

# Progress of corneal collagen cross-linking combined with refractive surgery

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## Abstract

• As a photochemical reaction that can stiffen the cornea, corneal collagen cross-linking (CXL) is the only promising method of preventing the progress of keratoconus, such as keratoconus and secondary ectasia following refractive surgery. The aim of CXL is to stabilize the underlying condition, with a small chance of visual improvement. Combining CXL with refractive surgery targeting both stabilization and reshaping of the corneal tissue for visual function improvement is a good treatment option. This review aims to provide a comprehensive and unbiased summary of the published research regarding combined CXL and refractive surgery, including measures and results, to help elucidate the future direction of CXL.

• **KEYWORDS:** cornea; cross-linking; refractive surgery; keratoconus; ectasia

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## INTRODUCTION

The mechanism of corneal collagen cross-linking (CXL) is that riboflavin as a photosensitizer which saturated cornea is exposed to ultraviolet irradiation and is excited into an activate state generating some reactive oxygen species, which lead to the formation of covalent bonds between collagen molecules that increase the stiffness of the cornea<sup>[1,2]</sup>. Since the 1990s, CXL has been used for the treatment of patients with disorders such as keratoconus, corneal ectasia after refractive surgery<sup>[3-7]</sup>, bullous keratopathy and infectious keratitis<sup>[8-9]</sup>, with great promise. However, global clinical studies have shown that vision function of most patients do not increase after this treatment. It is thought that the

combination of CXL with refractive surgery might improve visual outcomes in addition to providing corneal stabilization. This combined surgery has been termed 'CXL plus'<sup>[10]</sup>. The objective of this article is to review and summarize the most recent publications on CXL combined with refractive surgery. Through elucidating this method, we hope that more patients with visual impairment due to the corneal ectatic disorders can benefit from it.

## PHOTOREFRACTIVE KERATECTOMY

**Sequential Combination** In 2007, Kanellopoulos and Binder<sup>[11]</sup> reported on a patient with bilateral progressive keratoconus who underwent topography-guided photorefractive keratectomy (PRK) surgery on one eye, and who had undergone classical CXL on both eyes 12 months before. PRK was attempted to improve the post-CXL refractive error; a significant clinical improvement and apparent stability was successfully achieved after two surgeries. At 18 months after PRK, the uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) were improved from 20/100 to 20/20 and from 20/50 to 20/15, respectively. Simultaneously, the nomogram may need to be adjusted in the ablation of a cross-linked cornea to avoid overcorrection.

**Simultaneous Combination** In 2009, Kymionis and colleagues<sup>[12]</sup> demonstrated customized topography-guided PRK followed by immediate CXL in 12 patients with keratoconus, with a mean follow-up of 10.69 months. They reported promising results, with the offer of functional vision. The preoperative mean (logMAR) UCVA was  $0.99 \pm 0.81$ , and postoperatively it improved to  $0.16 \pm 0.15$ . In the same year, Kanellopoulos<sup>[13]</sup> evaluated the effect of different sequences and timing on the safety and efficacy of combined surgeries in a prospective study that included a total of 325 eyes with keratoconus. The first group (127 eyes) underwent CXL with subsequent topography-guided PRK performed 6 months later (sequential group), while the second group (198 eyes) underwent PRK and CXL in a combined procedure on the same day (simultaneous group). Statistically, the simultaneous group performed better on all parameters evaluated, including UCVA, BSCVA, spherical equivalent (SE) refraction and keratometry and less corneal haze. The author named the technique of CXL performed immediately

after topography-guided PRK as the 'Athens Protocol'. In 2010, case reports by Krueger and Kanellopoulos confirmed the stability of the Athens Protocol, with unchanged UCVA with a minimum follow-up of 30 months<sup>[14]</sup>.

