

Abstract

Hyperopic shift after corneal cross-linking in progressive keratoconus: 10-years observation of keratometry and vision.

Keratoconus is the most common progressive corneal ectatic disorder. The disease is characterized by bilateral thinning and protrusion of the cornea, leading to progressively increasing irregular astigmatism. Clinically, keratoconus manifests as a deterioration in visual acuity and frequent changes in spectacle correction. The global prevalence of keratoconus is estimated at 1.38 per 1,000 individuals. Initial symptoms typically appear between the ages of 10 and 30 years, predominantly in males. Identified risk factors include eye rubbing, asthma, allergies, a positive family history, and eczema. Delayed clinical manifestation poses diagnostic challenges, as early-stage keratoconus can be detected only through corneal topography while slit-lamp examination findings remain within normal range.

The goal of keratoconus management is irregular astigmatism correction and progression prevention. Visual rehabilitation may be achieved with spectacles, soft contact lenses, or rigid gas-permeable contact lenses. Patients who are intolerant to contact lenses may be candidates for surgical interventions, including intracorneal ring segment implantation or corneal transplantation. The golden standard for the treatment of progressive keratoconus is corneal collagen cross-linking (CXL). The primary outcome of the procedure is the arrest of progressive corneal steepening, reflected by stabilization or reduction of keratometric values, followed by stabilization or improvement in visual acuity. CXL may delay or eliminate the need for corneal transplantation, thereby positively affecting patients' quality of life.

The natural course of keratoconus was first comprehensively described in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study in 2007. During the 8-year follow-up period, visual acuity gradually deteriorated by an average of two letters, while keratometric values increased. An increase in corneal curvature of 1 diopter was associated with a decline in visual acuity of 0.49 letters. Corneal collagen cross-linking remains the only intervention with proven efficacy in stabilizing disease progression. The procedure was first performed by Wollensak in 1998 according to the Dresden protocol. The principle of the technique is based on the photosensitizing properties of riboflavin, which enhances the formation of additional

covalent bonds between corneal collagen fibers, thereby increasing corneal biomechanical stability.

The Dresden protocol involves topical anesthesia followed by removal of a 7-mm diameter area of the corneal epithelium. Subsequently, a 0.1% iso-osmolar riboflavin solution is applied to the exposed corneal stroma and allowed to saturate the tissue for 5 minutes. The cornea is then irradiated with ultraviolet A (UVA) light at a wavelength of 370 nm for 30 minutes, delivering a total energy dose of 5.4 J/cm². During irradiation, riboflavin instillation is continued every 5 minutes. This technique resulted in an average corneal flattening of 2 diopters and led to stabilization or improvement of visual acuity by at least one Snellen line in 65% of patients. Randomized clinical trials have subsequently confirmed the efficacy of CXL in keratometric parameters stabilisation.

A central corneal thickness below 400 µm is considered a contraindication to conventional Dresden protocol CXL because of the potential harmful effects of UVA radiation on the cornea, crystalline lens, and retina. Furthermore, the increased risk of stromal haze following conventional CXL limits its application in patients with advanced keratoconus. One modification enabling treatment of thinner corneas is the use of hypo-osmolar riboflavin, which induces transient corneal swelling and thereby increases corneal thickness. In this technique, after initial saturation with iso-osmolar riboflavin, the cornea is subsequently treated with hypo-osmolar riboflavin. The procedure demonstrates a safety and efficacy profile comparable to that of conventional CXL. During one-year follow-up, visual acuity and keratometric values remain stable, and corneal scarring has not been observed. Hypo-osmolar riboflavin may be used in corneas with a minimum thickness of 330 µm; however, keratoconus may continue to progress in thinner corneas despite intervention. Another limitation appears to be endothelial cell density, which may decrease following CXL, even when hypo-osmolar riboflavin is employed.

An alternative approach for thin corneas is epithelium-on (epi-on) or transepithelial corneal collagen cross-linking. The addition of agents that loosen intercellular desmosomal junctions, such as benzalkonium chloride (BAK) or ethylenediaminetetraacetic acid (EDTA), to the riboflavin solution enhances riboflavin penetration through the intact epithelium into the corneal stroma. Meta-analyses suggest that transepithelial CXL offers a more favorable safety profile; however, the procedure is associated with a higher risk of disease progression compared with conventional epithelium-off CXL. Currently, owing to the availability of more

sensitive diagnostic modalities, keratoconus is frequently detected at earlier stages, making conventional CXL the preferred treatment option. In patients with thinner corneas and more advanced disease, transepithelial CXL represents a safe alternative for slowing disease progression.

