinical trial conducted under the guidelines of the US Food and Drug Administration (ClinicalTrials.gov, NCT00647692 and NCT00674661) and approved and monitored by an investigational review board. This study was compliant with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all patients. Progressive keratoconus or ectasia was defined as one or more of the following changes over a period of 24 months: an increase of ≥1 diopter (D) in the steepest keratometry, an increase of ≥1 D in manifest cylinder, or an increase of ≥0.5 D in manifest refractive spherical equivalent.

CXL was performed according the methodology described by Wolfszank et al.\textsuperscript{20} Initially, a topical anesthetic was administered and the central epithelium was removed. After topical 0.1% riboflavin administration (0.1% in 20% dextran T-500 solution, Medico-Cross; Peschke Meditradte, GmbH, Zurich, Switzerland) every 2 minutes for a total of 30 minutes, riboflavin absorption was confirmed on slit-lamp examination. Ultrasonic pachymetry was performed. If the cornea was <400 \( \mu \)m, hypotonic riboflavin (0.1% in sterile water, Medico-Cross hypotonice; Peschke Meditradte, GmbH) was administered, after which ultrasonic pachymetry was performed to confirm that the stroma had swelled to >400 \( \mu \)m. The cornea was exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm\(^2\) (UV-X System; IROC, Zurich, Switzerland), and riboflavin administration was continued every 2 minutes for the duration of the treatment.

ORA AND PENTACAM MEASUREMENTS

Treatment Group

The ORA is a device used to measure in vivo corneal biomechanical properties. Two primary metrics are CH and CRF. CH is a measure of the difference between the 2 applanation pressures measured by the ORA (P1–P2), thought to represent the viscous dampening property of the cornea. CRF is a linear calculation (P1-P2), thought to better account for corneal thickness, that measures both the viscous and elastic properties of the cornea. Three ORA measurements were taken at each study visit, and the measurement with the highest waveform score was used for analysis. CH and CRF were measured at baseline and 1, 3, 6, and 12 months. To further analyze ORA measurements, the correlation among CH, CRF, and central corneal thickness (CCT) measured on the Pentacam (Oculus, Inc, Wetzlar, Germany) was analyzed at baseline and 1 year. Finally, the changes in CH and CRF at 1 year were correlated with 1-year visual acuity and topographic outcomes.

Control Groups

The sham control group received 0.1% riboflavin ophthalmic solution alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for a total of 30 minutes. After the administration of riboflavin, the cornea was aligned with the UVA light and 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 UVA/riboflavin treatment. ORA measurements were analyzed at 1 and 3 months and compared with the postoperative measurements of the treatment group at the same time points.

In addition, a fellow eye control group was analyzed as well. The fellow eyes of patients who did not undergo CXL treatment bilaterally were analyzed in this group. This group consisted of eyes with frank keratoconus or ectasia that did not undergo CXL, eyes with evidence of disease that did not meet the inclusion criteria of this study, and eyes with no evidence of disease. ORA measurements were analyzed at baseline and 12 months and compared with the postoperative measurements of the treatment group between the same time points. Similar to the treated group, in this control group, CH and CRF also were correlated with Pentacam CCT measurements.

OUTCOME MEASUREMENTS

Visual Acuity Measurements

UCVA and BSCVA were measured at 1 and 12 months postoperatively. Visual acuity measurements were obtained under controlled lighting conditions using a modified LightHouse Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity test (2nd ed.) with Sloan letters. The fluorescent tubes in the ETDRS chart light box were 40-W, frosted, cool, white bulbs and were replaced annually. New tubes were kept on for 96 hours. Room illumination was measured at a level of 50 to 100 foot candles using a photometer held 4 ft from the floor and directed toward the ceiling. Visual acuity was measured at a 4-m distance. If patients could not read any letters at 4 m, they were tested at a 2-m distance. Visual acuity was recorded and analyzed as the logarithm of the minimum angle of resolution value.

Topographic and Pachymetric Measurements

Topographic and pachymetric measurements were obtained using the Pentacam (Oculus, Inc). The Pentacam is a rotating Scheimpflug camera that generates a 3-dimensional model of the cornea and anterior segment. \( K_{\text{max}} \) and CCT measurements were obtained preoperatively and at 12 months postoperatively.
Statistical Analysis

Statistical analysis was performed using PASW Statistics 18 (SPSS, Inc, Chicago, IL). A paired 2-tailed Student t-test was performed to analyze the postoperative ORA changes over time and compared with baseline. An independent t-test was performed to determine the differences in postoperative changes between the treatment and control groups and the keratoconus and post-LASIK ectasia groups. To analyze the possible correlation of CCT, CXL outcomes, and ORA measurements, Pearson correlation coefficients were used. A P value of 0.05 was used as significance level.

RESULTS

A total of 69 eyes (46 keratoconus and 23 ectasia) of 56 patients underwent CXL and were followed for 1 year. The fellow eye and sham control groups each comprised 35 eyes of the 35 patients (23 keratoconus and 12 ectasia).

CH and CRF

Preoperative CH was 7.66 ± 1.16 and at 1 year postoperatively remained unchanged at 7.71 ± 1.77 (P = 0.78). Preoperative CRF was 5.80 ± 1.31 and at 1 year was 6.08 ± 1.77 (P = 0.10).

Postoperative Time Course of CH and CRF

The postoperative changes in CH were −0.09 ± 1.46, −0.18 ± 1.66, 0.24 ± 1.7, and 0.08 ± 1.79 between baseline and 1 month, 1 and 3 months, 3 and 6 months, and 6 and 12 months, respectively. All of these changes failed to reach statistical significance (P1-2 = 0.6, P1-3 = 0.4, P3-6 = 0.2, and P6-12 = 0.7) (Fig. 1, Table 1).

Initially, there was a significant increase in CRF between baseline and 1 month (0.5 ± 1.42; P = 0.004). After this increase in CRF, there were changes in CH between 1 and 3 months (−0.32 ± 1.36), 3 and 6 months (0.02 ± 1.42) and 6 and 12 months (0.08 ± 1.40). All of these changes failed to reach statistical significance (P1-3 = 0.05, P3-6 = 0.9, and P6-12 = 0.6) (Fig. 1).