In 2011, Kymionis and colleagues<sup>[15]</sup> and Kanellopoulos and Binder<sup>[16]</sup> reported that a simultaneous combination operation may also be used to treat cornea ectasia after laser *in situ* keratomileusis (LASIK). The uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) of the patient described by Kymionis and colleagues showed significant improvements from 20/100 to 20/40 and from 20/40 to 20/25, respectively<sup>[15]</sup>. In the research of Kanellopoulos and Binder, 27 of 32 eyes had an improvement in UDVA and CDVA of 20/45 or better (2.25logMAR) at last follow-up<sup>[19]</sup>. In 2012, the results of a year's follow-up following simultaneous CXL with topography-guided PRK, including 22 eyes of 15 patients with low-grade keratoconus, demonstrated that this protocol appeared safe and efficient, with safety and efficacy indices of 1.6 and 0.4, respectively<sup>[17]</sup>. In 2013, a study including 17 patients (34 eyes) who underwent PRK followed by CXL versus CXL alone suggested that the combined procedure was better in reducing corneal aberrations and stabilizing progressive keratoconus. The changes in UDVA were from  $0.63 \pm 0.36$  to  $0.19 \pm 0.17$  logMAR and from  $0.59 \pm 0.29$  to  $0.52 \pm 0.29$  logMAR, respectively<sup>[18]</sup>. Furthermore, a self-reported quality-of-life comparison found improvements in quality of life with simultaneous CXL with topography-guided PRK, over those reported with CXL alone<sup>[19]</sup>.

**Other Applications** Kanellopoulos has successfully treated corneal blindness from severe corneal scarring with the Athens Protocol<sup>[20]</sup>. The treated cornea improved translucency and was topographically stable, with CDVA increased from 20/100 to 20/40. This method may provide an effective alternative to existing surgical options, such as keratoplasty, for patients with severe corneal scarring.

**Complications** The formation of liner haze in posterior stroma or nodular epithelial hyperplasia has been reported for patients who have undergone topography-guided PRK followed by immediate CXL<sup>[21,22]</sup>. The authors thought that this was probably caused by an inflammatory stimulus triggered by the combined operation.

Almost all of the reports identified used topography-guided PRK in combined operations; the laser ablation profile was more suitable for keratoconus patients because of highly irregular astigmatism. In terms of the sequence, PRK followed by CXL seems better because removing the cross-linked stiffer anterior cornea possibly minimizes the benefit of CXL if CXL is followed by PRK. However, the long-term effects and safety of removing the Bowman layer

with laser ablation have not been established and may potentially lead to rapid deterioration and eventual corneal transplantation.

### **LASER IN SITU KERATOMILEUSIS**

**Sequential Combination** Kampik and colleagues<sup>[23]</sup> reported that the microkeratome and laser parameters for LASIK need adjusting after CXL due to the influence of the cornea stiffening effect. The *in vitro* animal study conducted to investigate the influence of CXL on LASIK concluded that CXL reduced the amount of refractive change after LASIK for myopia and increased flap thickness.