Long-term follow-up studies of patients with keratoconus undergoing CXL have demonstrated stabilization or improvement in visual acuity as well as corneal flattening. In a randomized clinical trial conducted by O'Brart in 2011, patients with bilateral keratoconus were randomly assigned to undergo corneal collagen cross-linking in one eye. After 18 months, the spherical equivalent in the treatment group decreased from -2.34 D to -1.52 D ($p = 0.06$), whereas it remained unchanged in the control group (-2.66 D before and -2.55 D after follow-up; $p = 0.7$). Keratometric values also decreased in the treatment group, from 47.1 D preoperatively to 46.5 D at 18 months postoperatively ($p < 0.001$). In contrast, keratometry remained stable in the control group (47.1 D before and 47.2 D after follow-up; $p = 0.3$).

In a randomized clinical trial published in 2008, Wittig-Silva compared the steepest corneal meridian in patients with keratoconus undergoing corneal collagen cross-linking with that of an untreated control group. After 36 months, the treatment group demonstrated a mean flattening of the steepest meridian of -1.03 ± 0.19 D, whereas the control group exhibited further corneal steepening of 1.75 ± 0.38 D. Simultaneously, visual acuity improved in the treatment group and deteriorated in the control group.

In a randomized clinical trial published in 2011, Hersh compared corneal collagen cross-linking with a sham procedure consisting of topical riboflavin application in patients with keratoconus and corneal ectasia. One year after intervention, the keratoconus subgroup demonstrated corneal flattening of 2.0 ± 4.4 D, as measured by the power of the steepest corneal meridian ($P = 0.002$). These studies collectively confirm the efficacy of CXL in halting the progression of keratoconus.

At the same time, long-term observations have demonstrated the dynamic nature of corneal remodeling following treatment. Published data regarding corneal parameters after cross-linking in patients with keratoconus over a decade-long follow-up remain scarce, and similar complications have not been reported to date.

The aim of the present study was to evaluate whether corneal shape continues to change 10 years after corneal collagen cross-linking in patients with keratoconus.

This retrospective cohort study included 49 eyes of 36 patients diagnosed with progressive keratoconus who underwent corneal collagen cross-linking at the LASER Eye Microsurgery Centre in Warsaw before 2014. Diagnosis was established based on subjective symptoms reported by patients and characteristic findings on corneal topography obtained with either the Galilei Z4 system (Ziemer Ophthalmic Systems AG, Port, Switzerland) or the Orbscan II system (Bausch & Lomb, Rochester, NY, USA). Diagnostic criteria included irregular astigmatism with an asymmetric inferior bow-tie pattern associated with corneal thinning and/or posterior corneal elevation.

Disease progression was defined as deterioration in visual acuity accompanied by either an increase in simulated keratometry (SimK) of at least 1.0 diopter or an increase in refractive astigmatism of at least 1.0 cylindrical diopter. Inclusion criteria comprised a diagnosis of progressive keratoconus, no history of previous ocular surgery, and the absence of other ocular or systemic diseases, with the exception of allergy, which frequently coexists with keratoconus.

The intervention consisted of corneal collagen cross-linking performed according to the Dresden protocol. All procedures were carried out by experienced surgeons (JI or IGL). Following topical anesthesia of the cornea with 0.5% proxymetacaine hydrochloride solution (Alcaine®, Alcon, Poland), the corneal epithelium was removed over a diameter of 7–9 mm using an epithelial debridement spatula. Subsequently, a 0.1% riboflavin solution with 20% dextran was applied to the exposed corneal stroma every 5 minutes for a total duration of 30 minutes. Five minutes after the first riboflavin instillation, the cornea was irradiated with UVA light at a wavelength of 370 nm from a distance of 1 cm for 30 minutes. The total delivered energy was 5.4 J/cm², with an irradiance of 3 mW/cm². At the conclusion of the procedure, a bandage contact lens was placed on the corneal surface and removed after complete re-epithelialization. Patients were instructed to use topical antibiotic drops four times daily until re-epithelialization and topical corticosteroid drops four times daily for two weeks.

Three time points were compared: preoperatively, 1 year after CXL, and 10 years after CXL. The primary outcome measures were simulated steep keratometry (SimK steep) [diopters],

simulated flat keratometry (SimK flat) [diopters], and best corrected distance visual acuity (BCDVA) [Snellen]. Secondary outcome measures included manifest refraction [diopters], spectacle correction [diopters], and thinnest corneal thickness (TCT) [μm]. SimK steep, SimK flat, and TCT were measured using the Galilei Z4 corneal topography system (Ziemer Ophthalmic Systems AG, Port, Switzerland), whereas visual acuity was assessed using Snellen charts. Refraction was measured using an autorefractometer Topcon KR-1 (Topcon Corporation, Japan).

The expected outcome was the arrest of keratoconus progression, reflected by stable keratometric values and preserved visual acuity. Based on clinical observations, we hypothesized that the cornea might become flatter 10 years after cross-linking.

