Keratoconus Progression After Corneal Cross-Linking in Eyes With Preoperative Maximum Keratometry Values of 58 Diopters and Steeper

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Purpose: To evaluate the effectiveness of cross-linking (CXL) in treating keratoconus eyes with Kmax values ≥58.0 D.

Methods: Retrospective analysis of outcomes of standard Dresden epi-off CXL in progressive keratoconus with preoperative Kmax ≥58.0 Diopters (D). Inclusion criteria were Kmax ≥58.0 D and minimum follow-up of 1 year. Corneal topography and tomography were performed preoperatively and at 1 and 2 years. Sixty-one eyes of 56 patients with mean age of 24.9 ± 8.6 years (mean ± SD, range 12–57 years) had 1-year follow-up. Fifty of these eyes had 2-year follow-up. The definition of progression was an increase in Kmax of ≥1.0 D over 1 year.

Results: Mean Kmax was 63.9 ± 6.1 D (mean ± SD, range 58.2–87.0 D) preoperatively (n = 61) and 62.9 ± 5.9 D (range 54.6–82.5 D) after 1 year. This represented a significant decrease in steepness ($P = 0.0029$). Mean pachymetry decreased significantly from 433.7 ± 44.8 μm preoperatively to 423.0 ± 41.8 μm ($P = 0.001$) at 1 year. Progression occurred in 14 of the 61 eyes (23%) at 1 year, and 5 (8.2%) steepened more than 2.0 D. In the group with 2-year follow-up, mean Kmax was 63.0 ± 5.0 D (range 58.2–87 D) before CXL and decreased to 61.5 ± 4.8 D (range 53.6–78.3 D) at 2 years ($P = 0.001$). Nine of the 50 eyes (18%) showed an increase of Kmax of ≥ 1 D.

Conclusions: The incidence of progression (23% at 1 and 18% at 2 years, respectively) is considerably higher than in previously reported results of CXL in eyes with mean Kmax ≥58.0 D. To the best of our knowledge, this study represents the largest number of such steep corneas analyzed with respect to long-term progression after CXL.

Key Words: Kmax, CXL, advanced keratoconus, keratoconus progression, Kmax, corneal topography

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Keratoconus is a corneal ectasia with progressive corneal thinning that causes decreased visual acuity and may lead to hydrops and scarring requiring penetrating keratoplasty.[1] Corneal cross-linking (CXL) with riboflavin and UVA has been shown to be a safe and valid treatment option for progressive keratoconus.[2–4] Although studies on the outcome of CXL in mild to moderate keratoconus have shown an arrest of progression with a low failure rate of 0% to 2.8%,[5–7] the efficacy of CXL treatment in severe keratoconus eyes has been studied only in small numbers of eyes or as a subgroup analysis. It has been reported that the post-CXL progression rate seems to be higher in advanced keratoconus, and a Kmax value of more than 58 Diopters (D) was suggested to be a relative contraindication for CXL.[7] The widely accepted tomographic definition of progression of keratoconus has been identified as an increase of maximal keratometry (Kmax) of 1 or more D over a period of 12 months.[8]

Ivarsen and Hjortdal[9] recently reported that CXL may be safely performed in eyes with advanced keratoconus, although it is associated with a slightly higher rate (3.6%) of progression. The authors defined progression as an increase of Kmax of 2 D or more, in contrast to the above-mentioned classical definition of progression. A 5% progression rate was documented in a recent study with 4-year follow-up in advanced keratoconus, although inclusion criteria were defined as Amsler–Krumeich classification stage 3 and 4 without taking the Kmax value into account.[10]

The aim of this study was to analyze the efficacy of CXL in eyes with progressive advanced keratoconus with Kmax ≥58.0 D and to compare these results with relevant published studies.

MATERIALS AND METHODS

Ethics

The study adheres to the tenets of the Declaration of Helsinki and was approved by the local ethics committee as a retrospective study.

Study Design

This retrospective case study collected data of 61 eyes of 56 patients with documented progressive keratoconus with Kmax 58.0 D or steeper preoperatively. All had undergone CXL at the Department of Ophthalmology, University

Hospital, Bern, Switzerland, between 2009 and 2014. The patients were examined under slit-lamp and corneal topography and tomography at all visits. The study covered 1- to 2-year follow-up.