Difference Between Keratoconus and Ectasia Eyes

There was no significant difference between patients with keratoconus and post-LASIK ectasia when the change in CH (P = 0.39) and CRF (P = 0.84) between baseline and 1 year follow-up was analyzed.

Control Eyes

In the sham control group, CH and CRF changed by 0.12 ± 1.1 (P = 0.5) and −0.05 ± 1.0 (P = 0.8) between baseline and 1 month and by 0.08 ± 1.0 (P = 0.6) and −0.07 ± 0.91 (P = 0.6) between baseline and 3 months, respectively. All of these changes failed to reach statistical significance.

In the fellow eye control group, CH and CRF changed by 0.17 ± 1.1 (P = 0.4) and 0.09 ± 1.0 (P = 0.6) between baseline and 12 months. All of these changes also failed to reach statistical significance.

Control Versus Treated Patients

When the change in CRF between baseline and 1 month was compared there was a significant difference between the sham control and treatment groups (P = 0.04); in the treatment group, there was a significant increase in CRF, whereas in the sham control group, there was no significant change. There was no significant difference between treated and control patients when the change in CH or CRF between baseline and 3 months (PCH = 0.14, PCRF = 0.26) and baseline and 1 year (PCH = 0.68, PCRF = 0.93) was analyzed.

Correlation Between ORA Measurements and CCT

CH and CRF at baseline and 12 months were significantly correlated with CCT at baseline and 12 months, respectively (CHbaseline with CCTbaseline = 0.56, P < 0.001; CH12 with CCT12 = 0.42, P < 0.001; CRFbaseline with CCTbaseline = 0.63, P < 0.001; and CRF12 with CCT12 = 0.51, P < 0.001). Similar to the treated group, in the fellow eye control group, CH and CRF at baseline and 12 months were significantly correlated with CCT at baseline and 12 months, respectively (CHbaseline with CCTbaseline = 0.60, P < 0.001; CH12 with CCT12 = 0.68, P < 0.001; CRFbaseline with CCTbaseline = 0.62, P < 0.001; and CRF12 with CCT12 = 0.74, P < 0.001).

Correlation Among ORA, Visual Acuity, and Topographic Measurements

In the entire cohort, UCVA, BSCVA, and Kmax were significantly improved 1 year after CXL (Table 2). The changes in CH and CRF between baseline and 1 year were not correlated with the changes in UCVA (rCH = −0.06, P = 0.6; rCRF = −0.10, P = 0.4), BSCVA (rCH = 0.03, P = 0.8; rCRF = 0.01, P = 0.9), or Kmax (rCH = −0.02, P = 0.8; rCRF = 0.02, P = 0.9).

DISCUSSION

CXL is a promising new treatment for the stabilization and strengthening of the cornea in keratoconus and post-LASIK ectasia. CXL is thought to cause cross-linking.
TABLE 1. ORA Measurements Over Time [All (69 Eyes), Keratoconus (46 Eyes), and Ectasia (23 Eyes)]

<table>
<thead>
<tr>
<th>ORA Measurements</th>
<th>Preoperatively</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>P Value Change From Baseline to 12 Months (KC vs Ectasia)</th>
<th>P Value Change From Baseline to 12 Months (Tx vs FE)</th>
<th>P Value Change From Baseline to 12 Months (Tx vs Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>7.66 ± 1.16</td>
<td>7.57 ± 1.9</td>
<td>7.39 ± 1.58</td>
<td>7.63 ± 1.96</td>
<td>7.71 ± 1.77</td>
<td>0.4</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>CRF</td>
<td>5.80 ± 1.31</td>
<td>6.31 ± 1.63**</td>
<td>5.99 ± 1.44</td>
<td>6.00 ± 1.64</td>
<td>6.08 ± 1.77</td>
<td>0.8</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>KC</td>
<td>7.76 ± 1.10</td>
<td>7.89 ± 2.04</td>
<td>7.48 ± 1.33</td>
<td>7.72 ± 1.84</td>
<td>7.91 ± 1.68</td>
<td>—</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Ectasia</td>
<td>5.89 ± 1.36</td>
<td>6.52 ± 1.66**</td>
<td>5.99 ± 1.34*</td>
<td>6.04 ± 1.60</td>
<td>6.20 ± 1.64</td>
<td>—</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>CRF</td>
<td>7.48 ± 1.29</td>
<td>6.95 ± 1.50*</td>
<td>7.21 ± 2.02</td>
<td>7.45 ± 2.23</td>
<td>7.31 ± 1.93</td>
<td>—</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>CRF</td>
<td>5.62 ± 1.21</td>
<td>5.88 ± 1.50</td>
<td>5.98 ± 1.66</td>
<td>5.94 ± 1.77</td>
<td>5.86 ± 1.95</td>
<td>—</td>
<td>0.7</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data were considered to be significant at \( P < 0.05 \).
*Significant change compared with baseline measurements.
**Significant change compared with previous visit measurement.

Kc, keratoconus; FE, fellow eye; Tx, treatment.

through the formation of reactive oxygen species, leading to the production of covalent cross-links between collagen molecules, with consequent stiffening of the stromal tissue.23 This strengthening of the corneal stroma slows the progression of keratoconus and ectasia and, in many cases, improves patients' visual, refractive, and topographic outcomes.12,24-26 With a low reported rate of complication,27,28 Indeed, in our previous report of the 1-year clinical results of CXL, we found an average \( K_{max} \) flattening of 1.7D and improvement in BCVA from 20/45 to 20/34 and improvement in a number of corneal topographic indices.12,29

In this study, the in vivo biomechanical measurements, CH and CRF remained unchanged 1 year after CXL. The lack of significant changes in CH and CRF is consistent with previously reported ORA results.13,14,10 Interpreting these results is challenging because postoperative changes to either the viscous or elastic component of the cornea may be too subtle for these ORA metrics to capture and may in part contribute to the lack of significant results.21,22 Moreover, the surface optical irregularity of these ectatic corneas may introduce error and variability into the ORA signal that may prevent meaningful quantitative comparison of preoperative and postoperative CH and CRF (Fig. 1).26,33 It is also possible that the biomechanical changes after CXL are inherently different than those measured by CH and CRF, and therefore, these metrics may not capture the true biomechanical effect of CXL over time.