To address the study objectives, statistical analyses were performed using JASP software (version 0.95.4). Descriptive statistics, the Shapiro–Wilk test of normality, one-way repeated-measures analysis of variance (ANOVA), and the Friedman test were applied. Statistical significance was set at $\alpha = 0.05$. Complete data from all three assessment time points were not available for every observation. Therefore, analyses for each variable included only those cases with complete datasets at baseline, 1-year follow-up, and 10-year follow-up. Consequently, sample sizes varied between analyses of different variables.

The distribution of SimK steep and SimK flat values approximated normality, whereas the remaining parameters significantly deviated from a normal distribution. Therefore, both parametric (ANOVA) and non-parametric (Friedman) analyses were performed. Statistically significant results were observed for six variables: spherical refraction, astigmatic axis, spherical correction, TCT, SimK steep, and SimK flat. The effect size was moderate for spherical refraction, small for astigmatic axis, strong for spherical correction, and very strong for TCT, SimK steep, and SimK flat. Bonferroni-corrected post hoc tests were subsequently conducted to identify differences between specific time points.

For simulated steep keratometry, the mean value before cross-linking was 48.38 ± 0.59 D and 48.40 ± 0.57 D at 1 year postoperatively. The difference was not statistically significant ($p = 1.0$), indicating stabilization of keratometric values following treatment. However, after 10 years, SimK steep decreased significantly to 47.05 ± 0.53 D ($p < 0.001$).

A similar pattern was observed for simulated flat keratometry. The mean preoperative value was 45.27 ± 0.56 D and 45.34 ± 0.55 D at 1 year postoperatively, with no significant

difference between the measurements ($p = 1.0$). After 10 years, however, SimK flat decreased significantly to 43.94 ± 0.51 D, compared with both previous measurements ($p < 0.001$). These findings suggest progressive corneal flattening occurring over the decade following cross-linking.

The observed keratometric changes did not affect best corrected distance visual acuity. Mean BCDVA was 0.65 before treatment, 0.68 at 1 year, and 0.67 at 10 years after treatment ($p = 0.629$).

The secondary outcomes were as follows. Mean spherical refraction was -0.85 ± 0.32 D preoperatively, -1.04 ± 0.33 D at 1 year, and -1.25 ± 0.33 D at 10 years ($p = 0.025$). Changes in cylindrical refraction did not reach statistical significance, although mean values were -1.91 ± 0.21 Dcyl before treatment, -1.90 ± 0.19 Dcyl at 1 year, and -1.53 ± 0.24 Dcyl at 10 years ($p = 0.085$).

The median astigmatic axis was 90° preoperatively, remained 90° at 1 year, and changed to 75° at 10 years ($p = 0.014$). Mean spherical spectacle correction was -3.21 ± 0.49 D before treatment, -3.05 ± 0.52 D at 1 year, and -2.16 ± 0.53 D at 10 years, with the decade-long change reaching statistical significance ($p < 0.001$). Changes in cylindrical spectacle correction, similarly to cylindrical refraction, did not achieve statistical significance. Mean cylindrical correction was -3.59 ± 0.34 Dcyl before treatment, -3.63 ± 0.35 Dcyl at 1 year, and -3.52 ± 0.33 Dcyl at 10 years ($p = 0.787$). The axis of cylindrical correction remained unchanged throughout follow-up.

The thinnest corneal thickness (TCT) measured 480.7 ± 5.33 μm before cross-linking, 468.2 ± 5.12 μm at 1 year, and 433.7 ± 7.71 μm at 10 years postoperatively ($p < 0.001$).

Based on these findings, it can be concluded that corneal shape continues to change in patients with keratoconus even 10 years after corneal collagen cross-linking. The observed long-term corneal flattening, accompanied by stable visual acuity, suggests ongoing corneal remodeling long after the initial stabilization of the disease process. compared with both baseline and the 1-year postoperative assessment. Both the steepest and the flattest simulated keratometric meridians decreased after 10 years. This change did not affect visual acuity, which remained stable throughout the follow-up period.

Over the 10-year observation period, mean astigmatism remained unchanged, whereas spherical refraction shifted toward greater myopia. However, this finding was not reflected in the spectacle correction used by patients, as spherical correction shifted toward hyperopia, while cylindrical correction remained unchanged. Corneal thickness measured at the thinnest point was significantly reduced compared with baseline, both at 1 year and at 10 years following the procedure.

In summary, previous studies have demonstrated that the primary effect of corneal collagen cross-linking is the arrest of progressive corneal protrusion, with treatment outcomes remaining stable over several years of follow-up. The present study indicates that, over a 10-year period, the cornea undergoes further flattening after cross-linking.

Although no significant changes in visual acuity were observed, such long-term corneal remodeling may influence visual performance, which depends on factors beyond visual acuity alone, including contrast sensitivity and higher-order optical aberrations. These parameters were not evaluated in the present study. Changes in corneal curvature in patients with keratoconus may facilitate the fitting of rigid contact lenses in individuals who were previously intolerant of this method of correction, potentially leading to improved visual function and, consequently, enhanced quality of life in patients with keratoconus.