Patient Characteristics

Sixty-one eyes had 1-year follow-up. Fifty of these eyes had 2-year follow-up. Mean age was 24.9 ± 8.6 years (mean ± SD, range 12–57 years) at treatment. Figure 1 shows the study design in a flowchart.

Surgical Treatment

CXL treatment was performed in accordance with the Dresden epi-off protocol.[5] In 20 cases, an accelerated CXL protocol was used. All patients were treated with tetracaine hydrochloride 1% and periocular betadine preoperatively. After the insertion of a lid speculum, a diluted betadine solution was used to wash the eye. Using a hockey knife, 8- to 9-mm diameter epithelial ablation was performed. An isoosmolar 0.1% riboflavin solution (prepared with dextran 20%) was applied repeatedly every 5 minutes alternating with tetracaine and BSS for a total of 20 minutes. If corneal pachymetry was below 400 μm after removal of the epithelium and application of riboflavin with dextran, the cornea was treated with hypotonic riboflavin eye drops (1% riboflavin with NaCl 0.9%) according to the thin cornea protocol, until a corneal thickness of ≥400 μm was achieved.[11,12] If pachymetry was over 400 μm, the standard protocol was applied. After confirmation of a pachymetry >400 μm and of a positive flare in the anterior chamber, UVA irradiation therapy with a 3-mW/cm^2 lamp (UV-XTM 1000; Innocross, Zug, Switzerland) was performed for 30 minutes. In the accelerated CXL protocol, a 9-mW/cm^2 lamp (UV-XTM 2000; IROC Innocross) with an irradiation time of 10 minutes was used. In both treatments, riboflavin application was continued every 2 minutes (alternated with BSS) during irradiation. Of the 61 treated eyes, 27 eyes were treated according to the thin cornea protocol, and 20 eyes were treated according to the accelerated CXL protocol. Of the 20 eyes with the accelerated CXL protocol, 10 eyes were treated with the thin cornea protocol beforehand.

Postoperatively, topical antibiotic treatment with ofloxacin eye drops 0.3% 4 times daily was administered until complete healing of the epithelium. After epithelial closure, fluorometholone 0.1% eye drops were prescribed for 4 weeks. No contact lenses were used intraoperatively and until complete healing of the epithelial defect postoperatively.

Corneal Topography and Tomography

Data were gathered preoperatively and at 1 and at 2 years after CXL. Tomography was performed using the rotating Scheimpflug imaging Pentacam HR (Oculus, Germany). The steepest radius of curvature of the anterior surface (Kmax) and thinnest corneal thickness (TCT) were analyzed. The topographic modeling system TMS-4 (Tomey Corp, Japan) was used to document corneal topography. Average keratometry values (AvK), cylinder (cyl), surface asymmetry index (SAI), and surface regularity index (SRI) were analyzed. These measurements were acquired at baseline and at every follow-up.

Postoperative progression was defined as an increase in Kmax of 1 D or more in 1 year.[7] A different definition of progression using an increase of Kmax of more than 2 D was used to compare the results to those of a recent study.[9] All data showing a progression of 1 D or more were reviewed by 2 independent investigators to confirm progression. In cases of nonconsensus, a third investigator was included.

Statistical analysis was performed using SPSS Statistics (IBM Corp). All data were investigated for normal distribution using the Shapiro–Wilk test. Because of the nonnormally distributed data, the Wilcoxon test was used to compare all data points (Kmax, TCT, AvK, cyl, SRI, and SAI) at 1 and 2 years with baseline and between 1 and 2 years. The correlation analysis was performed using the Spearman rho test. $P < 0.05$ was considered significant.

RESULTS

Subject Ages

The age of the subjects was 24.9 ± 8.6 years (mean ± SD, range 12–57 years) at the date of CXL.

Changes in the Kmax and Progression Rate

Preoperative Kmax was 63.9 ± 6.1 D (mean ± SD, range 58.2–87.0 D). At 1 year, it was significantly reduced to 62.8 ± 5.9 D ($P = 0.014$, range 54.6–82.5 D). For the eyes with 2-year follow-up, Kmax was 63.0 ± 5.0 D (range 58.2–87 D) before CXL and 61.5 ± 4.8 D (range 53.6–78.3D) at 2 years, showing a significant ($P = 0.001$) reduction of Kmax over 2 years compared with baseline. There was no significant change in Kmax between 1 and 2 years of follow-up (Fig. 2).

