DOI: 10.14744/eer.2022.08370
Eur Eye Res 2022;2(4):147–152

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

Visual and refractive effects of collagen cross-linking in keratoconus

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Abstract

Purpose: Evaluation of visual and refractive effects of collagen cross-linking (CXL) in progressive keratoconus (KCN).

Methods: A total of 95 eyes of 77 patients were retrospectively analyzed. The changes in uncorrected and corrected distance visual acuities (UDVA and CDVA, respectively); spherical or cylindrical refraction and spherical equivalent of refractive error (SPH, CYL, and SE, respectively); central corneal thickness (CCT); and mean keratometry values (K) in the Scheimpflug corneal tomography (Pentacam, Oculus®, Germany) were evaluated at the 1st, 3rd, and 6th post-operative months and the past visit, as compared to pre-operative values.

Results: During follow-up, there was a progressive improvement in the mean UDVA and CDVA. Significant improvement was seen in CDVA at the 3rd month (from 0.51±0.23 to 0.59±0.22), in UDVA at the 6th month (from 0.34±0.24 to 0.44±0.25), and in SPH and SE values at the last control (from −2.75±3.50D to −1.92±2.52D for SPH; from −3.51±4.45D to −3.07±3.05D for SE). The mean CCT decreased in the post-operative 1st month and gradually increased in the 3rd and 6th months (from 466.87±63.94 µm to 449.76±50.09 µm, 443.92±42.44 µm, and 454.30±46.86 µm for 1st, 3rd, and 6th months, respectively); almost returned to pre-operative values. There was no significant change in mean CYL and K values throughout the follow-up (from −2.40±2.11D to −2.45±1.77D for CYL; from 46.89±3.66D to 47.35±5.04D for K).

Conclusion: CXL seems to not only slow down the progression of KCN but also improve the visual acuity, which may be a result of ultrastructural changes that occur in the corneal stroma postoperatively, rather than a simple corneal flattening effect.

Keywords: Collagen cross-linking; cornea; corneal tomography; keratoconus.

Collagen cross-linking (CXL) is a revolutionary treatment method for keratoconus (KCN) that has been shown to halt or slow down disease progression. Increasing number of patients undergoing CXL resulted in decreased number of eyes proceeding to corneal graft surgery and associated life-time risks.[1] Preserving satisfactory vision with patients' own corneas also decreased the need for hardly available transplant-tissue, as well as hospital and treatment costs. In a recent study, CXL was found to be associated with a lifetime cost-savings of $43,759 per patient.[2]

Most of the studies published on CXL focused on its efficiency in halting disease progression, preventing visual decline, and delaying or reducing the need for corneal transplantation.[3,4] However, in clinical practice, it is not rare to observe patients with increased vision after CXL treatment. Recent studies emphasized evidence of im-

Cite this article as: Koksaldi S, Utine CA, Kayabasi M, Ozbek Z. Visual and refractive effects of collagen cross-linking in keratoconus. Eur Eye Res 2022;2:147-152.

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Submitted Date: 02.09.2022 **Revised Date:** 20.11.2022 **Accepted Date:** 29.11.2022

proved visual acuity, keratometry readings, and other definable measures of corneal topography regularity.[5–13]

In this study, we retrospectively evaluated the visual and refractive outcomes of CXL that had been performed with the intention to halt progression in KCN. We analyzed the visual and refractive changes following CXL surgery.

Materials and Methods

Retrospective review of the cohort of patients who underwent CXL for progressive KCN at the Cornea Division, Department of Ophthalmology, Dokuz Eylul University, between 2016 and 2020. The study adhered to the Tenets of the Declaration of Helsinki. Dokuz Eylul University Ethical Committee approval was obtained for this research (2021/08-11).

Patients who were diagnosed clinically with KCN, who had clinical evidence of progression (i.e., increase in maximum keratometric value of at least 1.0 D/year, decrease in best corrected visual acuity, and need for two or more contact lens examinations within a year) and central corneal thickness (CCT) ≥450 µm were recommended standard epithelium-off CXL surgery. All of the patients which aged between 12 and 37 years included in this study, had at least one of these clinical evidences of progression. Exclusion criteria included pregnancy, lactation, scarring of the apical cornea, previous corneal surgery, thinnest corneal thickness <450 µm, and having any sort of connective tissue disease.

