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Corneal Collagen Crosslinking: A Major Breakthrough in the Management of Keratoconus, Pellucid Marginal Degeneration, and Ectasia after LASIK

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Corneal collagen crosslinking (CXL) is recognized as a major therapeutic advance in the management of ectatic diseases. CXL treatment involves the use of riboflavin drops (vitamin B_2) and ultraviolet A (UV-A) light. The primary goal of CXL is to stabilize the corneal curvature and prevent the need for corneal transplantation. This treatment is being rapidly adopted by ophthalmologists around the globe as the standard of care for progressive ectasia. This issue of *Ophthalmology Rounds* discusses the ectatic disorders, the development and application of CXL, as well as the safety and future possibilities with this treatment.

A review of the literature reveals increasing evidence that CXL is an effective means of halting progressive corneal thinning and steepening in patients with keratoconus, pellucid marginal degeneration (PMD), and ectasia after laser-assisted *in situ* keratomileusis (LASIK).[1-5] Other potential applications are:

- reducing corneal edema in bullous keratopathy and Fuchs' corneal dystrophy
- treating infectious corneal ulcers
- enhancing corneal flattening after the insertion of intrastromal corneal rings
- strengthening the cornea prior to or after photorefractive keratectomy (PRK) treatment in patients with high myopia, or mild or "forme fruste" keratoconus
- reducing the fluctuations in vision and hyperopic shift following radial keratotomy.[6-9]

There are now over 45 peer-reviewed articles supporting the efficacy of CXL in arresting the progression of keratoconus, as well as isolated reports supporting its use for other potential indications.[10]

Keratoconus

Keratoconus is a degenerative disorder of the cornea where structural changes in the cornea cause it to thin and become conical in shape. With an incidence of approximately 1 in 2000,[11] the disease usually presents in adolescence and tends to peak in severity between 20-35 years of age. Approximately 10%-25% of patients with keratoconus require a corneal transplant,[12,13] but CXL offers the possibility to prevent a transplant.

The diagnosis of keratoconus is made based on clinical signs and topographic imaging (Table 1). One of the earliest signs on routine examination is an irregular scissors reflex on retinoscopy. As this ectatic disease progresses, Vogt's striae or stress lines appear as vertical lines in the deep stroma. The striae will temporarily disappear if slight pressure is applied to the cornea. A ring of yellow-brown pigmentation known as a Fleischer ring can be observed in about one-half of keratoconic eyes. The Fleischer ring is caused by deposition of the iron oxide, hemosiderin, within the corneal epithelium. Further progression can lead to breaks in Bowman's layer, resulting in apical scarring. A break in Descemet's membrane results in rapid stromal and often epithelial edema, referred to as corneal hydrops. An advanced cone can create a V-shaped indentation in the lower eyelid when the patient's gaze is directed downwards, known as Munson's sign. Although this finding is a classic indication of the disease, since it occurs late in the disease process. it has less primary diagnostic importance.

Today, sophisticated imaging allows for an early diagnosis of keratoconus. Computerized topography can involve curvature analysis or elevation topography. Asymmetrical astigmatism

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Table 1: Clinical signs of keratoconus may be early or late in the disease process

Early ↕ Late	• Posterior corneal curvature • Epithelial thickness abnormalities • High coma • Abnormal computerized topography • Irregular keratometry mires • Vogt's striae • Apical scarring • Munson's sign • Corneal hydrops

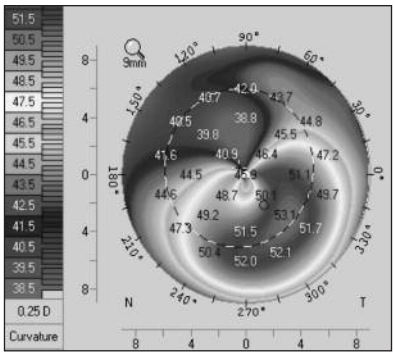
with inferior steepening is a typical topographic pattern (Figure 1).[14,15] Elevation topography allows for the comparison of the anterior surface or posterior surface with a best-fit sphere. Changes to the posterior corneal curvature may represent the earliest clinical sign of keratoconus (Figure 2).[16,17] Corneas are typically thinner in keratoconus, and it is characteristic to find the thinnest spot on the cornea in the steepest region associated with posterior corneal bulging. Clinical studies on the measurement of epithelial thickness indicate that eyes with keratoconus usually have a thinner epithelium overlying the cone and a thicker epithelium at the base of the cone.