**Simultaneous Combination** In a study by Celik and colleagues<sup>[24]</sup>, four patients underwent LASIK with concurrent accelerated CXL in one eye and LASIK only in the fellow eye to treat myopia or myopic astigmatism. During the surgery, 0.1% riboflavin solution was instilled into the corneal bed for 1.5min while the flap remained open, and ultraviolet A exposure was performed for 3min at a power of  $30\text{mw}/\text{cm}^2$  after flap closure. The attempted correction (SE) ranged from -5.00 to -8.50D in the LASIK-CXL group and from -3.00 to -7.25D in the LASIK-only group. The LASIK-CXL group had a UDVA and manifest refraction equal to or better than those in the LASIK-only group. Concurrent surgery appeared to be a promising modality for future applications to prevent corneal ectasia after LASIK treatment<sup>[24]</sup>. Tamayo reported similar work in a letter to the editor. The riboflavin instillation and irradiation times were 60s and 75s at  $30\text{mw}/\text{cm}^2$ , respectively, and the UDVA and manifest refraction SE postoperatively were improved to 20/18 and 0.49, respectively<sup>[25]</sup>. A similar study reported on 43 patients treated with femtosecond laser flap and the WaveLight excimer platform with a UVA irradiation power of  $10\text{mw}/\text{cm}^2$  for 3min<sup>[26]</sup>. This method appeared to be a safe and effective adjunctive treatment for refractive regression and potential ectasia. The mean UCVA changed from 0.2 to 1.2, BSCVA from 1.1 to 1.2, SE from -7.5 to -0.2D and keratometry from 44.5 to 38D. None of the cases developed signs of ectasia or significant regression during a mean follow-up duration of 3.5 years. The author said that this application could be viewed as a 'prophylactic customization of the biomechanical behavior of corneal collagen'<sup>[26]</sup>. A further investigation of a combined operation using topography-guided LASIK and the same ultraviolet A parameter applied in a contralateral eye study of 34 consecutive patients reached the same conclusion<sup>[27]</sup>. Eyes that underwent CXL demonstrated a mean regression from treatment of  $+0.22 \pm 0.31$ D, whereas eyes that did not undergo CXL showed a greater regression of  $+0.72 \pm 0.19$ D at 2 years postoperation. In a study that reported the long-term outcomes, safety, stability and efficacy of a pilot series of

simultaneous LASIK and CXL with an illumination of 3mw/cm<sup>2</sup> for 30min, the average SE was +3.4D after 4 years<sup>[28]</sup>; the authors suggested that this technique may be promising for ameliorating hyperopic regression.

Recently, this kind of concurrent operation has mostly been applied to myopic patients to decrease the incidence of corneal ectasia after LASIK and to improve the quality of sporting activities post-LASIK. Obviously, the effect of different irradiation parameters of UVA should be compared further.

#### **INTRACORNEAL RING SEGMENT IMPLANTATION**

**Riboflavin Injected into Incision of Intracorneal Ring Segment Implantation** Riboflavin solution can be instilled into the corneal stroma through the incision of intracorneal ring segment implantation (Intacs) surgery simultaneously to avoid removing epithelium. The result of a case of advanced keratoconus treated by combining CXL with MyoRing implantation was promising; riboflavin instilled by incision and ultraviolet A irradiation occurred first, and MyoRing implantation was the last step<sup>[29]</sup>. A non-comparative case series including 131 eyes (105 patients) applied a similar operation. UDVA and CDVA improved by 0.26 and 0.24 logMAR respectively. This method was safe and effective<sup>[30]</sup>.

**Riboflavin Instilled on the Surface of Corneal Epithelium** This kind of combination can be sequential. The combination of Intacs implantation and simple transepithelial CXL treatment in a 27-year-old patient has been reported by Kamburoglu and Ertan<sup>[31]</sup>. Following bilateral Intacs implantation, CXL was performed the following day in the left eye and after 1 month in the right eye. Eight months after the combined treatment, BSCVA, manifest refractions and mean keratometric values had improved, respectively, to 20/25 and 20/25, -1.50 and -1.25, and 47.20 and 44.20D, in the right and left eyes. Furthermore, a larger-scale study including 25 eyes of 17 keratoconus patients by Ertan and colleagues<sup>[32]</sup> using Intacs implantation with subsequent simple transepithelial CXL treatment, which was performed at a mean interval of 3.98±5.7 months, suggested an additive effect. CXL performed after Intacs treatment yielded an additional 1.2 Snellen lines of UCVA and an additional decrease in mean K (0.35D).

These procedures can also be concurrent. In 2007, Chan and colleagues<sup>[33]</sup> performed a retrospective, non-randomized, comparative case series involving 12 eyes of nine patients who underwent inferior-segment Intacs placement without CXL, and 13 eyes of 12 patients who underwent inferior-segment Intacs placement followed by immediate simple transepithelial CXL. The combination resulted in greater keratoconus improvements than Intacs insertion

alone, as a result of greater reductions in manifest cylinder, K steep, K average and the lower-upper ratio. The change in mean K was 1.34±1.27 and 0.21±2.70, respectively. Vicente and Boxer Wachler<sup>[34]</sup> showed that Intacs and cross-linking on the same day as an approach to treat keratoconus most benefited those patients with worse BSCVA and SE in gaining greater postoperative BSCVA improvement.