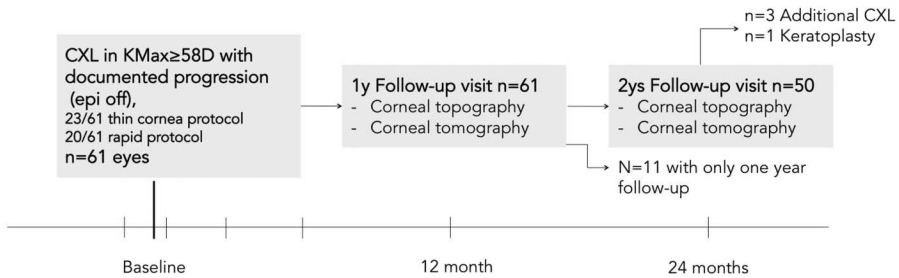

FIGURE 1. Study design.

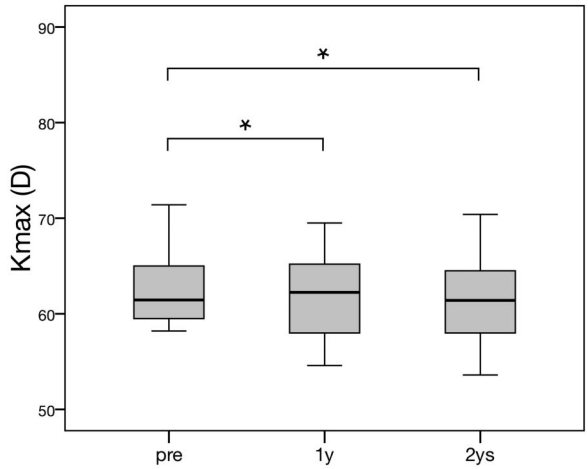

FIGURE 2. Changes in Kmax after 1 and 2 years. The boxplot shows a significant decrease of Kmax 1 and 2 years after cross-linking (*) ($P < 0.05$) in the 2-year follow-up group. No significant changes were found between 1 and 2 years.

The changes in Kmax showed large variations between individual eyes with ΔKmax of ±6 D after 1 year and +6 D and up to −10 D after 2 years. Figure 3 shows the ΔKmax for each individual patient with 2 years of follow-up (Fig. 3). No correlation between the preoperative Kmax value and the postoperative ΔKmax after 1 year was found ($P = 0.518$).

Progression (increase in Kmax of 1 D or more) occurred in 14 of the 61 eyes (23%) after 1 year. Five of these 14 eyes (35.7%) had undergone the accelerated CXL protocol, a proportion similar to that of accelerated protocol eyes included in the entire study (20 of 61 eyes, ie, 32.7%). Five of the 61 corneas (8.2%) had steepened > 2 D at 1 year. Twenty-nine of the 61 corneas (47.5%) showed a flattening of 1 D or more of postoperative Kmax. Twenty-four of the 61 eyes (39.3%) even showed a flattening of 2 D or more. No significant correlations between the preoperative Kmax value and the postoperative ΔKmax or the preoperative age and the postoperative ΔKmax could be found. This is shown in Figure 4 (preoperative Kmax) and Figure 5 (preoperative age).

For the eyes with 2-year follow-up, progression occurred in 9 of 50 eyes (18%). Five of these 50 eyes steepened more than 2 D (10%). Seven of these eyes had been progressive after 1 year already. As a matter of fact, 3 progressive eyes at 1 year halted their progression in the second year.

Subgroup analyses revealed no significant difference in the baseline Kmax and the postoperative Kmax values between the patients with the standard protocol versus the thin cornea protocol, and the standard protocol versus the accelerated protocol.

Of the 61 eyes, 3 eyes underwent second CXL, and 1 eye underwent penetrating keratoplasty. These retreatments were performed in cases with a confirmed increase of Kmax >2 D in at least 2 consecutive measurements and marked refractive changes or corneal thinning.

Changes in Thinnest Corneal Pachymetry

Mean pachymetry at the TCT point was 433.7 ± 44.8 μm preoperatively and significantly lower at 1 year (423.0 ± 41.8 μm, $P = 0.001$). For the 50 eyes with mean follow-up of 2 years, TCT was 440.5 ± 41.8 μm preoperatively and 425.6 ± 41.8 μm at 2 years ($P = 0.001$). No significant changes were found between 1 and 2 years in the 2-year follow-up group (Fig. 6).

