

# Corneal Collagen Cross-Linking Outcomes: Review

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**Abstract:** Keratoconus is a condition characterized by biomechanical instability of the cornea, presenting in a progressive, asymmetric and bilateral way. Corneal collagen cross-linking with riboflavin and UVA (CXL) is a new technique of corneal tissue strengthening that combines the use of riboflavin as a photo sensitizer and UVA irradiation. The studies showed that CXL was effective in halting the progression of keratoconus over a period of up to four years. The published studies also revealed a reduction of max K readings by more than 2 D, while the postoperative SEQ was reduced by an average of more than 1 D, and refractive cylinder decreased by about 1 D. No eyes lost any line of BCDVA. Moreover, there was no significant decrease in endothelial cell density. It was also found that CXL treatment was effective with reducing corneal and total wavefront aberrations. Corneal cross-linking has also led to an arrest and/or even a partial reversal of keratectasia in the treatment of iatrogenic ectasia after excimer laser ablation. A primary intervention such as CXL should be considered to potentially increase the biomechanical stability of the corneal tissue and postpone the need of lamellar or penetrating keratoplasty.

**Keywords:** Cornea, collagen, keratoconus, riboflavin, ultraviolet radiation.

## INTRODUCTION

Keratoconus is a condition characterized by biomechanical instability of the cornea, presenting in a progressive, asymmetric and bilateral way. The prevalence in general population is 50-200 per 100 000 [1]. A 20% of keratoconic patients will suffer of severe visual deterioration due to irregular astigmatism, myopia and corneal scarring, and optical means such as spectacles and rigid gas permeable contact lenses do not offer any visual rehabilitation [1].

Corneal collagen cross-linking with riboflavin and UVA (CXL) is a new technique of corneal tissue strengthening that combines the use of riboflavin and UVA irradiation. Riboflavin works as a photo sensitizer for the induction of cross links between collagen fibrils and at the same time act as a shield from the penetration of UVA in the underlying tissues [2]. A primary intervention, such as CXL should be considered to potentially increase the biomechanical stability of the corneal tissue and postpone the need of lamellar or penetrating keratoplasty.

## CLINICAL RESULTS

The first *in vivo* controlled clinical study by Wollensak *et al.* included 23 eyes with moderate or advanced progressive keratoconus. The study showed that CXL was effective in halting the progression of keratoconus over a period of up to four years [3]. In this study, a mean preoperative progression of keratometry (max K) by 1.42 D in 52% of eyes over a 6-month period immediately prior to the treatment was

followed by a postoperative decrease in 70% of eyes. The statistics also revealed a reduction of max K readings by 2.01 D, while the postoperative SEQ was reduced by an average of 1.14 D. At the same time, 22% of the untreated fellow control eyes had a postoperative progression of keratectasia by an average of 1.48 D.

In another study, conducted by Jankov *et al.*, it was found an arrest in the progression of keratoconus in a group of patients after CXL treatment. In a period of six months prior to the treatment all patients of this group presented a deterioration in terms of astigmatism and corneal stability. Max K readings decreased by more than 2 D (from  $53.02 \pm 8.42$  to  $50.88 \pm 6.05$  D), SEQ in less than 1 D (from  $-3.27 \pm 4.08$  to  $-2.68 \pm 3.02$  D), while refractive cylinder decreased by less 0.5 D (from  $-2.29 \pm 1.77$  to  $-1.86 \pm 0.92$  D). No eyes lost any line of BCDVA, 12 maintained the preoperative BCDVA, 7 gained one line, 5 gained two lines, and 1 patient gained three lines of BCDVA [4].

Agrawal, in his study found similar results among an Indian population of 37 eyes after one year of follow up, with 54% of the eyes gaining at least one line of BCDVA, astigmatism decreased by mean of 1.2D in 47%, K value of the apex decreased by mean of 2.73 D in 66% eyes and maximum K value decreased by a mean of 2.47D in 54% of eyes [5].

In their preliminary results Wittig-Silva *et al.*, found similar results regarding BCDVA and K reading, with no difference in spherical equivalent and endothelial cell density between treated and control eyes after 12 months follow-up [6]. Vinciguerra *et al.*, also found CXL treatment effective with reducing corneal and total wavefront aberrations one year after treatment [7].

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Corneal cross-linking has also been used successfully in the treatment of iatrogenic ectasia after excimer laser ablation. In a recently published study, CXL was performed in ten patients with a formerly undiagnosed *forme fruste* keratoconus or pellucid marginal corneal degeneration that underwent LASIK for the correction of myopic astigmatism and subsequently developed iatrogenic keratectasia [8]. CXL led to an arrest and/or even a partial reversal of keratectasia over a postoperative follow-up period of up to 25 months as demonstrated by pre- and postoperative corneal topography and reduction of maximal K-readings.

CXL treatment has an arresting effect in the progression of keratoconus. A small regression occurring may be explained as an effect of the rearrangement of corneal lamellae and the surrounding matrix [2]. Due to an increased number of cross-linking sites within the collagen molecule after CXL, stiffer fibrils and lamellae are likely generated. This process produces a rearrangement of corneal lamellae and the consequent relocation of the surrounding matrix, which, in turn, results in the reduction of the central corneal curvature.

Considering the collagen turnover in the cornea of several years, it is yet to be seen in the long-term studies whether the repeated treatment may be necessary.

## CONCLUSIONS

Keratoconus is a progressive ectatic disorder leading to visual deterioration due to irregular astigmatism and in advanced cases corneal scarring. Until recently, treatment options included spectacles, rigid gas permeable contact lenses and Intracorneal ring segments. Corneal Collagen cross-linking (CXL) with Riboflavin and UVA irradiation is a minimal invasive technique that modifies corneal stromal

structures and increases corneal stability. From the studies presented in the manuscript, it is shown the arresting effect of CXL in keratoconic patients. It is also proved the efficacy of the procedure in reducing the corneal curvature, spherical equivalent refraction and refractive cylinder in keratoconic eyes after the application of CXL. The safety of the method is also demonstrated from the fact that there was no discrepancy in terms of endothelial cell density between treated and no treated eyes.

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