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· Brief Report ·

# Long term efficacy and stability of corneal collagen cross linking for post-LASIK ectasia: an average of 80mo follow-up

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## Abstract
● **This study was designed to evaluate efficacy and stability of corneal collagen crosslinking (CXL) in halting the progression of post-laser *in situ* keratomileusis (LASIK) ectasia and provide long-term follow-up results with an average of 80mo. Patients with post-LASIK ectasia were treated with CXL between December 2007 and January 2012. Main outcome measures were uncorrected distance visual acuities (UDVA) and corrected distance visual acuities (CDVA), minimum and maximum keratometry (K) values, spherical and cylindrical refraction, and corneal thickness. The study evaluated 17 eyes for 13 patients (8 men, 5 women) with mean age of 31y (range 23 to 39) and mean follow-up of 80.7±15 (range 57 to 102)mo. UDVA and CDVA improved from logMAR 0.53±0.36 (20/63) to 0.49±0.4 (20/50) (*P*=0.43) and from 0.18±0.17 (20/28) to 0.16±0.16 (20/27) (*P*=0.55) respectively. In 15 eyes UDVA and in 13 eyes CDVA either remained stable or improved ≥1 Snellen lines (88.2%) and (76.5%) respectively. Although statistically insignificant, spherical and cylindrical refraction decreased post-CXL from -1.26±2.87 to -0.38±2.32 diopters (D) (*P*=0.054) and from -3.80±2.47 to -3.04±2.18 D (*P*=0.13) respectively. Kmax significantly decreased from 44.23±3.76 to 42.85±3.08 D (*P*=0.013) and Kmin decreased from 41.07±3.61 to 40.00±2.65 D (*P*=0.057). Corneal thickness decreased from 470±42 to 460±41 μm, but was statistically non-significant (*P*=0.063). Therefore, CXL is effective in halting and partially reversing the progression of post-LASIK ectasia on the long-term (mean follow-up of more than 80mo), thus highlighting the stability and maintained effect of CXL for such cases.**
● **KEYWORDS:** post-LASIK; ectasia; post-LASIK ectasia; corneal collagen cross linking

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## INTRODUCTION
Post-laser *in-situ* keratomileusis (LASIK) corneal ectasia, is one of the most serious complications of refractive surgery. Since the initial identification of post-LASIK ectasia by Seiler *et al*[1-2] in 1998, studies have attempted to identify predisposing factors for the development of this condition[3-5]. Others focused on the histopathologic and immunohistochemical features of the post-LASIK ectatic corneas[6].

Induction of corneal collagen cross-linking (CXL) using Riboflavin and an ultraviolet-A light (UVA) was first described by Spoerl *et al*[7]. In 2003 it was described by Wollensak *et al*[8] as a new way for stopping the progression of keratectasia in patients with keratoconus, and in 2005 as a potential intervention to halt the progression of post-LASIK ectasia by Kohlhaas *et al*[9].

While this approach has shown positive results for halting or reversing the effects of post-LASIK ectasia in the literature[10-12], most of these studies have a relatively short follow-up period, the longest among them was with an average of 42mo done by Yildirim *et al*[12]. The aim of this study is to provide long-term follow-up results (with an average of 80mo) of CXL done for post-LASIK ectasia which could be the longest in the literature.

## SUBJECTS AND METHODS
**Ethical Approval** All patients provided informed verbal consent. The study adhered to the Declaration of Helsinki and the Institution's Research Development Committee have granted ethical approval.