Every participant underwent a detailed ophthalmological examination preoperatively including measurement of uncorrected and corrected distance visual acuities (UDVA and CDVA, respectively), manifest spherical (SPH), cylindrical (CYL) and spherical equivalent (SE) of refraction, simulated mean keratometry (K) and CCT readings by Scheimpflug tomography (Pentacam, Oculus®, Germany), and slit-lamp and fundus examination. All examinations were repeated at post-operative 1st, 3rd, and 6th months and at the last follow-up. Last follow-up ranged 7–45 months postoperatively.

Surgical Procedure

All participants underwent CXL procedure with an accelerated protocol for 10 min and were operated by two experienced corneal surgeons (CAU and ZÖ). A central, 8.5 mm-diameter corneal epithelial debridement, was performed mechanically with a blunt hockey knife under topical anesthesia (proparacaine hydrochloride; Alcaine, Alcon). 0.1% riboflavin solution (Riboflavin, Ricrolin, Peschke Meditrade, Germany) was instilled every 2 min for a total 20 min. Then, 365 nm ultraviolet-A (UVA) light was applied for 10 min at an irradiance of 9 mW/cm^2, delivering a total dose of energy of 5.4 J/cm^2. While the eyes were exposed to UVA, riboflavin instillation was continued every 2 minutes. At the end of the procedure, a therapeutic contact lens was placed. Post-operative regimen included topical antibiotic (ofloxacin; Exocin, Allergan Inc.) and steroid (fluorometholone; FML, Allergan Inc.) drops 4 times daily; in addition to preservative-free artificial tears frequently (0.15% sodium hyaluronate; EyeStil, SIFI S.P.A.). The contact lens was removed on the 5th post-operative day and topical antibiotics were stopped when corneal epithelialization was completed. Topical steroids were tapered off in 3 weeks, and artificial tears were continued as per needed.

Statistical Analysis

Statistical analysis of the data was performed by one of the authors (CAU) using Microsoft Excel 2016 (Microsoft Corporation, Redmond, Washington, United States). The values were expressed as mean±standard deviation and a paired sample Student's t-test was used to analyze changes induced by the surgery. P values <0.05 were considered statistically significant.

Results

The records of 95 eyes of 77 patients (20 females and 57 males) were analyzed. Mean age was 21.10±5.46 years (Range: 12–37). Patients were followed up for an average of 17.72±11.90 months (Range: 7–45), postoperatively. Pre-operative and post-operative visual, refractive, and tomographic parameters are displayed in Table 1.

We detected a decrease in mean pre-operative manifest SE −3.51±4.45D to post-operative −3.07±3.05D that accompanied an increase in UDVA (pre-operative 0.34±0.24

Table 1. Pre-operative and post-operative visual, refractive, and topographic parameters

	Pre-operative	Post-operative last control	P-value
Mean UDVA	0.34±0.24	0.44±0.26	<0.05*
Mean CDVA	0.51±0.23	0.65±0.25	<0.05*
Mean SPH (D)	−2.75±3.50	−1.92±2.52	<0.05*
Mean CYL (D)	−2.40±2.11	−2.45±1.77	>0.05
Mean SE (D)	−3.51±4.45	−3.07±3.05	<0.05*
Mean K (D)	46.89±3.66	47.35±5.04	>0.05
Mean CCT (µ)	466.87±63.94	465.61±41.79	>0.05

UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; SPH: Spherical refractive error; D: Diopters; CYL: Cylindrical refractive error; SE: Spherical equivalent; K: Keratometry value; CCT: Central corneal thickness. *P significant at the value <0.05.

and post-operative 0.44±0.26) and CDVA (pre-operative 0.51±0.23 and post-operative 0.65±0.25) ($p<0.05$ for all). Interestingly, these improvements in visual acuities and refraction were not accompanied by any significant flattening effect at mean K values (pre-operative 46.89±3.66 D and post-operative 47.35±5.04 D) ($p>0.05$).