In this study, the treatment group was compared with a 3-month sham control group and a 12-month fellow eye control group. Ideally, all fellow eyes would have been compared with treatment eyes. However, the protocol for this trial allowed fellow eye CXL treatment 3 months after the first eye treatment. Therefore, the treatment patients were compared only with the fellow eyes of the patients who had unilateral treatment and 12-month follow-up in their fellow eyes. Some of the fellow eyes in this study had no topographic or visual signs of keratoconus or ectasia. Thus, disease progression would be expected to be minimal.

In the sham and fellow eye control groups, there were no significant changes in CH or CRF between baseline and 1 year. At 1 month, there was a significant difference between the mean increase in CRF in the treatment group (an increase in biomechanical strength) and the mean decrease in CRF in the sham control group (a decrease in biomechanical strength). This could be a result of an increase in corneal biomechanical strength that occurs 1 month after CXL. Of note, this is concomitant with the significant corneal thinning that is seen 1 month after CXL. Thinner corneas seem to be correlated with lower CRF values. This suggests that the increase in CRF is, indeed, an indication of corneal strengthening at 1 month. In previous work, we defined the postoperative time course of corneal haze after CXL34 a clinical analog to the post-CXL healing process. Thus, the increase in CRF that we observed at 1 month could also be a finding incidental to the epithelial and stromal remodeling process.

In this study, the ORA metrics of CH and CRF did not significantly change over a time course of 1 year after CXL. Ongoing development of interpretive models of the waveform itself may better capture the true biomechanical properties of the cornea after CXL. Indeed, such waveform analysis has been shown to identify and grade different clinical stages of keratoconus.17,18 Further clinical studies

TABLE 2. Visual Acuity and Topographic Measurements (All 69 Eyes)

<table>
<thead>
<tr>
<th>Preoperatively</th>
<th>1 Year</th>
<th>Significance (P &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncorrected visual acuity (logMAR)</td>
<td>0.84 ± 0.34</td>
<td>0.77 ± 0.38</td>
</tr>
<tr>
<td>Best spectacle visual acuity (logMAR)</td>
<td>0.35 ± 0.23</td>
<td>0.22 ± 0.19</td>
</tr>
<tr>
<td>( K_{max} ), D</td>
<td>58.4 ± 9.1</td>
<td>56.9 ± 8.1</td>
</tr>
</tbody>
</table>

logMAR, logarithm of the minimum angle of resolution.
using such analytic algorithms may help elucidate the in vivo, corneal, biomechanical changes consequent to the CXL procedure.

REFERENCES
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 \( \pm \) 52.9 (SD). After CXL, the cornea thinned at 1 month (mean change \(-23.8 \pm 28.7 \mu m; P<.001\)) and from 1 to 3 months (mean change \(-7.2 \pm 20.1 \mu m; P=.002\)), followed by a recovery of the corneal thickness between 3 months and 6 months (mean \(+20.5 \pm 20.4 \mu m; P<.001\)). 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 \(-6.6 \pm 22.4 \mu m; P=.01\)). 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 in particular as well as other corneal thinning processes, such as ectasia after laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK). Studies 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, and 4 of 7 Pentacam (Oculus, Inc.) topographic indices.

Anatomic and physiologic changes in the cornea after CXL remain to be thoroughly defined. In previous work, 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 have used confocal microscopy to evaluate the anatomic and cellular changes after CXL. Corneal thickness changes also have been noted after CXL.

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.\(^1\) 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 μm. 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.\(^1\) 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 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 ultraso\ntically and the epithelium was not removed. 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 images were 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 this study, the Scheimpflug 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...
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 ± 28.7 μm; P < .001) (Figure 1). There was further thinning between 1 month and 3 months (mean change −7.2 ± 20.1 μm; P = .002), followed by a significant increase between 3 months and 6 months (mean change +20.5 ± 20.4 μm; P < .001). The change in thinnest pachymetry between 6 months and 12 months (mean change +3.5 ± 22.9 μm; 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 ± 27.8 μm; P < .001) and further thinning between 1 month and 3 months (mean change −7.2 ± 20.8 μm; P = .002) (Figure 1). This was followed by a significant increase in apical pachymetry between 3 months and 6 months (mean change +19.6 ± 21.8 μm; P < .001) and between 6 months and 12 months (mean change +6.4 ± 22.3 μm; 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 ± 24.1 μm; P < .001) and further thinning between 1 month and 3 months (mean change −5.9 ± 21.6 μm; 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 ± 21.0 μm; P < .001) and between 6 months and 12 months (mean change +8.0 ± 20.4 μm; 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 ± 20.3 μm, −8.3 ± 21.4 μm, and −12.1 ± 23.4 μm, 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 ± +14.9 μm, +3.5 ± 15.5 μm, and +4.1 ± 16.0 μm, 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 ± 15.3 μm; P < .001), pachymetry at the corneal apex (mean change −28.2 ± 15.4 μm; P < .001), and thinnest pachymetry (mean change −29.5 ± 15.2 μm; P < .001) became significantly thinner from baseline to 3 months. From 3 to 12 months, the pachymetry became significantly thicker (mean...
At 1 year, the pupil-center pachymetry (mean change 8.9 ± 17.4 μm; P = .001) (Table 2), 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 ±
21.9 μm, +29.3 ± 25.1 μm, and +28.7 ± 24.1 μm, respectively; all \( P < .001 \). At 1 year, the pupil-center pachymetry (mean change \(-0.7 \pm 19.3 \text{ μm}; P = .8\) ), pachymetry at the corneal apex (mean change \(-1.9 \pm 21.3 \text{ μm}; P = .5\) ), and thinnest pachymetry (mean change \(-3.0 \pm 23.3 \text{ μm}; P = .3\) ) 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>
<thead>
<tr>
<th>Baseline to 12 Mo (KC vs EC)</th>
<th>Baseline to 12 Mo (Tx vs FE)</th>
<th>Baseline to 3 Mo (Tx vs Sham)</th>
<th>With UDVA</th>
<th>With CDVA</th>
<th>With ( K_{\text{max}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( .05 )</td>
<td>.4</td>
<td>&lt;.001</td>
<td>-0.09</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>( .03 )</td>
<td>&lt;.001</td>
<td></td>
<td>-0.15</td>
<td>0.19</td>
<td>-0.09</td>
</tr>
<tr>
<td>( .2 )</td>
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<td>-0.05</td>
<td>-0.29</td>
<td>0.31</td>
</tr>
<tr>
<td>( .01 )</td>
<td>.5</td>
<td>&lt;.001</td>
<td>-0.07</td>
<td>-0.02</td>
<td>-0.14</td>
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<tr>
<td>( .06 )</td>
<td>&lt;.001</td>
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<td>-0.06</td>
<td>0.09</td>
<td>-0.25</td>
</tr>
<tr>
<td>( .1 )</td>
<td>&lt;.001</td>
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<td>-0.10</td>
<td>-0.32</td>
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<tr>
<td>( .002 )</td>
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<tr>
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<td>-0.50*</td>
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<td>-0.04</td>
<td>-0.18</td>
<td>0.11</td>
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</table>

