

Cornea collagen cross linking (CCL) in treatment of keratoectasia



Aleksandar Stojanovic
Eye Dpt., University Hospital North
Norway, Tromsø and SynsLaser Kirurgi,
Tromsø/Oslo



Jia Zhang
Wenzhou Medical College, China and
SynsLaser Kirurgi, Tromsø/Oslo



and Tore Nitter
Øyelegesenteret i Tromsø

Keratoectasia is a noninflammatory progressive corneal thinning and protrusion that occurs either as a primary degenerative disease or iatrogenically. Diseases like keratoconus and the related less prevalent conditions pellucid marginal degeneration and keratoglobus are usually bilateral and develop mainly after puberty, resulting in moderate to severe impairment of visual function. Most reported estimates of the prevalence of keratoconus fall between 50 and 230 per 100 000. It occurs in people of all races and has no gender predominance.¹ Corneal weakness occurring in keratoconus seems to be caused by enzymatic digestion and intralaminar displacement and slippage in the stromal tissue.^{2,3} Keratoectasia that occurs iatrogenically has similar characteristic to keratoconus and it occurs mostly after LASIK.^{4,5}

It appears that not all patients with keratoectasia have equal risk

of progression. The risk in older patients and patients with diabetes seems to be smaller than that of younger and non-diabetic patients. This is explained by intermolecular cross-linking (chemical binding caused by enzymatic reaction), which naturally occurs in corneal stroma of these patients, preventing weakening of their cornea.⁶ This observation was the key factor in development of corneal collagen cross-linking (CCL), a parasurgical treatment aimed at stopping the ectatic process and at postponing and even replacing the corneal transplantation as the only current alternative for treatment of progressive corneal ectasia.

Principle and procedure

CCL is based on photooxidative mechanism,^{7,8} where ultraviolet-A (UVA) irradiation of the corneal stroma, saturated by riboflavin, causes release of reactive oxygen species

(ROS), which stimulates covalent bond formations between fibers (= cross-linking), illustrated in Fig. 1. As a result, increased stiffness, thermal stability and enzyme resistance of the cornea occur.⁹⁻¹¹

The original treatment protocol, introduced by Seiler et al. in Dresden Germany in 1997, begins with mechanical epithelium debridement in topical anaesthesia and application of topical 0.1% riboflavin-5-phosphate and 20% dextran solution (1 drop every 3 minutes) until corneal saturation is confirmed by presence of flare in the anterior chamber. UVA irradiation is then applied for 30 minutes by use of a timer controlled UVA-illuminator, which delivers homogeneous UVA light of 365 nm wavelength onto the cornea. Figure 2 shows the procedure.

The riboflavin saturation enables cross linking effect and also protects endothelium, lens and retina from UVA. The riboflavin saturated stroma attenuates UVA irradiation to an insignificant (non-harmful level of 5%) at the depth of 300 μ m. For safety reason a minimal corneal thickness of 400 μ m is required, which implies that keratoectasia patients with cornea thinner than 400 μ m cannot be treated by the current CCL technique.

Boxer-Wechler in USA and Pinelli in Italy introduced CCL without deepithelialization in 2004; instead of deepithelialization they applied

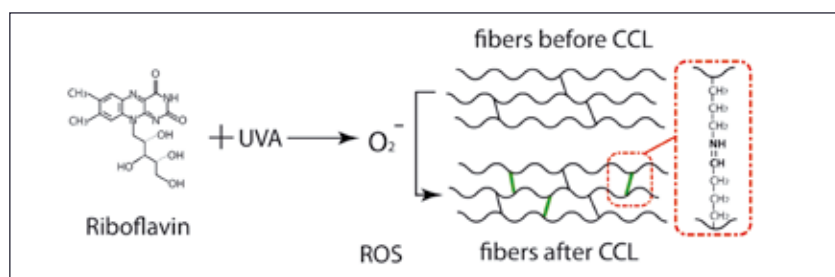


Figure 1: Biomechanical mechanism of CCL: Corneal stroma saturated by riboflavin and exposed to UVA irradiation causes photooxidative reaction where release of reactive oxygen species (ROS) stimulates covalent bond formations between fibers (= cross-linking).