At the last control, there was an increase in mean UDVA, CDVA, and a decrease in mean SPH and SE values compared to the pre-operative period ($p<0.05$ for all) (Fig. 1–4). Significant improvement was detected in CDVA at the 3rd month, in UDVA at the 6th month, and in SPH and SE values at the last control.

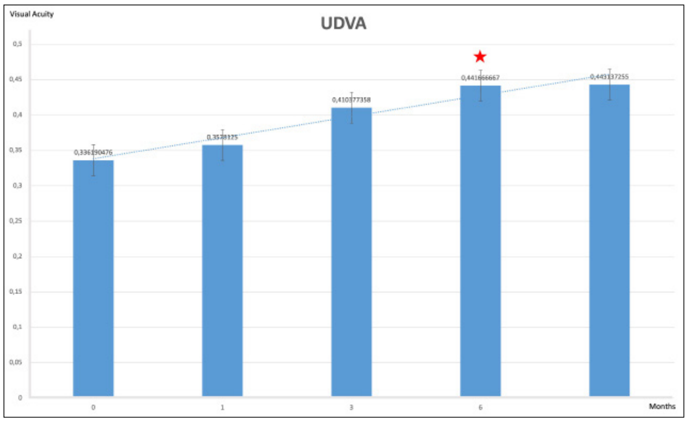

Fig. 1. Change in uncorrected distance visual acuity at pre-operative, post-operative 1st, 3rd, and 6th months, and last control. Statistically significant values are shown as asterisks.

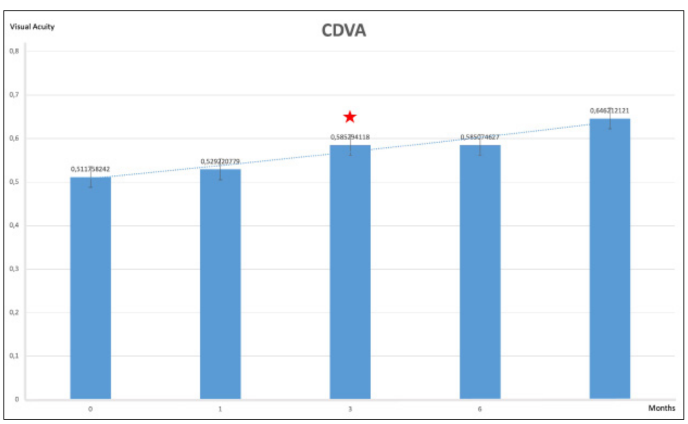

Fig. 2. Change in corrected distance visual acuity at pre-operative, post-operative 1st, 3rd, and 6th months, and last control. Statistically significant values are shown as asterisks.

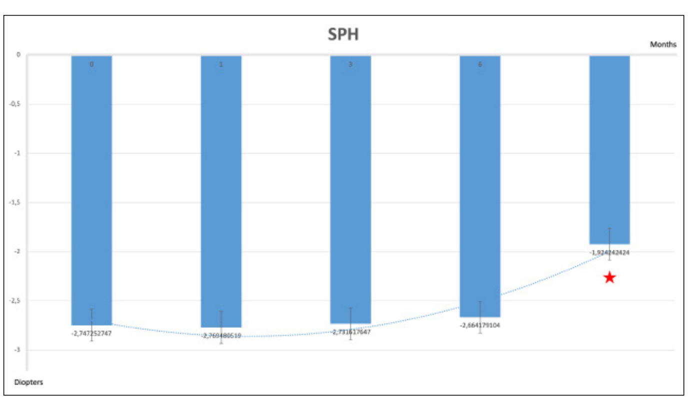

Fig. 3. Change in spherical refraction error in at pre-operative, post-operative 1st, 3rd, and 6th months, and last control. Statistically significant values are shown as asterisks.