The etiology of keratoconus remains unknown.[18] Keratoconus likely arises from a number of factors: genetic, environmental, or cellular.[19,20] A genetic predisposition to keratoconus has been observed,[21,22] with a reported incidence of concordance in identical twins.[23] Most genetic studies agree on an autosomal-dominant mode of inheritance.[22] In addition, keratoconus is found at a higher frequency in those with Down syndrome. Keratoconus has been associated with atopic diseases, including asthma, allergies, and eczema; further findings suggest an excess of eye rubbing contributes to the progression of keratoconus.[24-27]

Pellucid Marginal Degeneration

PMD is a degenerative corneal ectatic disease that is often confused with keratoconus. It is characterized by thinning in the periphery of the cornea[23] and corneas typically have a normal thickness in the centre. The inferior cornea exhibits a peripheral band of thinning. There is usually high against-the-rule astigmatism. Computerized topography will show a classic butterfly appearance. No known cause for the disease has been found[23] and, like keratoconus, PMD represents a contraindication to LASIK.

Figure 1: Computerized videokeratography of keratoconus with inferior steepening.



Corneal ectasia post-LASIK

Corneal ectasia is a rare, potentially devastating complication following LASIK. Ectatic changes may occur as early as 1 week after LASIK, but usually are delayed by many years.[28] The actual incidence of ectasia is undetermined, although incidence rates ranging from 0.04%–0.6% have been reported.[29-31]

Risk factors for corneal ectasia include the following:

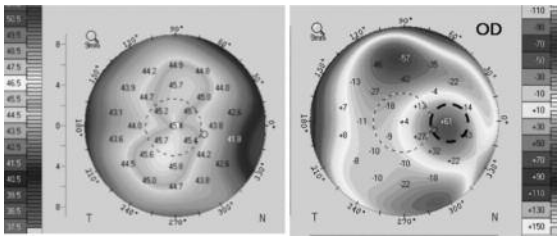
- Abnormal preoperative topography, as seen with keratoconus, PMD, or forme fruste keratoconus, is a significant indicator of risk. Low preoperative corneal thickness is also a predictor of ectasia.
- Low residual stromal bed (RSB) thickness is an important factor after LASIK because tensile strength analysis[32] indicates greater strength in the anterior 40% relative to the posterior 60% of the stroma. LASIK reduces anterior corneal structural integrity. It is clear that a corneal bed cut-off of 250 µm does not absolutely discriminate against the development of ectasia; however, the risk of ectasia increases reciprocally relative to RSB thickness.
- Young age may be a significant risk factor for ectasia in patients without other risk factors. One hypothesis is that some of these individuals would have developed delayed-onset forme fruste keratoconus even without a LASIK procedure.
- High myopia, especially >12 D, is associated with a higher risk of ectasia. Despite this finding, post-LASIK ectasia has been reported in numerous patients with low myopia[33] and even hyperopia.[34]

Other risk factors include eye rubbing, family history of keratoconus, refractive instability, and best-corrected spectacle visual acuity (BCSVA) <20/20 preoperatively.

Development of Corneal Crosslinking

CXL has been a major breakthrough in the mechanical and biochemical stability of ectatic diseases. The CXL concept derives from the recognition that individuals with diabetes have a lower tendency to develop keratoconus due to natural crosslinking from high blood-

Figure 2: Computerized topography (left) shows a relatively normal bow-tie pattern of astigmatism. However, posterior corneal elevation (right) shows a focal area of bulging, which is characteristic of keratoconus.



glucose levels and exposure to UV light. The basic research on CXL was conducted from 1993 to 1997 by Theo Seiler and Eberhard Spöerl in Germany.[35] The research indicates that new bonds are formed across adjacent collagen fibres to enhance the cornea's mechanical strength,[36] such that CXL increases corneal rigidity by 328%.[37] The procedure was found to be effective in the treatment of keratoconus, PMD, and ectasia following laser vision correction.

The idea of crosslinking is not new. The practice has been used for over 70 years in the material science field for the conversion of silicone oil to rubber. Dentists have been using crosslinking for over 25 years. Natural crosslinking occurs in normal aging as a change in connective tissues of the body. This may account for the slower progression of keratoconus with age.