*Significant change compared with baseline measurements \(( P < .05 )\)

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

<table>
<thead>
<tr>
<th>Group/Area</th>
<th>Preop</th>
<th>1 Mo Postop</th>
<th>3 Mo Postop</th>
<th>6 Mo Postop</th>
<th>12 Mo Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dextran riboflavin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil</td>
<td>491.4 ± 45.7</td>
<td>462.3 ± 41.7*</td>
<td>462.7 ± 46.0*</td>
<td>477.7 ± 44.9*</td>
<td>482.6 ± 49.9*</td>
</tr>
<tr>
<td>Apex</td>
<td>486.6 ± 46.8</td>
<td>457.6 ± 42.7*</td>
<td>458.4 ± 44.9*</td>
<td>473.5 ± 43.3*</td>
<td>477.3 ± 49.8*</td>
</tr>
<tr>
<td>Thinnest</td>
<td>472.5 ± 45.4</td>
<td>443.4 ± 44.1*</td>
<td>443.0 ± 44.8*</td>
<td>459.6 ± 42.3*</td>
<td>458.2 ± 47.3*</td>
</tr>
<tr>
<td><strong>Hypotonic riboflavin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil</td>
<td>462.5 ± 42.4</td>
<td>440.1 ± 50.5*</td>
<td>431.1 ± 45.4*</td>
<td>452.2 ± 42.9*</td>
<td>461.7 ± 40.2*</td>
</tr>
<tr>
<td>Apex</td>
<td>446.8 ± 47.2</td>
<td>426.6 ± 53.6*</td>
<td>415.6 ± 51.5*</td>
<td>437.3 ± 46.0*</td>
<td>444.9 ± 48.7*</td>
</tr>
<tr>
<td>Thinnest</td>
<td>425.9 ± 49.8</td>
<td>404.6 ± 49.5*</td>
<td>394.3 ± 48.5*</td>
<td>416.7 ± 46.8*</td>
<td>423.0 ± 49.7*</td>
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</tbody>
</table>

\*Significant change compared with baseline measurements \(( P < .05 )\)

\*Significant change compared with previous visit measurement \(( P < .05 )\)
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 $-1.5 \pm 18.4 \, \mu m$ ($P=.6$), $+0.07 \pm 21.2 \, \mu m$ ($P=.98$), and $-2.3 \pm 23.9 \, \mu m$, ($P=.6$), 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 $-0.67 \pm 13.9 \, \mu m$ ($P=.8$), $-1.9 \pm 15.9 \, \mu m$ ($P=.5$), and $-1.6 \pm 19.2 \, \mu m$ ($P=.6$), 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 ($P=.2$).

**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...
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 and ectasia. The increase in biomechanical stiffness after CXL slows the progression of keratoconus and ectasia and, in many cases, improves the patient’s visual and topographic outcomes. 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.

Corneal thinning is generally concomitant with the early CXL postoperative course. A previous study found that intraoperative ultrasound pachymetry decreased after the initial 30 minutes of riboflavin administration, and several others 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. In contrast to our results, Vinciguerra et al. 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, 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), changes in corneal hydration and edema, keratocyte apoptosis, and changes in glycosaminoglycans might be implicated.

In a previous study, 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, 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. 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. 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).

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.

In our previous work, we found differences in CXL outcomes between keratoconus and ectasia. Recent
studies, as well as our previous analysis, found that ectatic corneas appear to have a less robust response to CXL than keratoconic corneas.7,15 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 μm thickness, has been suggested in CXL treatment.33 Because intraoperative pachymetry could relate to postoperative pachymetry changes,17 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.34

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 month 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.

Furthermore, in keratoconic corneas, Pentacam central corneal thickness measurements were found to be more reproducible and repeatable than measurements with ultrasound pachymetry. How- ever, 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, typically seen clinically after CXL.

Indeed, difficulty measuring post-CXL pachymetry has been reported using the Orbscan scanning-slit to- pography device (Bausch & Lomb). 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. 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 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.

REFERENCES


OTHER CITED MATERIAL
Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis

Steven A. Greenstein, Kristen L. Fry, OD, MS, Jalpa Bhatt, Peter S. Hersh, MD

PURPOSE: To determine the natural history of collagen crosslinking (CXL)--associated corneal haze measured by Scheimpflug imagery and slitlamp biomicroscopy in patients with keratoconus or ectasia after laser in situ keratomileusis.

SETTING: Cornea and refractive surgery subspecialty practice, United States.

DESIGN: Prospective randomized controlled clinical trial.

METHODS: The treatment group received ultraviolet-A/riboflavin CXL therapy. The control group received riboflavin alone without epithelial debridement. To objectively measure CXL-associated corneal haze, corneal densitometry using Scheimpflug imagery was measured and the changes in haze were analyzed over time. A similar analysis was performed using clinician-determined slitlamp haze. Correlation of CXL-associated corneal haze with postoperative outcomes was analyzed.

RESULTS: The mean preoperative corneal densitometry was 14.9 ± 1.93 (SD) (Pentacam Scheimpflug densitometry units). Densitometry peaked at 1 month (mean 23.4 ± 4.40; P<.001), with little change at 3 months (mean 22.4 ± 4.79; P = .06) and decreased between 3 months and 6 months (19.4 ± 4.48; P<.001) and between 6 months and 12 months. By 12 months, densitometry had not completely returned to baseline in the entire cohort (mean 17.0 ± 3.82; P<.001) and the keratoconus subgroup; however, it returned to baseline in the ectasia group (16.1 ± 2.41; P = .15). The postoperative course of slitlamp haze was similar to objective densitometry measurements. Increased haze, measured by densitometry, did not correlate with postoperative clinical outcomes.