This retrospective study was carried out at Sharif Eye Centers-Amman, Jordan to assess the long-term efficacy of CXL in halting the progression of post-LASIK corneal ectasia. Evaluated 17 eyes for 13 patients (8 males, 5 females) of whom 4 patients had bilateral treatment on separate occasions. Mean patient age at the time of the procedure was 31 (range

**Table 1 Results of post-CXL compared to pre-CXL values for all parameters** mean±SD

| Parameters | UDVA (logMAR) | CDVA (logMAR) | Kmax (D) | Kmin (D) | Spherical refraction (D) | Cylindrical refraction (D) | Corneal thickness (μm) |
|---|---|---|---|---|---|---|---|
| Pre-CXL values | 0.53±0.36 | 0.18±0.17 | 44.23±3.76 | 41.07±3.61 | -1.26±2.87 | -3.80±2.47 | 470±42 |
| Post-CXL values | 0.49±0.4 | 0.16±0.16 | 42.85±3.08 | 40.00±2.65 | -0.38±2.32 | -3.04±2.18 | 460±41 |
| *P* (paired *t*-test) | 0.43 | 0.55 | 0.013 | 0.057 | 0.054 | 0.13 | 0.063 |

CXL: Corneal collagen cross linking; UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; Kmin: Minimum keratometry; Kmax: Maximum keratometry.

23 to 39)y. Mean follow-up was 80.7±15 (range 57 to 102) mo. All LASIK operations were carried out at the high-volume specialised eye center where a total of 16 800 eyes undergone LASIK operations within a 7-year period.

Post-LASIK ectasia was diagnosed in patients who had topographic evidence of corneal ectasia and steepening, progressive corneal thinning, increase in myopia and astigmatism, decrease in their uncorrected distance visual acuities (UDVA) and corrected distance visual acuities (CDVA) during several consecutive post-operative follow-ups.

Exclusion criteria included corneal thickness less than 400 μm, maximum K kmaxvalue more than 58 diopters (D), herpetic keratitis, pregnant or lactating patient and other ocular surgeries.

**Examination and Study Measurements** All patients had complete ophthalmic examination pre and post-CXL. This included UDVA, CDVA, slit lamp biomicroscopy, fundus examination, corneal topography by TMS-4 (Placido cone, Tomey, USA) and Pentacam (Scheimpflug images, Oculyzer, Wavelight, Alcon, USA), Ocular Response Analyzer (ORA, Reichert, USA), corneal ultrasound pachymetry (Tomey, USA); K values were obtained from Pentacam. Pachymetry was obtained from corneal ultrasound pachymetry.

**Surgical Technique** All cases were carried out under topical anesthesia and complete sterile field using. The eye was first prepared by applying topical anesthetic eye drops, followed by a few drops of povidone-iodine. The epithelium was then mechanically removed without using alcohol, debridement was performed beginning from the hinge proceeding away in order to minimize the chances of moving or wrinkling the flap and was made over an 8 mm zone.

Riboflavin 0.1% with 20% dextran was used to saturate the cornea as a photosensitizer and was instilled every 3min for 30min. Once the cornea was saturated, corneal pachymetry was carried out to assess corneal thickness as greater than 400 μm is required before applying UVA light source. In cases where thickness was found to be less than 400 μm; hypotonic riboflavin was instilled to induce corneal swelling and pachymetry was performed again to evaluate corneal thickness to ensure a 400 μm thickness is achieved before ultraviolet application.

UVA (365 nm, 3 mW/cm², 5.4 J/cm$^2$, UV-X$^{TM}$ system, IROC AG) was applied for a duration of 30min. Riboflavin eye drops were administered regularly every 5min to maintain corneal saturation. At the end of the procedure, the cornea was rinsed with balanced salt solution, topical antibiotic and topical NSAIDs eye drops were instilled and a bandage contact lens applied. Patients were kept on these eye drops until contact lenses were removed. At the third post-operative day, corneas were checked for epithelial healing, once complete; contact lenses were removed. Patients were then started on topical steroid eye drops that were tapered over 4wk.

**Main Outcomes Measures and Follow-up** Main outcome measures were UDVA, CDVA, minimum K (kmin) and kmax values, spherical and cylindrical refraction, and corneal thickness. These measures were taken at the last follow-up visit and compared to the same tests done prior to CXL.

**Statistical Analysis** Statistical analysis was done using the SPSS Windows software (version 16.0, USA). Parameters were analyzed using the paired *t*-test. Comparison between post-operative and pre-operative data was done for all parameters and a difference of a *P* value less than 0.05 was considered to be statistically significant. Each eye was individually analyzed as each eye was operated on at separate occasions.