**Riboflavin Instilled on the Surface of De-epithelial Cornea** Good results in terms of visual acuity, K value and postoperative residual refractive error have been obtained with Intacs implantation 6 months after CXL. Mean UCVA was 1.11, 0.75 and 0.23 (logMAR) at preoperation, 6 months after CXL and 6 months after Intacs implantation<sup>[35]</sup>. Another study including 15 eyes of 11 patients found that femtosecond laser channel creation can be performed 6 months after classical CXL, although the laser power must be modified. Further results have shown that channel dissection and Intacs implantation should be performed before or concurrent with CXL for less energy use, better dissection and less corneal haze<sup>[36]</sup>. Regarding the influence of treatment sequence, a study has suggested that Intacs implantation followed by classical CXL results in the greater keratoconus improvements than classical CXL followed by Intacs implantation<sup>[37]</sup>. Another study evaluating the safety and efficacy of combined Intacs insertion and classical CXL performed in one or two sessions has suggested that the same-session procedure appears to be more effective in terms of improvement in the corneal shape; furthermore, the stromal haze was more marked and persistent in the two-session group<sup>[38]</sup>.

Various surgical procedures involving CXL combined with Intacs insertion have been investigated. Although the sequences and involvement of the corneal epithelium have been different, the combined methods have all delivered promising results and additional effects over a single operation. This might be because during CXL, the riboflavin concentration is increased around Intacs and hence might increase collagen cross-linking at that site. Intacs implantation might alter the pattern and distribution of collagen changes. Further controlled research with long follow-ups is required.

**Conductive Keratoplasty** Conductive keratoplasty followed by classical CXL, as performed by Kymionis and colleagues<sup>[39]</sup> in two patients with keratoconus, was associated with an immediate significant corneal topographic improvement after surgery, but the effect regressed after 3 months. Compared with PRK and LASIK, conductive keratoplasty is a tissue-saving technique that is considered effective in correcting corneal irregularities without the disadvantage of inducing a weakening effect. However, the

procedure should perhaps be improved to reduce the occurrence of refractive regression.

### **INTRAOCULAR LENS**

**Anterior Chamber Intraocular Lens** In a study of the Artiflex (Ophtec BV) foldable anterior iris-claw phakic intraocular lens implanted 6 months after CXL for keratoconus patients, all eyes achieved a UDVA of 0.3logMAR or better without complications<sup>[40]</sup>. Toric iris-claw phakic intraocular lens implantation was applied when refraction and topography had stabilized after CXL in eyes with proven progressive keratoconus. The long-term results, with a mean follow-up of 36.9 months, were promising: 94% patients had a postoperative UDVA of 20/40 or better and 82% of patients had an attempted SE correction within  $\pm 0.50D$ <sup>[41]</sup>.

**Posterior Chamber Intraocular Lens** In 2011, a case report was presented in which a posterior chamber toric implantable Collamer lens was implanted 12 months after CXL. The UDVA of the 29-year-old woman with keratoconus improved from counting fingers to 20/40 at 3 months postoperatively<sup>[42]</sup>. The results of the same two-step CXL and toric implantable Collamer lens implantation procedure at an interval of 6 months in 16 eyes of 10 patients with keratoconus seemed satisfactory. Mean UDVA improved from  $1.67 \pm 0.49$  to  $0.17 \pm 0.06$  logMAR and CDVA improved from  $0.15 \pm 0.06$  to  $0.12 \pm 0.04$  logMAR<sup>[43]</sup>.

Considering the irregular astigmatism associated with keratoconus, the choice of intraocular lens was important and the toric intraocular lens was popular. However, it is unknown whether glares and halos occurred. Moreover, a longer follow-up period is needed to monitor for complications such as cataract formation and pigmentary dispersion.