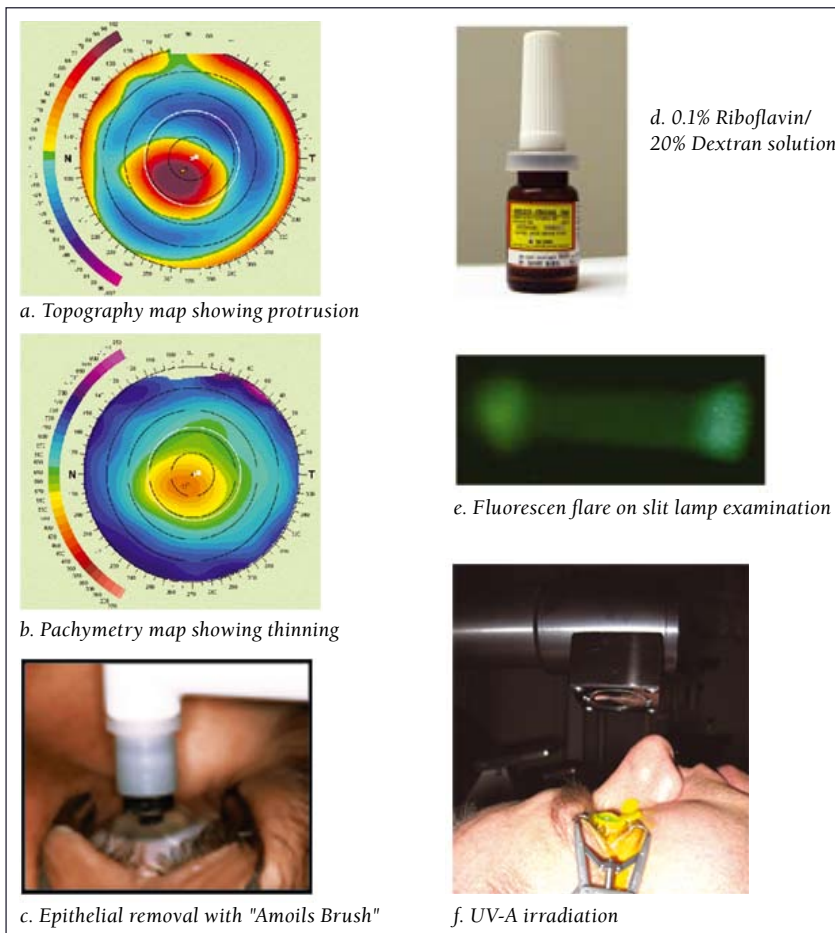


Figure 2: Diagnosis and CCL treatment of keratoectasia: a. and b. illustrate diagnosis of keratoectasia showing patient's corneal topography and pachymetry maps. Original treatment protocol is illustrated by c. epithelial removal, d. application of riboflavin solution, e. observation of flare (confirmation of stromal saturation) and d. UVA irradiation (3mW/cm² within a circle of 9 mm in diameter).

Tetracaine in order to loosen the tight epithelial junctions allowing penetration of riboflavin.

Indications

CCL is used to stop further progression of primary or iatrogenic keratoectasia in order to postpone or prevent corneal transplantation in advanced cases, or to halt the development of progressive keratoectasia and visual deterioration in early cases.

What happens to the cornea after CCL?

1. Changes of the corneal physical properties

Wollensak and colleagues have shown a three-fold in vitro increase in stress-strain resistance in CCL treated human corneas,⁹ while CCL treated pig corneas showed higher shrinkage temperature¹⁰ and increased enzymatic digestion time.¹¹

An estimate of the corneal in-vivo

biomechanical properties may be obtained by measurement of the corneal hysteresis with a newly introduced "Ocular response Analyzer." Once this measurement method is refined and standardized it may provide an objective estimate of the effect of the CCL.

2. Micro-changes

An incomplete disappearance of keratocytes in the anterior stroma has been registered immediately after CCL by use of confocal microscopy; nevertheless, keratocyte repopulation has been observed already 3 months after the treatment, to be almost complete after 6 months.¹²

Since only the anterior 300 μm of stroma is reached by the treatment, a thin stromal demarcation line, visible biomicroscopically, is formed at this depth due to the different reflection properties between the cross-linked and untreated corneal

stroma.¹³ An initial stromal edema with "sponge" or "honeycomb" appearance has been observed by confocal microscopy immediately after CCL, tending to disappear within 3 months.¹²

Is it safe?