## RESULTS

UDVA and CDVA: post-operative UDVA compared to pre-operative UDVA showed that 15 eyes either remained stable or improved 1 or more Snellen lines (88.2%), 2 eyes lost 1 or more lines (11.8%). Post-operative CDVA compared to pre-operative CDVA showed that 13 eyes either remained stable or improved 1 or more Snellen lines (76.5%), 4 eyes lost 1 or more lines (23.5%) as seen in Figure 1. Although post-CXL UDVA and CDVA improved compared to pre-CXL values, this improvement was not statistically significant (Table 1).

Regarding Kmax and Kmin: both post-operative Kmax and Kmin compared to pre-operative values showed that 16 eyes either remained stable or decreased (improved) by 1 D or more (94.1%), one eye had an increase by 1 D or more (5.9%) as seen in Figure 2.

Statistical significance was seen for the improvement of Kmax values (*P*=0.013), but not for the improvement of the Kmin values (*P*=0.057).

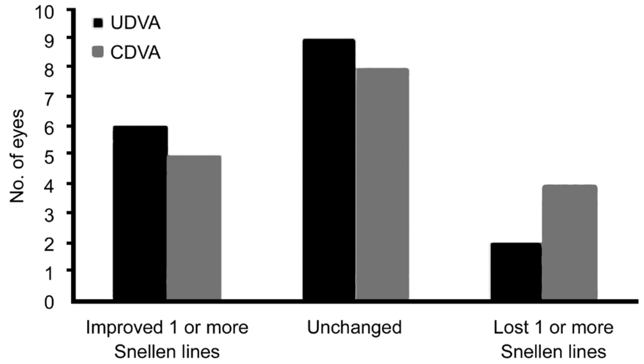


**Figure 1 Postoperative compared to preoperative change in UDVA and CDVA.**

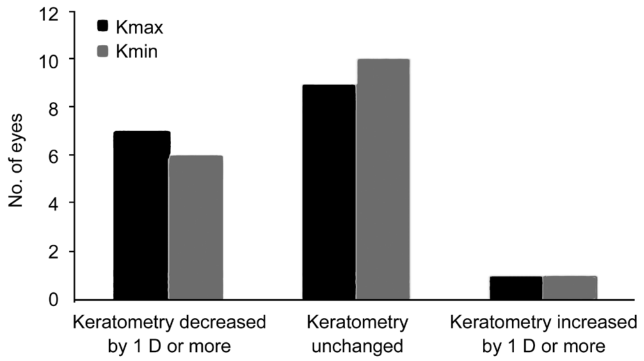


**Figure 2 Postoperative compared to preoperative change in keratometry** Kmax: Maximum keratometry; Kmin: Minimum keratometry.

Although not statistically significant, both the spherical and cylindrical refraction has decreased post-CXL when compared to pre-CXL refraction. Corneal thickness was noted to decrease after CXL, the drop-in thickness was not statistically significant.

## DISCUSSION

Prior to the Era of CXL, post-LASIK ectasia cases were managed by intraocular pressure reduction, rigid gas permeable contact lenses, intrastromal corneal ring segment insertion and corneal grafts[13]. None of these methods addressed the underlying pathology in order to halt the progression of ectasia. It was until CXL introduced by Wollensak *et al*[8] as a method for the treatment of keratoconus by preventing the progression of the disease and by Kohlhaas *et al*[9] for post-LASIK ectasia. Several studies later reviewed the use of CXL in strengthening the unstable cornea in both keratoconus and post-LASIK ectasia[14-16].

A study by Hersh *et al*[17] compared the effects of CXL on keratoconus group with the post-LASIK ectasia group and found that the type of ectasia was not a significant factor in predicting the visual outcome after CXL. They also showed that UDVA, CDVA, Kmax and average K values all improved. However, keratoconus patients had more improvement in topographic measurements than patients with post-LASIK ectasia. Another study by Yam and Cheng[18] showed that the change in CDVA at 1y was comparable for the keratoconus and post-LASIK ectasia cases after CXL. It is outside the scope of our study to compare the effect of CXL in keratoconus cases and post-LASIK ectasia cases and is limited to the effect of CXL in post-LASIK ectasia.