CONCLUSIONS: The time course of corneal haze after CXL was objectively quantified; it was greatest at 1 month, plateaued at 3 months, and was significantly decreased between 3 months and 12 months. Changes in haze did not correlate with postoperative clinical outcomes.

Financial Disclosure: Drs. Greenstein and Fry and Ms. Bhatt have no financial or proprietary interest in any material or method mentioned. Additional disclosures are found in the footnotes.


Corneal collagen crosslinking (CXL) is a treatment designed to decrease the progression of keratoconus in particular as well as other corneal-thinning processes, such as post-laser in situ keratomileusis (LASIK) ectasia. Studies suggest that CXL can also have beneficial visual and optical effects by decreasing corneal steepness, improving corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA), and improving topography irregularity indices.

In the CXL procedure, riboflavin (vitamin B2) is administered in conjunction with ultraviolet-A (UVA) (365 nm) irradiation. Riboflavin acts as a photosensitizer for the production of reactive oxygen species (singlet oxygen). The free radicals produced by the interaction of riboflavin and UVA light cause the formation of chemical bonds within the corneal stroma and consequent mechanical stiffening of the cornea.

Collagen crosslinking appears to have its predominant effect in the anterior 300 μm of the cornea. Studies of the cornea after CXL report several changes. These include increased collagen fiber diameter, keratocyte apoptosis and subsequent keratocyte changes, resistance to thermal shrinkage, change
in corneal-swelling properties, and increased resistance to collagenase degradation. A typical corneal haze has generally been noted on clinical examination after CXL. Studies show that the depth of the CXL can be observed by following the demarcation line seen in the corneal stroma or by grading the corneal haze at the slitlamp. Moreover, corneal haze after CXL has been confirmed and its etiology, in part, has been defined using confocal microscopy.

In the cohort in the present study, more than 90% of eyes had the clinical appearance of stromal haze on slitlamp examination after CXL. Subjective grading of corneal haze at the slitlamp, however, is subject to observer interpretation and is difficult to measure objectively. Therefore, to better quantitate and explore the natural history of this CXL-associated corneal haze, we used Scheimpflug image densitometry measurements in a prospective randomized controlled trial. We also sought to analyze the correlation between densitometry and visual acuity after CXL.

**Patients and Methods**

Patients were enrolled as part of a multicenter prospective randomized controlled clinical trial conducted under guidelines of the U.S. Food and Drug Administration (trials NCT00647699 and NCT00674661) and approved and monitored by an investigational review board. All patients provided informed consent, and all work performed for this study was compliant with the U.S. Health Insurance Portability and Accountability Act. Two patient cohorts were treated, 1 with progressive keratoconus and 1 with corneal ectasia after LASIK. The inclusion criteria included age 14 years or older, axial superior ratio greater than 1.5 on topography mapping, CDVA worse than 20/20, removal of contact lenses for a specified period of time depending on the type of lens, and a diagnosis of progressive keratoconus or LASIK-induced ectasia. Progressive keratoconus 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 keratometry (K), an increase of 1.00 D or more in manifest cylinder, or an increase of 0.50 D or more in the manifest refraction spherical equivalent. Exclusion criteria included a history of corneal surgery, corneal pachymetry less than 300 μm, a history of chemical injury or delayed epithelial healing, and pregnancy or lactation during the course of the study.

**Surgical Technique**

Patients were initially randomized to a treatment group (riboflavin-UVA) or a control group (riboflavin only). All control patients had CXL (riboflavin-UVA) after 3 months, at which time a new baseline was established for them. Corneal crosslinking was performed according to the methodology described by Wollensak et al. In brief, a topical anesthetic agent was administered and the central 9.0 mm epithelium removed by mechanical debridement. Riboflavin was then administered systemically every 2 minutes for 30 minutes. Complete riboflavin absorption throughout the stroma and into the anterior chamber was confirmed by slit-lamp examination. Ultrasonic pachymetry was performed to confirm corneal thickness of 400 μm or more. If the cornea was thinner than 400 μm, hypotonic riboflavin was administered, 1 drop every 10 seconds for 2-minute sessions, until the stroma had swelled to more than 400 μm. The cornea was then exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm², with continued administration of riboflavin drops every 2 minutes. At the conclusion of the procedure, antibiotic and corticosteroid drops were administered and a bandage soft contact lens was placed. The contact lens was removed after epithelialization. Antibiotic drops and corticosteroid drops were continued 4 times daily for 1 week and 2 weeks, respectively. In the control group, the epithelium was not removed. Riboflavin drops were administered every 2 minutes for 30 minutes. For the next 30 minutes, the patient had a sham treatment with continued administration of riboflavin drops.

**Postoperative Follow-up**

Scheimpflug images of all eyes were taken with a Pentacam rotating Scheimpflug camera (Oculus, Inc.) before the procedure and at the 1-, 3-, 6-, and 12-month follow-up visits. The Scheimpflug device generates a 3-dimensional model of the cornea and anterior segment. As an objective measure of CXL-associated corneal haze, corneal densitometry was measured over the central 4.0 mm along 1 meridian using the Scheimpflug image. The meridian of the image used was determined as follows: At the initial visit, the coordinate of maximum steepness (maximum keratometry [K] value) were identified on the Scheimpflug device. The axis nearest to the maximum K value was determined, and the Scheimpflug image at this axis was used for analysis. A central 4.0 mm segment of the cornea was delineated manually using perimetry software included with the device (Figure 1). The tracing encompassed the entire thickness of the cornea, and the perimetry software automatically calculated the mean density of that area. The Scheimpflug device quantifies the density of the cornea on a scale from 0 to 100.
These measurements were obtained at 1, 3, 6, and 12 months using the Scheimpflug image taken at the same axis as at the baseline visit.

As a clinical correlate, corneal haze was observed at each visit by slitlamp biomicroscopy by the same investigator (P.S.H.) and graded on a scale from 1 to 4. The slitlamp examination grading was as follows: 0 = clear cornea; 1 = focal areas of minimal stromal clouding or reticulation; 2 = diffuse mild stromal clouding or reticulation; 3 = diffuse stromal clouding or reticulation somewhat obscuring view of iris details; 4 = focal or diffuse areas of dense stromal haze obscuring iris detail (Figure 2). Similar to the analyses using densitometry measurements, the change in slitlamp haze was compared with baseline grading and analyzed over time.