### **MULTI-OPERATION**

**Intacs +Photorefractive Keratectomy +Collagen Cross – Linking** Two different-scale clinical trials have performed Intacs implantations followed by same-day PRK and CXL in patients with keratoconus. UDVA, CDVA, and sphere and cylinder refractive measurements all significantly improved after this multi-operation combination, with most eyes gaining two lines of CDVA or more<sup>[44,45]</sup>. A similar protocol has been applied with a patient with pellucid marginal degeneration. The UDVA improved from finger counting to 20/63 and remained stable during the 9-month follow-up period<sup>[46]</sup>. A study of simultaneous wavefront-guided PRK and CXL at least 6 months after previous Intacs implantation found that it satisfactorily changed the UDVA, CDVA and central K values from  $0.20 \pm 0.12$  to  $0.55 \pm 0.15$ , from  $0.58 \pm 0.13$  to  $0.77 \pm 0.17$  and from  $50.91 \pm 5.50$  to  $46.61 \pm 4.52D$ , respectively<sup>[47]</sup>. Another study applied a three-step sequence,

in which topography-guided transepithelial PRK was performed after Intacs implantation and transepithelial CXL, to treat 10 patients (16 eyes) with progressive keratoconus. The time interval between each of the three operations was 6 months. The three-step procedure seemed promising: logMAR mean UDVA and mean CDVA were significantly improved from  $1.14 \pm 0.36$  and  $0.75 \pm 0.24$ , respectively, preoperatively to  $0.25 \pm 0.13$  and  $0.13 \pm 0.06$  after completion of the three-step procedure. Mean SE was significantly reduced from  $-5.66 \pm 5.63$  to  $-0.98 \pm 2.21D$ <sup>[48]</sup>.

**Lamellar Keratoplasty +Photorefractive Keratectomy + Collagen Cross–Linking** Simultaneous topography-guided PRK followed by CXL after lamellar keratoplasty for keratoconus has been studied by Spadea and Paroli<sup>[49]</sup>. The combination of PRK and CXL, conducted a mean of  $40.1 \pm 12.4$  months after lamellar keratoplasty, provided safe and effective results. All eyes gained at least one Snellen line of UDVA<sup>[49]</sup>.

**Photorefractive Keratectomy +Collagen Cross–Linking+ Intraocular Lens** This combination was used on a patient with ocular injury to improve visual function. One year after combined topography-guided partial PRK and collagen cross-linking (Athens Protocol) to treat corneal ectasia, the cornea appeared to be stable. Phakic intraocular lens (Verisyse) implantation was later performed when the patient became contact-lens intolerant. The UDVA after 3 years was 20/25<sup>[50]</sup>.

Clearly, patients undergoing multi-operation combinations should be carefully selected. The influences of sequence and interval need to be investigated in large-scale clinical trials.

### **SUMMARY**

The combination of CXL with different refractive surgeries perfectly meets the needs of keratectasia patients in terms of halting disease progression and improving visual function. It can sometimes be difficult to choose the most suitable refractive operation protocol. In a study by Fadlallah and colleagues<sup>[43]</sup>, Intacs implantation was used for patients with poor best corrected visual acuity, while topography-guided PRK was selected for patients for mild refraction errors and a phakic intraocular lens was considered suitable for patients with moderate to severe ametropia. Further controlled trials may be helpful in making such decisions. Otherwise, it becomes a prophylactic method voiding corneal ectasia after refractive surgery to myopia patients such as LASIK combined with CXL<sup>[51]</sup>. The former application may be named 'CXL plus'; the latter, 'refractive surgery plus'. Furthermore, combination operations may be used to treat corneal scarring. Although the detailed operating procedures, including type of surgery, laser ablation profile, operation sequence, method of dealing with the corneal epithelium and

ultraviolet A irradiation parameter, have differed, the results of combination operations are promising. Further comparative studies of different operative factors and randomized controlled clinical trials may increase the popularity and application of combination operations.

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