There are two potential damage mechanisms: the UVA irradiation alone and the photochemical damage due to induced free radicals.¹⁴⁻¹⁶ The former is self-limiting since the human corneal stroma saturated with riboflavin reduces the UVA irradiation through a 300 μm stroma to the level below the damage threshold to endothelium.^{16,17} The latter can cause keratocytes apoptotic damage, but it appears to be recoverable by keratocyte repopulation.¹² Human endothelium damage has not been reported so far, and the endothelial cell density, lens transparency, and intraocular pressure seems to remain unchanged after CCL.^{18,19}

Risk of complications connected to deepithelialization (delayed reepithelialization, keratitis, etc.) may be increased after CCL because of higher incidence of atopic diseases and dry eyes in keratoconus patients, but there is currently no published evidence to support this.

Clinical results

Uncorrected visual acuity (UCVA) and best spectacle corrected visual acuity (BSCVA) improvement and decrease of keratometry-values have been commonly reported in the published literature.

According to the first published clinical study done by Wollensak et al (2003), where 23 eyes were treated, mean follow-up time was 23.2 months and the progression of keratoconus stopped in all eyes. Mean decrease of maximum keratometry-values by 2.01 D and mean spherical equivalent reduction by 1.14 D was found in 16 eyes, while mean BSCVA improved by 1.25 lines in 15 eyes.¹⁸

Caporossi and colleagues (2006) showed encouraging results as well. At 3 months after CCL, UCVA and BSCVA increased by 3.6 and 1.66 lines respectively and topographic analysis showed a mean keratometry-values reduction by 2.1 D.

