Corneal Changes in Progressive Keratoconus After Cross-linking Assessed by Scheimpflug Camera

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ABSTRACT

PURPOSE: To evaluate corneal changes after corneal cross-linking (CXL) in progressive keratoconus with Scheimpflug imaging.

METHODS: This prospective analysis included 40 eyes from 22 patients with progressive keratoconus. Corneal CXL was performed in 25 eyes (CXL group) and 15 fellow eyes served as controls (control group). Uncorrected (UDVA) and corrected distance visual acuity (CDVA), thinnest corneal thickness (ThCT), posterior elevation, and Holladay equivalent keratometry values (K1, K2) were determined with Pentacam (Oculus Optikgeräte GmbH) before and 1 year after CXL. Area under the receiver operator characteristic (ROC) curve and multivariable general estimating equation models were used to determine the most sensitive parameters of corneal changes.

RESULTS: Manifest sphere (−2.55±3.21 to −1.48±2.39 diopters [D], P=.02), UDVA (0.23±0.25 to 0.31±0.25, P=.001), and CDVA (0.58±0.28 to 0.72±0.19, P=.019) improved significantly in the CXL group. Significant decreases were found in ThCT (472.53±33.18 to 440.53±38.67 μm, P<.001), posterior elevation (68.33±28.69 to 22.67±16.21, P<.001), and keratometry values (K1 [45.06±4.55 to 43.51±4.67 D, P<.001], K2 [48.39±5.41 to 46.71±5.67 D, P<.001]) in the CXL group. These parameters remained stable in controls (P>.05). According to ROC analysis, posterior elevation change was the most characteristic parameter of corneal change after CXL (area under the curve=0.99). General estimating equation model showed that CXL (P=.001) and initial ThCT (P=.007) were significant predictors of decrease in posterior elevation with a significant negative interaction of initial ThCT on CXL effect (P=.005).

CONCLUSIONS: Posterior elevation is a sensitive parameter to monitor corneal remodeling after CXL. Corneal CXL showed augmented effect on corneal protrusion in eyes with thinner corneas. [J Refract Surg. 2012;28(9):645-649.]
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Corneal keratoconus is a bilateral, noninflammatory, progressive disorder characterized by corneal thinning and protrusion that induces myopia and myopic astigmatism.1,2 For treating corneal ectasia, corneal collagen cross-linking (CXL) is a safe and effective technique, using a combination of photosensitizer riboflavin (vitamin B2) and ultraviolet-A (UVA) irradiation at 370 nm. The photosensitizer riboflavin is excited into its triplet state, generating reactive oxygen species that induces chemical covalent bonds bridging amino groups of collagen fibrils, strengthening inter- and intrafibrillar cohesion.3-7 After CXL, qualitative examination of corneas with confocal microscopy and optical coherence tomography showed microscopic alterations in the stromal tissue to the depth of 200 to 350 μm. Deep stromal tissue beyond 350 μm does not seem to be reached by the treatment.4-8,10 Long-term results have demonstrated the ability of CXL to slow the progression of keratoconus. In addition, clinical studies have suggested improvement in uncorrected (UDVA) and corrected distance visual acuity (CDVA) and reshaping of the anterior corneal surface, evaluated by topographic and anterior elevation parameters.11-13 With the advent of the Scheimpflug camera (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany), measurement of the anterior and posterior corneal surface elevation data and detailed pachymetry map construction have become possible.14,15 Height data provide a more accurate representation of the true shape of the cornea because they are independent of axis, orientation, and position.16-18 According to the classic Placido-based topographic findings in keratoconus, the...
most specific changes in the curvature are steepening and protrusion of the cornea usually inferior to the visual axis.¹,¹⁹ Recent studies, based on elevation data obtained by Orbscan (Bausch & Lomb, Rochester, New York) and Pentacam measurements, indicate that deformation occurs not only at the anterior but also at the posterior corneal surface of keratoconic eyes. Corneal thickness and posterior elevation at minimum pachymetry proved to be highly reliable diagnostic parameters of the disease.²⁰,²¹ However, no consensus exists on the best clinical parameter to monitor the treatment efficacy after CXL. The purpose of this study was to evaluate corneal changes after CXL in progressive keratoconus assessed by Scheimpflug imaging.

**PATIENTS AND METHODS**

**PATIENTS**

This prospective analysis included 40 eyes from 22 patients (mean age: 29.92 years) with keratoconus. Cross-linking was performed in 25 eyes with progressive keratoconus (CXL group) and 15 eyes served as controls (control group). Disease progression was demonstrated by increase of keratometry (K) values (>1.00 diopeters [D] in 6 months) and subjective loss of vision (loss of >2 lines of CDVA in 1 year). The 15 control eyes had mild to moderate keratoconus and no detectable disease progression during the follow-up period.

All eyes underwent a complete ophthalmologic examination including slit-lamp microscopy and keratometry. Rabinowitz criteria were used for diagnosing keratoconus.²² A written, informed consent was obtained from each patient prior to surgery.