Changes in AvK, cyl, SRI, and SAI

SRI showed a significant decrease from 1.7 ± 0.4 to 1.6 ± 0.4 ($P = 0.01$) after 1 year. There was no significant change in average keratometry (AvK), cylinder (cyl), or SAI 1 year after CXL.

After 2 years, there was a significant decrease of AvK from 52.2 ± 4.3 D to 51.5 ± 3.8 D ($P = 0.042$) compared

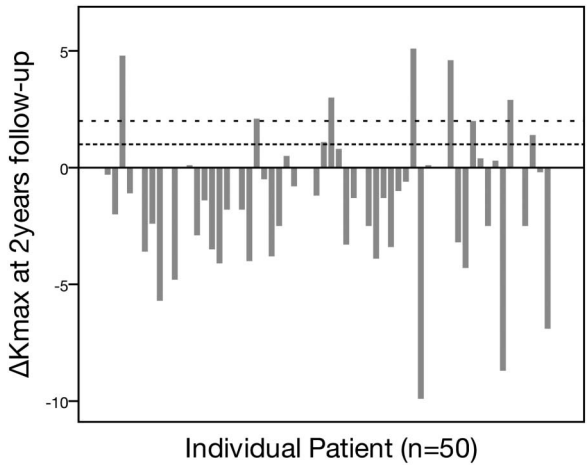

FIGURE 3. ΔKmax of all individual patients completing 2-year follow-up. ΔKmax is defined as the difference in Kmax before CXL and after 2 years. The dashed lines show an increase of Kmax of 1 D (——) or 2 D (- - - -), respectively.

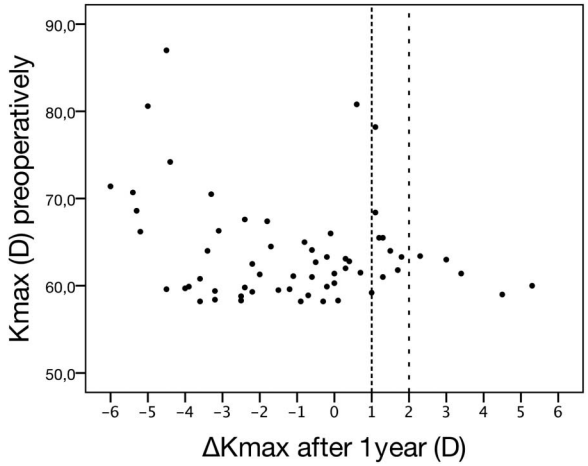

FIGURE 4. ΔKmax (D) after 1 year compared with the preoperative Kmax value shows no significant correlation with the preoperative Kmax value. The dashed lines show an increase of Kmax of 1 D (——) or 2 D (- - - -), respectively.

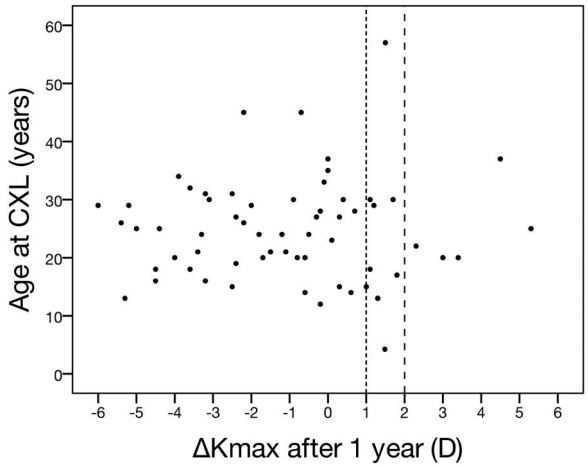

FIGURE 5. ΔKmax (D) after 1 year compared with preoperative age (years) shows no significant correlation with preoperative age. The dashed lines show an increase of Kmax of 1 D (——) or 2 D (- - - -), respectively.

with baseline. SAI also showed a significant change from 3.6 ± 1.8 to 2.9 ± 1.4 (P = 0.005). There was no significant change in cyl or SRI.

Complications

We did not observe any severe or persisting complications. However, postoperative pain and transient corneal haze were common.