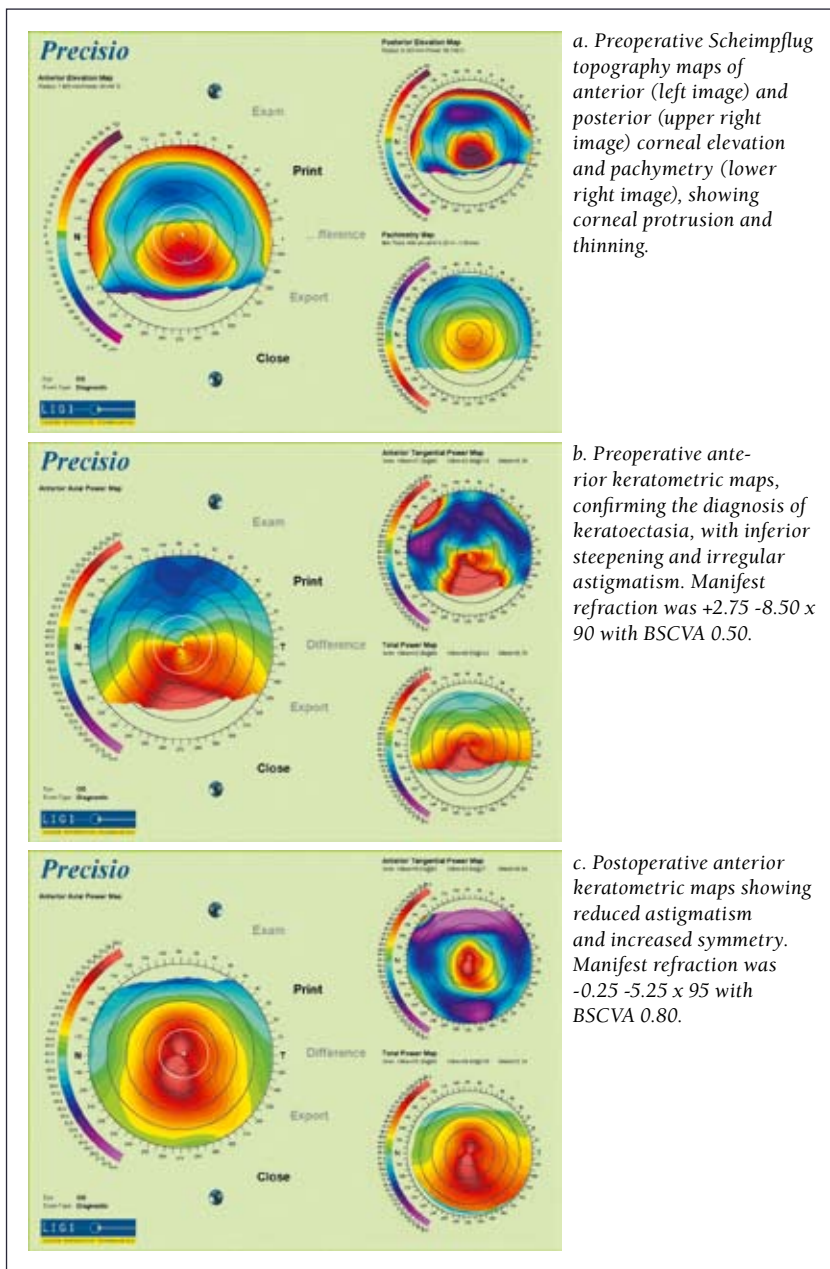


Figure 3: Combined treatment with CCL and topography guided custom excimer laser ablation of the left eye in a 23-year-old patient with keratoconus:

a. Preoperative Scheimpflug topography maps of anterior (left image) and posterior (upper right image) corneal elevation and pachymetry (lower right image), showing corneal protrusion and thinning.

b. Preoperative anterior keratometric maps, confirming the diagnosis of keratoectasia, with inferior steepening and irregular astigmatism. Manifest refraction was +2.75 -8.50 x 90 with BSCVA 0.50.

c. Postoperative anterior keratometric maps showing reduced astigmatism and increased symmetry. Manifest refraction was -0.25 -5.25 x 95 with BSCVA 0.80.

Topo-aberrometric analysis showed a trend toward increasing corneal symmetry between the vertical hemimeridians as well as reduction in astigmatism.¹⁹

For the sake of simplifying the procedure and to avoid possible complications caused by deepithelialization, as well as for the sake of patients' comfort, CCL without epithelium removal has been tried. This approach was supported by fluoroscopic findings that riboflavin penetrates cornea within 30 minutes of application even without epithelial removal. Pinelli et al. (2007)

found that there was no significant difference in visual, refractive and keratometric improvements between the deepithelialized group and the non-deepithelialized one.²⁰

CCL stiffens the stroma and halts the ectatic process, but it does not directly address the patient's refractive error, although it typically causes a minor flattening of the cornea (for up to 2 D). Hence the high and/or irregular astigmatism, which is omnipresent in advanced cases of keratoectasia and causes visual disability non-correctable with spectacles and/or soft contact

lenses, remains mostly unchanged after CCL. Consequently, only stopping the progression of keratoectasia in such cases does not represent a good enough solution for the patient. A combination of CCL with other types of treatments, in order to regularize corneal optics and achieve better vision, has therefore been tried. To address this, Kanellopoulos (2007) reported a case where he used CCL followed by topography-guided PRK, performing the two procedures 12 months apart. After CCL BSCVA improved from 0.4 to 0.5 and after topography-guided PRK (on the same eye) BSCVA improved further to 1.2, without any topographic evidence of keratoconus progression. In the meantime the untreated eye deteriorated.²¹

Recently, a combination of CCL and topography guided custom ablation in the same session has been performed²² and Figure 3 shows a case treated in this manner at the Eye department of the University Hospital North Norway.

