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

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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.

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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.[1,2] In addition to stabilizing the corneal architecture, results in clinical studies suggest that CXL can have beneficial effects on corneal optics and vision,[3–7] with few reported complications.[8,9] In our previous reports of 1-year CXL outcomes,[10–12] 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.[A,B] 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.[1] 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.[13] This was repeated until adequate corneal thickness was obtained.

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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/cm^2. 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

PATIENT QUESTIONNAIRE

Please grade your experience with each of the following symptoms by checking within the appropriate boxes below, using a scale of 1 through 5 (1 being "none" and 5 being "severe").

Please grade each eye.

RIGHT EYE	None (1)	Mild (2)	Moderate (3)	Marked (4)	Severe (5)
Light Sensitivity					
Difficulty Driving at Night *(If you drive at night)*					
Reading Difficulty *(Requires glasses to read)*					
Double Vision					
Fluctuation in Vision					
Glare *(Scatter from bright light that decreases vision)*					
Halos *(Rings around lights)*					
Starbursts *(Star-shapes around lights)*					
Dryness					
Pain					
Foreign Body Sensation *(Feels like something is in your eye)*					
Other:					

LEFT EYE	None (1)	Mild (2)	Moderate (3)	Marked (4)	Severe (5)
Light Sensitivity					
Difficulty Driving at Night *(If you drive at night)*					
Reading Difficulty *(Requires glasses to read)*					
Double Vision					
Fluctuation in Vision					
Glare *(Scatter from bright light that decreases vision)*					
Halos *(Rings around lights)*					
Starbursts *(Star-shapes around lights)*					
Dryness					
Pain					
Foreign Body Sensation *(Feels like something is in your eye)*					
Other:					

Figure 1. Sample patient questionnaire.

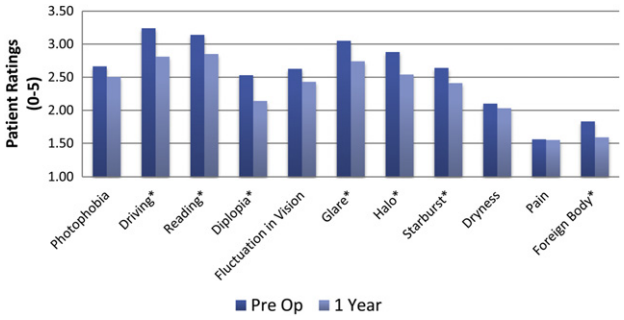

Figure 2. Mean rating of subjective visual parameters preoperatively and 12 months after CXL. An asterisk denotes statistical significance ($P < .05$).

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 ($P = .90$).

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

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

*Statistically significant ($P < .05$)

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 ($P = .05$). 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

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

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

*Statistically significant ($P < .05$)

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

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

*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 crosslinking 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 logMAR ± 0.34 (SD) (20/137) to 0.77 ± 0.37 logMAR (20/117) ($P=.04$), and the mean CDVA improved from 0.35 ± 0.24 logMAR (20/45) to 0.23 ± 0.21 logMAR (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 ± 2.33 μm, 4.40 ± 2.32 μm, 4.36 ± 2.30 μm, and 4.04 ± 2.27 μm, respectively. At 1 year, these anterior corneal HOAs significantly decreased to 4.27 ± 2.25 μm, 4.01 ± 2.29 μm, 3.96 ± 2.27 μm, and 3.66 ± 2.22 μm, 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 ± 1.0 μm, 2.60 ± 1.03 μm, 2.57 ± 1.03 μm, and 0.98 ± 0.46 μm, respectively. At 1 year, these ocular HOAs significantly decreased to 2.59 ± 1.06 μm, 2.42 ± 1.07 μm, 2.39 ± 1.07 μm, and 0.88 ± 0.49 μm, 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 ± 1.93 (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 continued to improve but had not completely returned to baseline (mean 17.0 ± 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 ± 52.9 μm. 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 ± 28.7 μm, $P<.001$) and from 1 to 3 months (mean change = −7.2 ± 20.1 μm, $P=.002$), followed by a recovery of the corneal thickness between 3 months and 6 months (mean change = +20.5 ± 20.4 μm, $P<.001$). At 1 year, corneal thickness remained slightly decreased from baseline to 12 months (mean change −6.6 ± 22.4 μm, $P=.01$).

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 measures 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

1. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135:620–627
2. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. J Cataract Refract Surg 2007; 33:2035–2040
3. Vinciguerra P, Albè E, Trazza S, Rosetta P, Vinciguerra R, Seiler T, Epstein D. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. Ophthalmology 2009; 116:369–378
4. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg 2008; 34:796–801
5. Grewal DS, Brar GS, Jain R, Sood V, Singla M, Grewal SPS. Corneal collagen crosslinking using riboflavin and ultraviolet-A light for keratoconus: one-year analysis using Scheimpflug imaging. J Cataract Refract Surg 2009; 35:425–432
6. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet A corneal collagen cross-linking for keratoconus in Italy: the Siena Eye Cross Study. Am J Ophthalmol 2010; 149:585–593
7. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen; preliminary refractive results in an Italian study. J Cataract Refract Surg 2006; 32:837–845
8. Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA-riboflavin cross-linking of the cornea. Cornea 2007; 26:385–389
9. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009; 35:1358–1362
10. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one year results. J Cataract Refract Surg 2011; 37:149–160. Available at: http://www.vision-institute.com/UserFiles/File/CXL%20results%20published2011.pdf. Accessed December 16, 2011
11. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg 2011; 37:1282–1290
12. Greenstein SA, Fry KL, Hersh MJ, Hersh PS. Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. J Cataract Refract Surg 2012; 38:292–302
13. Hafezi F, Mrochen M, Iseli HP, Seiler T. Collagen crosslinking with ultraviolet-A and hypoosmolar riboflavin solution in thin corneas. J Cataract Refract Surg 2009; 35:621–624
14. Greenstein SA, Fry KL, Bhatt J, Hersh PS. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refract Surg 2010; 36:2105–2114
15. Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg 2011; 37:691–700
16. Greenstein SA, Fry KL, Hersh PS. In vivo biomechanical changes after corneal collagen crosslinking for keratoconus and corneal ectasia: 1-year analysis of a randomized, controlled, clinical trial. Cornea 2012; 31:21–25

OTHER CITED MATERIAL

A. National Institutes of Health Clinical Trials. Corneal Collagen Cross-linking for Progressive Keratoconus (CXL) NCT00647699. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00647699. Accessed December 16, 2011
B. National Institutes of Health Clinical Trials. Corneal Collagen Cross-linking for Ectasia (CXL) NCT00674661. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00674661. Accessed December 16, 2011