The aim of this study is to provide long-term follow-up results regarding the efficacy and stability of CXL for post-LASIK ectasia. Our results would, in part, agree with the results of previous short-term follow-up studies describing the use of CXL for post-LASIK ectasia[11-12,19]. Although both UDVA and CDVA improved in our study, this was not statistically significant as shown by Yildirim *et al*[12], Li *et al*[11], and Richoz *et al*[19]. The improvement seen in both spherical and cylindrical refraction was not statistically significant either, while the cylindrical refraction was significant in Yildirim *et al*'s study[12]. Improvement in Kmax values was statistically significant in this study and similar to results found by others[11-12,19]. The difference levels of statistical significance observed between studies may be related to the small sample sizes used.

The main aim of the procedure is to halt the progression of the ectatic cornea. Concordant with the findings of others[11-12,17-19], the UDVA and CDVA, refractive and the topographic parameters all improved. While some of our results did not attain statistical significance, the observed improvements remain clinically meaningful.

Corneal thickness changes has been noted to vary among studies post CXL; some increasing in a significant way post-operatively[11] and some not significantly decreasing such as in our study and others[12]. However, since corneal thickness was measured by ultrasound pachymetry in all of these studies, changes could not be explained. These differences could be explained by changes in the refractive index between crosslinked anterior and non-crosslinked posterior stroma as marked by stromal demarcation line[20] if different methods were used to measure the corneal thickness.

Greenstein *et al*[21] assessed corneal thickness changes after CXL for keratoconus and corneal ectasia using Scheimpflug images (Pentacam) over one year. At one year follow-up, pachymetry measures were found to be slightly elevated compared to the pre-operative findings. In keratoconus patients it was found to be slightly below pre-operative measures[21].

The changes in ORA parameters were not significant. Corneal hysteresis (CH) changed from 7.27±1.14 pre-operatively to 7.24±1.07 post operatively ($P$=0.92), while corneal resistant factor (CRF) changed from 5.98±1.22 to 5.66±1.35 ($P$=0.38). According to previous published studies[22-26], no significant changes pre- and post-corneal cross linking in CH and corneal resistance factor were found. Posterior corneal elevation value increased from 45.43±28.11 to 56.64±34.30, however this increase was not clinically significant (*P*=0.13). Unlike the other outcome measure values, posterior corneal elevation values were relative as the tomographic best fit sphere results were not consistent for each eye pre and post operatively.

Recently, two-year outcomes were provided for accelerated CXL for post-LASIK ectasia[27]. In accelerated CXL; the total energy dose remains the same when using irradiation at 9 mW/cm$^2$ for 10min compared to 3 mW/cm$^2$ for 30min but with reduced operation time. The results showed that UDVA and CDVA had a slight drop that was not statistically significant in both. Keratometric values did not show significant changes. Although there are differences in the results when compared to our study and to others[11-12,19], longer follow-up periods and comparative studies between standard and accelerated CXL for post-LASIK ectasiaare required to validate these differences.

Because of the originally described low incidence of post-LASIK ectasia[4], and due to more advanced corneal imaging, more careful patient selection for LASIK refractive surgery, and the increased use of phakic intra ocular lenses when treating higher refractive errors, all which could be responsible for even a lower incidence of post-LASIK ectasia; it could be challenging to conduct a study with a high number of cases of post-LASIK ectasia and to follow them up for long periods of time.

All of the previous studies about CXL performed for post-LASIK ectasia followed-up patients for a period of less than 5y. Accordingly, questions about the stability and efficacy of CXL beyond that period have to be answered. This study provides long-term evidence regarding the efficacy and stability of corneas after CXL treatment for post-LASIK ectasia.

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