Chan and colleagues showed that a combination of CCL and intracorneal ring segment implantation could also regularize the cornea and improve visual performance more effectively than CCL alone.²³

Conclusions

CCL has become very popular in the treatment of keratoectasia. It decreases the need for corneal transplantation by halting the ectatic process in progressive cases. It may also stabilize the recipient cornea as well as stiffen the donor cornea in keratoconus patients already transplanted with penetrating keratoplasty and in this way prevent or reduce the development of postoperative astigmatism. However, the most important indication for CCL will probably be corneal stabilization in latent or early keratoconus, when the patient still has good vision. In the future, the tissue stabilization effect of CCL may also be used on sclera, while the increase of enzymatic resistance may be used in treatment of corneal melting and for bacterial or fungal growth inhibition.²⁴

Referencer: www.oftalmolog.com ■

References

1. Feder R, Kshetry P: Noninflammatory ectatic disorders. In Krachmer JH, Mannis MJ, Holland EJ, editors: *Cornea*, 2nd Edition. Vol 1, 2005, Elsevier, pp 955-956.
2. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42:297-319.
3. Meek KM, Tuft SJ, Huang Y, Gill PS, Hayes S, Newton RH, Bron AJ. Changes in collagen orientation and distribution in keratoconus corneas. *Invest Ophthalmol Vis Sci*. 2005;46:1948-56.
4. Argento C, Cosentino MJ, Tytiun A, Rapetti G, Zarate J. Corneal ectasia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2001;27:1440-8.
5. Pallikaris IG, Kymionis GD, Astyrakakis NI. Corneal ectasia induced by laser in situ keratomileusis. *J Cataract Refract Surg*. 2001;27:1796-802.
6. Seiler T, Huhle S, Spoerl E, Kunath H. Manifest diabetes and keratoconus: A retrospective case-control study. *Graefes Arch Clin Exp Ophthalmol*. 2000;238:822-5.
7. Spoerl E, Seiler T. Techniques for stiffening the cornea. *J Refract Surg*. 1999;15:711-3.
8. Kymionis G, Portaliou D. Corneal crosslinking with riboflavin and UVA for the treatment of keratoconus. *J Cataract Refract Surg*. 2007;33:1143-4; author reply 1144.
9. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. *J Cataract Refract Surg*. 2003;29:1780-5.
10. Spoerl E, Wollensak G, Dittert DD, Seiler T. Thermomechanical behavior of collagen-cross-linked porcine cornea. *Ophthalmologica*. 2004;218:136-40.
11. Spoerl E, Wollensak G, Seiler T. Increased resistance of crosslinked cornea against enzymatic digestion. *Curr Eye Res*. 2004;29:35-40.
12. Mazzotta C, Balestrazzi A, Traversi C, Baiocchi S, Caporossi T, Tommasi C, Caporossi A. Treatment of progressive keratoconus by riboflavin-UVA-induced cross-linking of corneal collagen: ultrastructural analysis by Heidelberg Retinal Tomograph II in vivo confocal microscopy in humans. *Cornea*. 2007;26:390-7.
13. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea*. 2006;25:1057-9.
14. Wollensak G, Spoerl E, Reber F, Seiler T. Keratocyte cytotoxicity of riboflavin/UVA-treatment in vitro. *Eye*. 2004;18:718-22.
15. Wollensak G, Spoerl E, Wilsch M, Seiler T. Keratocyte apoptosis after corneal collagen cross-linking using riboflavin/UVA treatment. *Cornea*. 2004;23:43-9.
16. Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea*. 2007;26:385-9.
17. Wollensak G, Spoerl E, Reber F, Pillunat L, Funk R. Corneal endothelial cytotoxicity of riboflavin/UVA treatment in vitro. *Ophthalmic Res*. 2003;35:324-8.
18. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620-7.
19. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. *J Cataract Refract Surg*. 2006;32:837-45.
20. Pinelli R. Corneal collagen cross-linking with riboflavin (C3-R) treatment opens new frontiers for keratoconus and corneal ectasia. *Eyeworld*, May, 2007
21. Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty. *Cornea*. 2007;26:891-5.
22. Stojanovic A, Zhang J, Nitter T. Combination of topography guided transepithelial surface ablation and corneal collagen cross-linking in a single procedure for treatment of advanced keratoectasia: early results in three eyes. 2008; to be submitted
23. Chan CC, Sharma M, Wachler BS. Effect of inferior-segment Intacs with and without C3-R on keratoconus. *J Cataract Refract Surg*. 2007;33:75-80.
24. Pinelli R et al. C-3 Riboflavin Treatments: Where Did We Come From? Where Are We Now? *Cataract & Refractive Surgery Today Europe*. 2007 Summer: 36-46.