DISCUSSION

CXL is an effective treatment to arrest the progression of keratoconus. Postoperative progression rates in eyes with mild to moderate keratoconus (Kmax < 55 D) have been found to be between 0% and 2.4%.[7] In contrast, keratoconus with very steep corneas (Kmax ≥ 58 D) has been shown to have a higher incidence of postoperative progression. Accordingly, the concept of a relative contraindication for CXL in corneas with a preoperative Kmax of 58 D or more is used.[7]

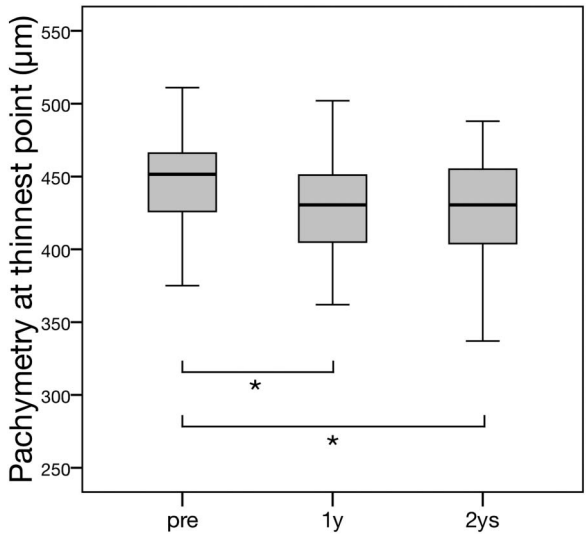

FIGURE 6. Thinnest pachymetry at 1 and 2 years decreased significantly compared with the preoperative value (*) (P < 0.05). No significant changes were found between 1 and 2 years.

This study evaluates post-CXL progression in corneas with a Kmax ≥58.0 D. To the best of our knowledge, it represents the largest group of such eyes analyzed. Although a significant overall postoperative decrease of mean Kmax was found, progression rates of 23% (after 1 year) and 18% (after 2 years) were much higher than in all previously published studies.[9,10]

If progression is defined as an increase of Kmax of more than 2D, as applied in the study by Ivarsen and Hjortdal,[9] the rate was still higher at 8.2% after 1 year and 10% after 2 years, compared with the published data of 3.6% after mean follow-up of 22 months.

In contrast, in our study, 29 of 61 eyes (47.5%) showed significant flattening of the cornea with a reduction of Kmax of 1 D or more after 1 year, demonstrating an effective treatment in these eyes. The incidence of postoperative progression in the accelerated protocol group was not higher than in the eyes treated with 3 mW/cm^2. This is consistent with similar findings in recently published studies.[12,13] Bulk reduction of Kmax postoperatively occurs in the first year after CXL. There is no significant further reduction in the second year. Interestingly, the preoperative Kmax value does not correlate with the postoperative change in Kmax.

Significant reductions in TCT were observed after 1 and 2 years compared with baseline, but no significant changes were found between 1 and 2 years, suggesting that the change in TCT occurs in the first year. These changes in thickness are similar to previous reports showing a dip of TCT in the tomography reading in the first 6 months with stabilization thereafter. The reason for this change is still unknown and may be due to a postoperative artifact.[14]

The high rate of progression shown in this study justifies the following conclusions:

1. The relative contraindication for CXL in steep corneas can be confirmed because of a higher rate of progression, although an overall reduction of Kmax is seen. The higher risk of progression has to be discussed with the patient before CXL is performed.

In the population of this study, some of the treated patients had cognitive impairment. Therefore, CXL often was recommended instead of keratoplasty because of the reduced compliance anticipated. This may also have contributed to the incidence of progression because of excessive rubbing.[15,16]

1. The definition of progression as an increase of Kmax of 1 D or more may be too strict in cases of severe keratoconus because of high intersession variability of Pentacam measurements, especially in advanced cases.[17,18] Repeated measurements may help to detect diagnostic traps such as transient pseudoprogression, and therefore avoid false conclusions.

The use of a multidevice approach combining a Placido disk-based with a Scheimpflug-based measurement system is likely to improve data capture and the reliability of progression assessment.[18]

In the cases of tomographically documented keratoconus progression, repeat CXL has to be considered, taking into account the best-corrected visual acuity of both eyes and its evolution since CXL, as well as the degree of postoperative compliance. It was shown that repeat CXL seems to have a high rate of success in halting further progression.[16]

In summary, this study shows that in very steep keratoconus eyes and progressive disease, much higher tomographic progression than previously reported is seen after CXL. The higher rate of postoperative progression has to be discussed with the patient preoperatively, and lamellar or penetrating keratoplasty has to be considered an alternative first-line treatment. To the best of our knowledge, our study covers the largest number of such corneas analyzed 1 and 2 years after CXL.

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