Basic research on CXL safety

CXL with riboflavin solution and UV-A light at 370 nm was shown to be safe when using an irradiance of 3 mW/cm^2 with a minimum corneal thickness of 400 µm.[37] With a thickness ≥400 µm, there is a minimal amount of energy delivered to the corneal endothelium, and this level is below the threshold for any damage. The damage thresholds for keratocytes[38] and endothelial cells[39] are 0.45 and 0.35 mW/cm^2, respectively. In a 400-µm-thick cornea saturated with riboflavin, the irradiance at the endothelial level was 0.18 mW/cm^2, which is lower than the damage threshold by a factor of 2.[39,40] Studies measuring the amount of radiant energy entering the eye demonstrate that it is below the damage threshold for the iris, lens, and retina. In the development of cataracts, various dose values have been discussed in the literature concerning wavelengths between 290–365 nm.[41-43] The retina is damaged by thermal or blue light-induced photochemical damage in the wavelength range of 400–1400 nm.[44] Studies using confocal microscopy have demonstrated that when keratocytes are depleted to a depth of 300 µm, repopulation takes up to 6 months.[38]

CXL results in the creation of additional chemical bonds inside the corneal stroma by means of photopolymerization.[37] Since UV light causes an effect only where it is absorbed, a desirable treatment design assures that most of the irradiation is absorbed in the corneal stroma. This is achieved by the use of UV light at 370 nm, a wavelength that corresponds to one of the absorption maxima of the riboflavin chromophore. Riboflavin acts as a photomediator, creating free radicals to induce new chemical bonds.

Technique of CXL

The standard crosslinking technique involves removal of the central corneal epithelium (8–9 mm in diameter), the application of riboflavin drops, and exposure to UV-A light of 370 nm (±5 nm) for 30 minutes (Figure 3).[37] Removal of the epithelium can be accomplished by a variety of techniques, including the use of a rotary brush, a dilute concentration of alcohol, or mechanical debridement. Riboflavin (0.1%) drops are administered to rinse the cornea every 2 minutes for 30 minutes before the procedure, and then every 5 minutes during irradiation. The energy of the crosslinking device is measured preoperatively and should be around 3 mW/cm^2 , and should deliver a homogenous illumination. After the UV-A light exposure for 30 minutes, an antibiotic, nonsteroidal and steroid drops are inserted, along with a bandage contact lens. Typically, the contact lens remains in place for 5 days or until the epithelium becomes intact.

Contraindication to CXL

Corneas <400 µm represent a contraindication to CXL; however, the use of a hypotonic riboflavin solution to induce corneal swelling will allow satisfactory transient stromal edema to permit safe crosslinking. At the Bochner Eye Institute, we found that there is a 95% chance of inducing satisfactory swelling for corneas between 300 and 399 µm with hypotonic drops.

Clinical Outcomes of CXL

The first CXL treatments were performed in Europe in 1998, but in North America, it has been a relatively new treatment over the past 3 years. The success of CXL is gauged by a lack of progressive ectasia. In addition, often some corneal flattening occurs with asymmetric changes that can result in improved BCSVA.

Wollensak et al[45] published their initial outcomes on CXL in 2003, reporting on 16 eyes of 15 patients with progressive keratoconus. A subsequent publication examined 22 eyes of 24 patients, with a follow-up time of between 3 months and 4 years. The results indicated that progression of keratoconus was halted in all treated eyes. In 70% of eyes, there was a regression with a mean reduction of the maximal keratometry readings by about 2 diopters and a refractive error of approximately 1 diopter. Visual acuity improved slightly in 65% of eyes.

Since the initial study, 8 other studies have reported their results (Table 2).[10] The study methodologies are variable and, as such, are not directly comparable; however, all reports demonstrated varying degrees of improvement in visual acuity and a reduction in keratometry with a progressive improvement trend for the duration of follow-up. To date, the longest study (7 years) is by Raiskup-Wolf et al.[3] They found a decrease in maximum keratometry of 2.7 D in the first year, 2.2 D at 2 years, and 4.8 D at 3 years. BCSVA improved by 1 line/year in 54% of patients in the first 3 years. Two patients had continued progression and required repeat crosslinking procedures.

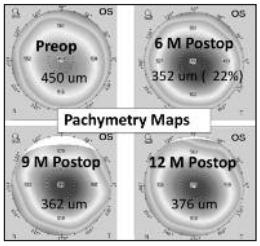
In the only randomized, prospective, controlled clinical trial of CXL in progressive keratoconus published to date, Wittig-Silva et al[4] reported on 66 eyes of 49 patients with documented progression of keratoconus. Interim analysis of treated eyes demonstrated a flattening of the steepest simulated keratometry (K-max) by an average of 0.74 D at 3 months, 0.92 D at 6 months, and 1.45 D at 12 months. A trend toward improvement of BCSVA was also observed. In the control eyes, mean K-max steepened by 0.60 D after 3 months, 0.60 D after 6 months, and by 1.28 D after 12 months. BCSVA decreased by a logMAR of 0.003 over 3 months, 0.056 over 6 months and 0.12 after 12 months.[4]