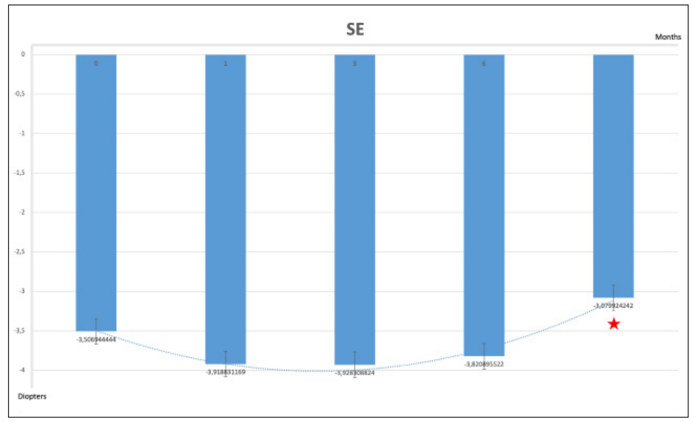

Fig. 4. Change in spherical equivalent of refraction error in at pre-operative, post-operative 1st, 3rd, and 6th months, and last control. Statistically significant values are shown as asterisks.

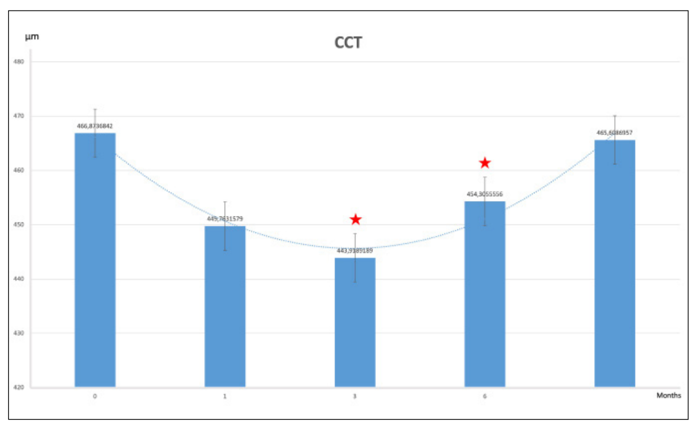

Fig. 5. Change in central corneal thickness at pre-operative, post-operative 1st, 3rd, and 6th months, and last control. Statistically significant values are shown as asterisks.

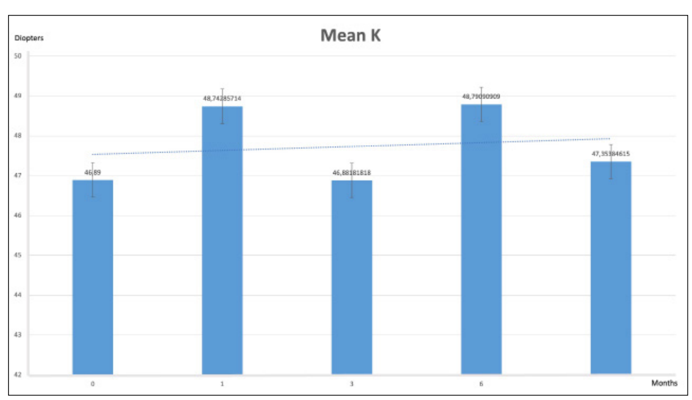

Fig. 6. Change in mean keratometry values (K) at pre-operative, post-operative 1st, 3rd, and 6th months, and last control. None of the changes were statistically significant.

No significant change was detected in mean CYL, K, or CCT values (p>0.05). CCT showed a decrease in 1st month followed by a gradual increase in 3rd and 6th months close to pre-operative values (Fig. 5). Interestingly, mean K reading was not significantly different from pre-operative value, in any visit (Fig. 6). Yet, UDVA and CDVA improved with a decrease in manifest SE of refraction in the last follow-up compared to the pre-operative visit (Fig. 4) (p<0.05).