To determine whether CXL-associated corneal haze affected clinical outcomes, an analysis was performed to determine whether densitometry-measured absolute corneal haze or change in haze had an association with any of the following parameters: CDVA, mean K value, maximum K value, and thinnest pachymetry. The latter 3 parameters were measured with the Scheimpflug device.

**Statistical Analysis**

The data are presented as the mean density ± SD or the mean slitlamp haze grade ± SD. Analysis was performed using PASW software (version 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 change in haze from baseline. An independent t test was used to compare postoperative haze in the keratoconus subgroup and the ectasia subgroup and in patients who received hypotonic riboflavin intraoperatively and those who did not. Analysis of variance was used to compare the entire cohort and the keratoconus and ectasia subgroups with the corresponding control groups at baseline, 1 month, and 3 months. Pearson correlation coefficients were used to analyze the possible correlation between haze severity and haze change and the clinical outcomes. A P value less than 0.05 was used to determine statistical significance.

**RESULTS**

Fifty eyes of 44 patients had CXL and were followed for 1 year. These eyes were divided into 2 subgroups: keratoconus (n = 31) and post-LASIK ectasia (n = 19). These groups were analyzed together and individually.

The control group comprised 41 eyes (28 keratoconus and 13 ectasia). These eyes were followed for 3 months and analyzed together and within the individual groups. They were also compared at baseline and at the 1- and 3-month follow-up with the patients who received riboflavin–UVA therapy. Table 1 shows the demographics in the treatment group and control group.

**Scheimpflug Densitometry**

**Control** In the control group, the mean densitometry 1 month and 3 months after CXL was unchanged from baseline in all eyes, in the keratoconus subgroup, and in the ectasia subgroup. The preoperative mean densitometry was 14.7 ± 2.04 (Figure 3, upper left). At 1 month, mean densitometry was 14.9 ± 2.44 (P = .62), 14.7 ± 2.28 (P = .75), and 15.3 ± 2.82 (P = .059) in all eyes, in the keratoconus subgroup, and in the ectasia subgroup, respectively. At 3 months, the mean densitometry was 14.4 ± 1.84 (P = .27), 14.3 ± 1.77 (P = .49), and 14.6 ± 2.04 (P = .35), respectively.

**Combined Keratoconus and Ectasia** Table 2 shows the Scheimpflug densitometry measurements in the combined keratoconus and ectasia cohort. There was a significant increase in mean densitometry between baseline and 1 month (P < .001) (Figure 3, upper right). There was no significant change between 1 month and 3 months (change −1.01 ± 4.57; P = .15). Between 3 months and 6 months (change −3.0 ± 4.69; P < .001) and between 6 months and 12 months
Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treated Group</th>
<th>Control Group</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Entire Cohort Ectasia Keratoconus</td>
<td>Entire Cohort Ectasia Keratoconus</td>
</tr>
<tr>
<td>Eyes/patients (n)</td>
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<td>Age (y)</td>
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<tr>
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<td>Mean UDVA ± SD</td>
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<td>Mean CDVA ± SD</td>
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<td>Cylinder (D)</td>
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<td>(Scheimpflug)</td>
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<tr>
<td>Range</td>
<td>320.0 to 571.0</td>
<td>306.0 to 535.0</td>
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</table>

CDVA = corrected distance visual acuity; K = keratometry; UDVA = uncorrected distance visual acuity

(change $-2.43 \pm 3.21; P < .001$), there was a statistically significant decrease in mean densitometry. Although the mean densitometry decreased at 6 months and 12 months, it remained elevated compared with baseline values ($P < .001$).

**Keratoconus** In the keratoconus subgroup, there was a statistically significant increase in mean densitometry between baseline and 1 month ($P < .001$ (Table 2 and Figure 3, lower left). There was no significant change between 1 month and 3 months (change $-1.49 \pm 4.65; P = .08$) or between 3 months and 6 months (change $-1.67 \pm 5.02; P = .07$). There was a statistically significant decrease in mean densitometry between 6 months and 12 months ($-2.24 \pm 3.49; P = .001$). Although the mean densitometry decreased at 6 months and 12 months, it remained elevated compared with baseline values ($P < .001$).

**Ectasia** In the ectasia subgroup, there was a statistically significant increase in mean densitometry between baseline and 1 month ($P < .001$ (Table 2 and Figure 3, lower right). There was no significant change between 1 month and 3 months (change $-0.22 \pm 5.17; P = .86$). Between 3 months and 6 months (change $-5.16 \pm 3.17; P < .001$) and between 6 months and 12 months (change $-2.73 \pm 2.77; P < .001$), there was a statistically significant decrease in mean densitometry. In contrast to the combined group and keratoconus subgroup, there was no significant difference in mean densitometry between 12 months and baseline ($P = .15$).

**Slitlamp Biomicroscopy**

The findings of 1-year slitlamp haze analysis corroborated the results of the Scheimpflug densitometry measurements. Natural history over time followed a similar course and, at 1 year, there was remaining CXL-associated corneal haze in the combined group and the keratoconus subgroup; however, CXL-associated corneal haze had returned to baseline levels in the ectasia group (Figure 4).

**Combined Keratoconus and Ectasia** In the combined group, the mean preoperative slitlamp-graded haze was $0.2 \pm 0.64$ (scale 0 to 4). At 1 month, the haze increased to $1.6 \pm 0.75$ ($P < .001$). Between 1 month and 3 months, there was no significant change (change $-0.10 \pm 0.87; P = .3$). Between 3 months and 6 months (change $-0.4 \pm 0.86; P = .001$) and between 6 months and 12 months (change $-0.5 \pm 0.81; P < .001$), there was a significant decrease in mean slitlamp haze. At 1 year, slitlamp haze remained significantly elevated compared with baseline values (mean $0.6 \pm 0.88; P = .001$).
Keratoconus  In the keratoconus subgroup, the mean preoperative slitlamp haze was 0.3 ± 0.73. At 1 month, the mean haze increased significantly to 1.6 ± 0.76 ($P < .001$) (Figure 4). There was no significant change in mean slitlamp haze between 1 month and 3 months (change 0.0 ± 0.78; $P = 1.0$). Between 3 months and 6 months (change −0.4 ± 0.80; $P = .01$) and between 6 months and 12 months (change −0.5 ± 0.81; $P = .001$), there was a significant decrease in slitlamp haze. At 1 year, slitlamp haze remained significantly elevated compared with baseline values (mean 0.7 ± 0.91; $P = .01$).