Table 2: Summary of Efficacy Studies Performed to Date

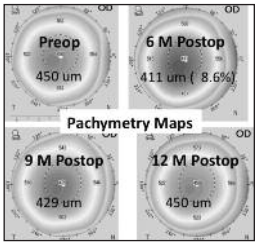
Authors	Year	Type of Study	No. of Eyes	Follow-up
Caporros[46]	2006	Prospective, nonrandomized	10 eyes	6 months
Hoyer[47]	2009	Retrospective	153 eyes	12 months
Wittig-Silva[4]	2008	Prospective, randomized	66 eyes	Up to 12 months
Raiskup-Wolf[3]	2008	Retrospective	241 eyes	Min. 6 months
Jankov[48]	2008	Prospective, nonrandomized	25 eyes	4-7 months
Vinciguerra[49]	2009	Prospective, nonrandomized	28 eyes	12 months
Agrawal[50]	2009	Retrospective	37 eyes	12 months
Grewal[51]	2009	Prospective, nonrandomized	102 patients	12 months

Complications following CXL are uncommon, but a few have been reported: herpes simplex virus keratitis, sterile infiltrate, and a corneal ulcer secondary to *Escherichia coli*.[10] At the Bochner Eye Institute, we presented 12-month data on 30 consecutive eyes in 19 patients; they had an average age of 34.4 years with a range of 17–44 years.[52] There were 12 right eyes and 18 left eyes. All corneas were clear preoperatively. The minimum corneal thickness was 400 µm. Pachymetry data revealed an average minimum corneal thickness of 461 µm (range 401–548 µm); after 3 months, the average thickness had decreased to 431 µm (range 337–514 µm). By 6 and 12 months, the average thickness increased to 441 µm and 442 µm, respectively. An examination of the percentage of corneal thinning from preoperative average measurements indicated that at 3 months, corneal thickness decreased by 6.5%, at 6 months the decrease was 4.3%, and 4.1% at 9–12 months. Further, a significant variability exists in the degree of corneal thinning from patient to patient and, within the same patient, from right to left eye (Figures 3 and 4). When examining the steepest diopter region of the cornea, the average decrease in corneal curvature was 1 diopter at 12 months.

Figures 3, 4: Pachymetry post-CXL with changes at 6, 9, and 12 months.

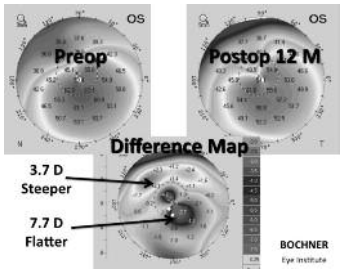


Pachymetry post-CXL with changes at 6 M, 9 M, and 12 M.



Pachymetry post-CXL of the patient's other eye depicted in Fig. 4. Note variable reaction between eyes as these maps show a return to preoperative levels by 12 M.

Figure 5: Computerized topography with a difference map post-CXL. Significant changes noted with an area of 7.7 D flattening.



In analyzing the effects from CXL, the change in the steepest power or average K-max does not provide all the important information. Difference maps allow an appreciation of the change in curvature (Figure 5). Although there is some mild postoperative corneal haze, it tends to peak at 6 months and gradually decreases over time. One of the most important clinical signs is the change in BCSVA (Figure 6). At 12 months postoperatively, in the aforementioned series of 30 eyes, 60% of eyes gained ≥1 lines, 33.3% were the same, and 6.6% demonstrated a 1-line decrease in BCSVA.

Post-CXL, the epithelium usually becomes intact by 4-6 days. Typically, the normal healing response to any corneal abrasion, a pseudodendrite, is found. BCSVA may be worse during the initial 1-2 months as the epithelium undergoes remodelling; eventually, remodelling results in a thinner layer of cells over the cone and a thicker layer over the base to reduce irregular astigmatism.