Discussion

Cross-linking was initially described to increase the biomechanical strength of ectatic corneas.[14] Its clinical use has been accepted worldwide to halt or slow down disease progression, combined with other means to achieve visual improvement. It revolutionized the management of KCN and other corneal ectasias by successfully preventing disease progression and delaying or reducing the need for penetrating keratoplasty (PK), as proven in many clinical studies.[3,4,15] Cross-linking has also been used to manage other conditions such as infectious ulcers and bullous keratopathy due to the benefits of ultrastructural changes in the corneal stroma after the procedure.[3,16]

Cross-linking treatment is most often applied in younger patients. Young age is associated with more severe forms of KCN and faster progression. Objective criterias used in deciding whether there is progression in KCN patients are as

Table 2. Key findings of the previous studies about CXL treatment in KCN patients

Author [References]	Follow-up (months)	Study design	Number of eyes	Key findings
Sedaghat et al.[5]	12	Prospective	97	At 1-year-follow-up, UDVA improved from 0.31 to 0.45, CDVA changed from 0.78 to 0.84 (p<0.001), mean of average keratometry value decreased from 49.62 to 47.95 D (p<0.001).
Greenstein et al.[6]	12	Prospective	71	One year postoperatively, the index of surface variance was significantly decreased from baseline (mean change−10.5±18.2; p<0.001); the index of vertical asymmetry was significantly decreased from baseline (mean change −0.11±0.23; p<0.001); the keratoconus index was significantly decreased over baseline (mean change −0.04±0.08; p<0.001).
Uysal et al.[7]	12	Retrospective	111	Significant improvement in mean UDVA (p<0.001), CDVA (p<0.001).
Badawi et al.[8]	12	Retrospective	136	Significant improvement in post-operative CDVA and mean K_{max} (p≤0 001 and 0.032, respectively).
Aixinjueluo et al.[9]	12	Prospective	30	Significant decrease in Kmax (p<0.0001), AveK (p=0.003) and TCT (p=0.002), and a significant improvement in CDVA (p=0.001).
Grišević et al.[10]	12	Prospective	34	Pre-operative UDVA was 0.26±0.18, while in 3 months of post-operative period it increased to 0.32±0.18. After 6 months the difference in values was statistically significant, 0.36±0.18 (p=0.002). After 12 months the difference in values was statistically much higher and significant, 0.42±0.22 (p<0.001).
Soeters et al.[11]	28	Cohort	119	One year after CXL, corrected distance visual acuity improved in all age groups, with the highest improvement in pediatric eyes (−0.23±0.40 logMAR, p=0.044).
Godefrooij et al.[12]	22	Prospective cohort	112	Lower pretreatment CDVA was found to be the sole independent factor predicting an improvement in CDVA 1 year after CXL (p<0.01).
Derakhshan et al.[13]	6	Prospective	31	Postoperatively, UDVA increased by 2 Snellen lines and CDVA improved by 1.7 Snellen lines (p<0.001). Spherical equivalent of refractive error decreased by 0.55D, maximum and mean K values decreased by 0.65 D and 0.51 D, respectively (p<0.05 for all comparisons). Evidence of regression was present in 71% of treated eyes.

AveK: Average keratometry; CDVA: Corrected distance visual acuity; CXL: Corneal cross-linking; D: Diopters; K: Keratometry; KCN: Keratoconus; K_{max}: Maximum keratometry; TCT: Thinnest corneal thickness; UDVA: Uncorrected distance visual acuity.

follows: increase of 1.0 D or more in the steepest K reading within 1 year; if previous K was not available, an increase of 0.5 D or more in manifest SE or an increase of 1.0 D or more in astigmatism in manifest CYL; decreased CCT more than 5% in 6 months; and loss of more than 2 lines of CDVA in 1 year[1,4,5] All of the patients included in this study had one or more criteria's among these and had underwent CXL treatment.