Ectasia  In the ectasia subgroup, the preoperative mean slitlamp haze was 0.1 ± 0.46. At 1 month, the mean slitlamp haze increased to 1.6 ± 0.83 ($P < .001$) (Figure 4). There was no significant change between 1 month and 3 months (change −0.3 ± 1.00; $P = .2$). Between 3 months and 6 months (change −0.5 ± 0.96, $P = .04$), there was a significant decrease in slitlamp haze, followed by no significant change between 6 months and 12 months (change −0.4 ± 0.83; $P = .07$). At 1 year, slitlamp haze returned to baseline levels (mean 0.4 ± 0.90; $P = .06$).

Comparison Between Groups

Treatment Versus Control  There were no significant differences between the treatment group and the control group at baseline in mean Scheimpflug densitometry measurements ($P = .99$). However, at 1 month and 3 months, there was a significant difference between the treatment group and the control group in all eyes, in the keratoconus subgroup, and in the ectasia subgroup ($P < .001$).

Keratoconus Versus Ectasia  Between 3 months and 6 months, there was a significant difference in the change in densitometry between the keratoconus subgroup and the ectasia subgroup. During this period, the mean CXL-associated corneal haze measured by densitometry decreased significantly more in the ectasia subgroup (mean change −3.16 ± 3.17) than in the keratoconus subgroup (change −1.67 ± 5.01) ($P = .01$). Changes in densitometry over other time periods were not significant between the 2 subgroups. At 12 months, there was a statistically significant difference in postoperative haze measured by densitometry compared with baseline measurements between the keratoconus subgroup and the ectasia subgroup ($P = .01$). The mean densitometry was 17.5 ± 4.41 and 16.1 ± 2.41, respectively.

Effect of Hypotonic Riboflavin on Haze  There was no significant difference between patients who received hypotonic riboflavin and those who did not in the change in densitometry from baseline to 1 month ($P = .3$), from 1 month to 3 months ($P = .7$), from 3 months to 6 months ($P = .4$), or from 6 months to 12 months ($P = .9$).
Clinical Outcomes Correlations

In the entire cohort, the absolute measurement of CXL-associated corneal haze measured by densitometry at 12 months was significantly correlated with CDVA ($r = -0.71$), the maximum K value ($r = 0.53$), the mean K value ($r = 0.70$), and the thinnest pachymetry ($r = -0.68$). However, the changes in densitometry both between baseline and 1 month and between baseline and 12 months were not correlated with the change in any clinical outcome from baseline to 12 months in any group. These correlation patterns were similar in the keratoconus subgroup and the ectasia subgroup. Table 2 shows the data for all clinical correlations.

DISCUSSION

Collagen crosslinking is a promising new treatment for stabilizing and strengthening the cornea in keratoconus and ectasia. In the clinical setting, a typical corneal haze is noted after CXL in most cases. In the clinical setting, a typical corneal haze is noted after CXL in most cases. Although corneal haze has been described after CXL and its etiology explored in confocal microscopy studies, the natural course of clinical corneal haze after CXL has not been fully elucidated or objectively quantified to date. Therefore, the purpose of this randomized controlled prospective study was to define the natural course of this haze to guide the clinician in his or her expectations when examining a patient at different time points after CXL. To do this, we used densitometry measurements obtained from Scheimpflug imagery as an objective measure of corneal haze. Moreover, to corroborate the clinical relevance of the Scheimpflug densitometry measurements, we performed a similar analysis using slitlamp biomicroscopy grading. Haze after CXL is different in clinical character from haze after other procedures, such as excimer laser photorefractive kerotomy. The former is a dust-like change in the corneal stroma or a midstromal demarcation line, whereas the latter has a more reticulated subepithelial appearance.

Similarly, the mechanisms leading to haze formation may be different and further studies should help to clarify the molecular and cellular changes over time after CXL. To differentiate the unique corneal haze after CXL from haze and scarring after other corneal surgeries and diseases, we refer to it in this paper as CXL-associated corneal haze.

Regarding the occurrence and natural course after CXL, we found a significant postoperative increase in haze measured by both Scheimpflug densitometry and slitlamp assessment. The increase peaked at
1 month (Figure 5, A and B) and plateaued between 1 month and 3 months (Figure 5, C). Between 3 months and 6 months, the cornea began to clear and there was a significant decrease in CXL-associated corneal haze. From 6 months to 1 year postoperatively, there continued to be a decrease in haze measurements (Figure 5, D and E). Although CXL-associated corneal haze persisted above baseline levels at 1 year based on slitlamp grading and Scheimpflug densitometry measurements, a statistically significant finding, the actual change from preoperative measurements was small and its clinical significance requires further study.

Our findings indicated a possible difference in the natural history of CXL-associated corneal haze between the keratoconus subgroup and the ectasia subgroup. Although the maximum CXL-associated corneal haze measured by Scheimpflug densitometry and slitlamp biomicroscopy was similar in the 2 subgroups at 1 month, there was a difference in the rate of clearing of the haze. Between 3 months and 6 months, the decrease in corneal haze was more significant in the ectasia group than in the keratoconus group. A significant decrease in CXL-associated corneal haze was not observed in the keratoconus groups until 6 months, whereas haze decreased after 3 months in the ectasia group. At 12 months, there was a statistically significant difference in postoperative CXL-associated corneal haze compared with baseline measurements when comparing the keratoconus and ectasia groups; haze remained somewhat increased in the keratoconus group and returned to baseline in the ectasia group. These distinctions could suggest actual differences in the pathophysiology of the 2 diseases or simply statistical anomalies resulting from a smaller number of eyes in the ectasia group. Further follow-up is required to determine whether the values fully return to baseline in the keratoconus eyes as well.