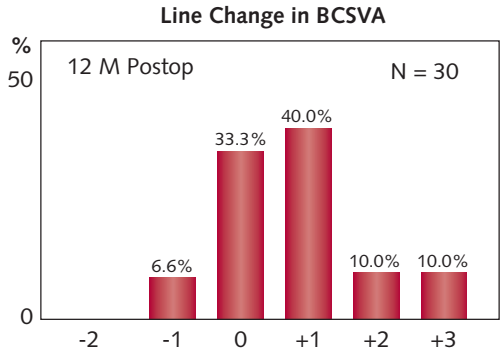
Post-LASIK ectasia and CXL

Following laser vision correction, post-LASIK ectasia is a relatively rare but serious complication. Patients typically do well in terms of uncorrected visual acuity and BCSVA for years until ectasia develops. The topographic findings with ectasia are similar to those of keratoconus. The biomechanical properties of the cornea are weakened; the condition may be secondary to preoperative keratoconus, due to minimal residual bed depth from the correction of high myopia, a result of thin preoperative pachymetry, or a thicker flap than intended. Reports of success in ectasia cases using CXL have been presented[52] and, currently, CXL is the only procedure that prevents progressive thinning and bulging of the cornea.

Topographically-linked Ablation

One approach to improving the visual rehabilitation of keratoconus eyes is the use of a topographically-guided laser ablation to reduce irregular astigmatism (Figure 7).[9] In this scenario, the epithelium is removed either by a laser or by a rotary brush, alcohol, or debridement. Topographically

Figure 6: Line change in BCSVA post-CXL.[52]

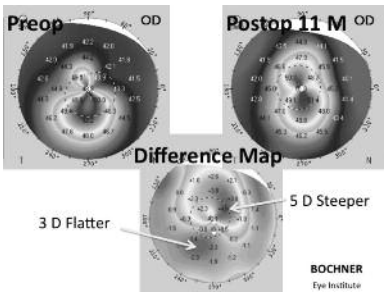


guided ablation to flatten the steep area of the cornea and reduce the asymmetric astigmatism follows. Typically, smaller optical zones of 5 mm are used to reduce the amount of tissue required for removal. Subsequent to the laser ablation, treatment with the riboflavin eye drops and the UV-A light source is applied. In addition to the laser ablation to reduce the irregular astigmatism, a portion of the prescription can be treated. Because the CXL procedure will induce flattening, typically <50% of the prescription is treated in this way. To preserve the biomechanical properties of the cornea, usually <50 µm of tissue is removed.

Intrastromal Corneal Rings

If patients continue to experience significant irregular astigmatism following CXL even with the adjunctive use of topographically-guided laser ablation, intrastromal corneal rings may be beneficial in reducing irregular astigmatism. Initially, the procedure of inserting 1–2 intrastromal corneal rings was developed for the correction of low degrees of myopia. In France, Colin et al[53] began using intrastromal corneal rings for the correction of keratoconus; today,this is the most common indication. The corneal channels may be constructed by a mechanical dissector or with a femtosecond laser. With the laser, the channel can be made easily and with enhanced depth accuracy. Depending on the topographic pattern, 1–2 rings are inserted. After the rings are inserted, a suture is used to close the small corneal wound, which is typically removed in 6–8 weeks. The ring procedure offers the benefits of reversibility and potential exchangeability, since it involves no removal of tissue. Early studies on intrastromal corneal rings involved using 2 segments to cause a general flattening of the cornea.[54] A later study reported that better results could be obtained for those cones located nearer the periphery of the cornea using a single ring segment. This allows preferential flattening of the cone below, but also to steepening the over-flat upper part of the cornea.[55]

Figure 7: Computerized topography post-CXL and topographically linked ablation. Significant improvement in irregular astigmatism is achieved by steepening superiorly and flattening inferiorly.



Potential Future Advances in CXL

CXL is one of the most significant advances in the therapeutic treatment of keratoconus, PMD, and ectasia following LASIK. There are significant ongoing research and clinical studies to investigate enhancing outcomes. One particular question is whether the corneal epithelium can be left intact during CXL. Special formulated drops have been developed to induce the breakage of corneal epithelial bonds and facilitate the passage of the riboflavin solution into the stroma. Research and clinical data have demonstrated less stiffening of the cornea with a transepithelial laser approach in which the corneal epithelium is left intact. The level of stiffening required to prevent progressive disease remains unknown. An additional question is whether the energy level of the UV-A light source can be changed to shorten the procedure. Answers to these and other questions will only be provided by further research.

Summary

CXL can prevent progressive disease; as a result, performing CXL at an earlier disease stage offers better final vision. It is important for clinicians to make an early diagnosis of keratoconus, which is greatly aided by the use of computerized topography. If there is a family history of keratoconus, topography would be helpful at an early age. However, if there is no family history of keratoconus, it should be suspected with finding a scissors reflex on retinoscopy, a decrease in BCSVA, or increasing astigmatism, and a topographic evaluation should be performed. Today, over 300 centres in Europe are performing CXL. The procedure has been approved in 65 countries around the world and is becoming the standard of care for keratoconus with progressive disease.

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