Cross-linking aims to make the collagen network firm enough to display significant changes in biomechanical, thermomechanical, and morphological parameters that stabilize the ectatic cornea.[4,5] A number of preclinical and clinical studies proved that CXL increases corneal stiffness by up to 328.9%.[17] Furthermore, recent studies demonstrated beneficial visual and corneal topographical effects of CXL,[7] including anatomical flattening of the cornea that improved vision.[5] Other studies also showed that CXL improves visual acuity, average K values, and other definable measures of corneal topographic regularity (Table 2).[5–13]

Global consensus of KCN and ectatic diseases published in 2015 reported that 83.3% of ophthalmologists are performing CXL as a treatment modality for KCN. Furthermore, those who do not currently have access to this technique are willing to use this procedure once it becomes available.[18] Other management options for KCN, such as rigid gas permeable lenses and PK which improve visual acuity, do not have any proven influence on disease progression.[10] However, CXL is the only management which promises to prevent disease progression and also improves vision, as demonstrated in recent clinical studies.[5–13] The mechanism of improved vision in KCN eyes after CXL is not clear, yet. Significant flattening of the cornea is commonly believed to be the cause of a decreased refractive error and improved vision. Hence, simultaneous keratorefractive surgery and CXL in thin corneas (such as in LASIK Extra) have not gained wide acceptance, with the fear of a shift in target refraction.[19] Besides, decreased corneal steepness, decreased refractive error and corneal astigmatism, as well as improvement in other definable topographic indices may be the underlying mechanisms in improvement of vision.[13]

Unlike many clinical studies, Grišević et al.[10] also reported no significant change in K values, 3 and 6 months after CXL. We propose that this improvement in vision might also be a result of intrastromal organization at molecular level, such as structural regularity and distribution of collagen.[20,21] Collagen network reorganization together with keratocyte repopulation within the stroma might take a role in this steady and progressive improvement in the visual acuity in post-operative 6 months. In addition, decreased manifest refractive error might be a result of decreased accommodative efforts due to better vision quality. Since cycloplegic refraction or contrast sensitivity was not performed, this is only hypothetical in the absence of any significant change in corneal steepness data. Both of these hypotheses warrant further investigation.

In addition, mean CCT in this study decreased in the 1st post-operative month and gradually increased in the 3rd and 6th months, and returned to pre-operative levels at the last visit. The reason of corneal thinning after CXL might be the anatomical and structural variations in the corneal collagen, keratocyte apoptosis, or rearrangement of the collagen lamellae which reorganize as thick bundles.[22,23] In the literature, there are studies that found permanent significant reduction in mean CCT postoperatively; as well as others that report a return to pre-operative CCT values similar to our findings, which was explained by post-operative epithelial hyperplasia.[24,25]

Limitations of this study include a small sample of patients and not having confocal microscopy examinations that could explain the ultrastructural changes at the stromal level after CXL, as well as cycloplegic refraction of the patients. However, this study highlights the unexpectedly great amounts of visual improvement along with decrease in refractive errors.

Conclusion

This study has demonstrated that patients who had CXL surgery for progressive KCN experienced not only prevention of disease progression but also improvement of refractive parameters, along with better visual outcomes. A significant decrease in manifest SPH and SE refractive errors and a significant increase in UDVA and CDVA were observed. Surprisingly, mean keratometric findings were not changed significantly, but corneal thickness decreased significantly in the 1st post-operative months that returned to pre-operative values in follow-up visits after 6 months. The increase in visual acuities may be a result of ultra-structural changes at the molecular level in corneal stroma after CXL; and decreased manifest refractive error might be a result of less accommodation due to relieved vision. Future studies with larger sample size and confocal microscopic examinations together with visual and cycloplegic refractive measurements are warranted to elucidate these hypotheses.

Ethics Committee Approval: This study was approved by Dokuz Eylul University Non-interventional Clinical Research Ethics Committee (date: 12.04.2021; number: 2021/12-42).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: C.A.U.; Design: S.K., C.A.U.; Supervision: C.A.U., Z.O.; Resource: C.A.U.; Materials: C.A.U., Z.O.; Data Collection and/or Processing: S.K., M.K.; Analysis and/or Interpretation: C.A.U., Z.O.; Literature Search: S.K., M.K.; Writing: S.K., M.K.; Critical Reviews: C.A.U., Z.O.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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