To protect the corneal endothelium during CXL, it is suggested that the corneal thickness before UV exposure should be more than 400 μm. Therefore, per the study protocol, if corneal thickness was less than 400 μm on ultrasound pachymetry after the initial 30-minute riboflavin loading, hypotonic riboflavin was used to swell the cornea to the 400 μm limit. We found no difference in CXL-associated corneal haze densitometry measurements between eyes requiring hypotonic riboflavin and those not requiring hypotonic riboflavin.

| Table 2. (Cont.) |
|------------------|------------------|------------------|------------------|------------------|
|                  | 3 Mo Postoperative | 6 Mo Postoperative | 12 Mo Postoperative | P Value, Change from Baseline |
|                  | r Value           | r Value           | r Value           | r Value           |
|                  | With CDVA         | With UDVA         | With CDVA         | With UDVA         | With CDVA         |
|                  | Mean ± SD (95% CI)| Mean ± SD (95% CI)| Mean ± SD (95% CI)| Mean ± SD (95% CI)| To 12 Mo | To 3 Mo |
|                  |                   |                   |                   |                   |          |        |
| 0.48<sup>1</sup> | 19.4 ± 4.8<sup>5</sup> | 0.41<sup>1</sup> | 0.60<sup>1</sup> | 0.55<sup>1</sup> | 0.71<sup>1</sup> | .01 | .001 |
| (18.1 to 20.7)  |                   |                   |                   |                   |          |        |
| 0.61<sup>1</sup> | 19.8 ± 4.8<sup>1</sup> | 0.46<sup>1</sup> | 0.63<sup>1</sup> | 17.5 ± 4.4<sup>1</sup> | 0.58<sup>1</sup> | 0.73<sup>1</sup> | – | .001 |
| (18.0 to 21.5)  |                   |                   |                   | (15.9 to 19.1)   |          |        |
| 0.32            | 18.8 ± 4.1<sup>1</sup> | 0.01            | 0.54<sup>1</sup> | 16.1 ± 2.4<sup>1</sup> | 0.26        | 0.45            | – | .001 |
| (16.8 to 20.7)  |                   |                   |                   | (14.9 to 17.2)   |          |        |

Figure 4. Time course of CXL-associated corneal haze measured by slitlamp biomicroscopy. For comparison, the CXL-associated corneal haze measured by Scheimpflug densitometry is shown.
We found clinical correlations between CXL-associated corneal haze and some outcome parameters. The absolute degree of haze was correlated with poorer UDVA and CDVA, thinner pachymetry, and higher maximum K and mean K values. However, in this analysis, we did not differentiate between patients who had increased densitometry at baseline and those who had increased CXL-associated corneal haze postoperatively. Higher baseline haze likely results from the keratoconus severity per se, and the latter likely will most affect the absolute measurements of clinical outcomes. Therefore, we performed a further analysis to evaluate the correlation between the change in densitometry between baseline and 1 month (the peak change in haze) and baseline and 12 months and the change in clinical outcome measurements at 12 months. Using this methodology, there was no correlation between the change in CXL-associated corneal haze and the change in visual acuity and topographic clinical outcomes in any group. It is noteworthy that the increased stromal haze after CXL observed in confocal microscopy studies did not appear to affect visual acuity outcomes as well. Although increased CXL-associated corneal haze might be thought of as an indication of the efficacy of the CXL action (ie, more CXL-associated corneal haze = greater cross-linking response) or, conversely, as an adverse outcome (ie, more CXL-associated corneal haze causing decreased visual function), the data indicate that CXL-associated corneal haze is not a predictor of patient outcomes, belying both hypotheses. Further study, for instance assessing contrast sensitivity or low-contrast acuity, may help elucidate the clinical sequelae of corneal haze induced by CXL.

Regarding the mechanism of haze formation after CXL, it may be a result of back-scattered and reflected light, which decreases corneal transparency. Transparency of the cornea is a result of the regular spacing and small uniform diameter of the collagen fibrils and the cellular structure of stationary keratocytes. After CXL, the cornea initially thins and then thickens toward baseline over 1 year, a time course which parallels the haze density measurements found in this study. Thus, this supports a hypothesis that concomitant changes in the corneal lamellar array and spacing may lead to an increase in light scatter and a decrease in transparency. Furthermore, Wollsenak et al. report a significant increase in collagen fibril diameter, with increased spacing between collagen fibrils, after CXL. This may also play a role in decreased corneal transparency.

In vitro and ex vivo studies show that CXL leads to an almost immediate loss of keratocytes in the corneal stroma. In a confocal microscopy study, Mazzotta et al. found that in eyes with keratoconus, activated keratocytes repopulated the corneal stroma starting at 2 months and that the repopulation was almost complete at 6 months. It is possible that these activated keratocytes contribute to the development of CXL-associated corneal haze. Moreover, stationary keratocytes have crystallins in their cytoplasm; the crystallins have a refractive index similar to that of the ECM. During wound healing, migratory keratocytes have changes in their crystalline proteins, leading to an increased scattering of light and a possible increase in haze.

Other factors also may contribute to CXL-associated corneal haze. These include stromal swelling pressure changes, proteoglycan–collagen interactions, and glycosaminoglycan hydration. Further study is needed to elucidate the pathophysiology of the development and time course of CXL-associated corneal haze.

Figure 5. Example of CXL-associated corneal haze over time using Scheimpflug imagery. A: Preoperative visit. B: One month postoperatively. C: Three months postoperatively. D: Six months postoperatively. E: One year postoperatively.
Although our study shows an objective measurement of CXL-associated corneal haze over time, the haze measurements have some limitations. Densitometry was measured over a 4.0 mm central image of the cornea and along only 1 meridian. Furthermore, although Scheimpflug densitometry affords a quantitative measurement, its specific correlation to clinical corneal haze remains to be assessed. However, the close approximation of our densitometry findings to our results using slitlamp haze grading suggests that densitometry, indeed, does measure clinical corneal haze.

A further limitation of this study was the short follow-up in the control group. Because the study protocol allowed crossover of control eyes to full CXL treatment after the 3-month follow-up, the control group was followed for only 3 months, compared with the 12-month follow-up in the treated group. However, no significant changes were observed in any of the control groups at any time period.

The study protocol also did not allow deepithelialization of the control group corneas. Because epithelial removal alone could cause haze formation during the healing process, further study using a control group in which the epithelium is removed during the sham procedure may further elucidate the source of the haze response.

In conclusion, this study quantitatively evaluated the natural history of corneal haze after corneal collagen crosslinking. After CXL, the corneas in our study developed haze that peaked between 1 month and 3 months and diminished over time, approaching baseline at 1 year.

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