**MEASUREMENTS**

All eyes were examined with the Pentacam HR used by three trained examiners (K.K., K.M., G.L.S.) before and 1 year after CXL during the follow-up period. Scheimpflug pachymetry, Holladay equivalent keratometry readings, and elevation data measurements were performed. Readings were taken as recommended in the instruction manual, as detailed previously.²⁰ The following data were exported to Microsoft Excel (Microsoft Corp, Redmond, Washington): Holladay equivalent keratometry values in the flat (K1) and steep (K2) meridian, thinnest corneal thickness (ThCT), and posterior elevation values at minimum pachymetry. For height data measurement, the toric ellipsoid reference surface was used.²³

Severe cases with stromal haze or scar formation were excluded, because these pathologies may alter the optical transparency of the cornea and image acquisition of the Pentacam.

Patients who wore rigid contact lenses were asked to stop use for 4 weeks, and soft contact lenses were stopped for at least 1 week before assessment.

Cross-linking was conducted under sterile conditions in the operating room. The patient’s eye was anesthetized with oxybuprocaine-hydrochloride 4 mg/mL drops. The central part of the corneal epithelium, in a circle with an 8.0-mm diameter, was removed to facilitate diffusion of riboflavin into the stroma. A 0.1% riboflavin solution (10 mg riboflavin-5-phosphate in 10 mL dextran 20% solution) was applied every 5 minutes starting 25 minutes before irradiation. The irradiation was performed from a 1-cm distance for 30 minutes using a UVA double diode at 370 nm and an irradiance of 3 mW/cm² (equal to a dose of 5.4 J/cm²). The required irradiance was controlled in each patient immediately before treatment to avoid a potentially dangerous UVA overdose.

Within the first 7 days, all treated patients received antibiotic drops (levofl oxacin 5 mg/mL drops five times daily). After reepithelialization of the cornea, steroid drops (flurometholone) were given as prophylaxis to prevent the formation of significant subepithelial haze.

**STATISTICAL ANALYSIS**

Statistical analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, Illinois). In all analyses, P<.05 was considered statistically significant. Normal distribution assumption could be accepted for all parameters according to the Shapiro-Wilks W-test. For group comparisons of continuous variables, the Student t-test for paired samples was used.

Area under the receiver operating characteristic (ROC) curve was calculated to find the most sensitive parameter of corneal changes after CXL. Multivariable regression analysis including tests of interactions was performed using general estimating equation to determine the influence of initial corneal thickness on the effect of CXL. The generalized estimating equation method was used to account for the correlation between fellow eyes in the regression analysis. Model fit was assessed using the value of the corrected quasi-likelihood under independence model criterion, main effects and interaction terms were kept in the model if they were associated with P<.05, and the overall fit of the model improved as indicated by a decrease in the corrected quasi-likelihood under independence model criterion.

**RESULTS**

Uncorrected distance visual acuity and CDVA were significantly better in the control group before treatment (Table 1). No statistically significant difference
was noted between the two groups in manifest sphere and cylinder refraction before and after CXL. Manifest sphere improved significantly in the CXL group 1 year after treatment (Table 1).

After 1 year, both UDVA and CDVA improved significantly in the CXL group ($P < .001$ and $P = .019$, respectively) whereas these parameters did not change in the control group ($P > .05$) (Table 1).

At baseline, no significant differences were noted in corneal thickness (ThCT) and Holladay equivalent keratometry readings (K1 and K2) between groups, but posterior elevation at the thinnest point of the cornea showed significantly higher values in the CXL group ($P < .001$). One year after CXL, a significant difference between groups was observed for ThCT ($P < .001$), but not posterior elevation and keratometry values ($P > .05$). After 1 year, a significant decrease was found ($P < .001$) in ThCT, posterior elevation, K1, and K2 values in the CXL group, although these parameters did not worsen significantly in the control group ($P > .05$) (Table 1).

Figure 1 shows the results of ROC curve analysis for change in posterior elevation and keratometry values. According to area under the ROC values, posterior elevation change proved to be the most characteristic parameter of corneal flattening after CXL followed by keratometry values, K2 and K1 (Table 2).

Results of the general estimating equation model showed that both CXL ($P = .001$) and initial ThCT ($P = .007$) had significant effects on changes in posterior elevation values at 1 year with a significant negative influence of higher initial corneal thickness on CXL effect ($P = .005$) (Fig 2).

**DISCUSSION**

Our results show significant changes in the shape of keratoconic corneas after CXL demonstrated by

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**TABLE 1**

**Visual Acuity and Corneal Parameters Measured By Pentacam***

<table>
<thead>
<tr>
<th></th>
<th>CXL Group</th>
<th>Control Group</th>
<th>$P$ Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Year</td>
<td>Baseline</td>
</tr>
<tr>
<td>UDVA (decimal)</td>
<td>0.23±0.25</td>
<td>0.31±0.25‡</td>
<td>0.57±0.35</td>
</tr>
<tr>
<td>CDVA (decimal)</td>
<td>0.58±0.28</td>
<td>0.72±0.19‡</td>
<td>0.83±0.26</td>
</tr>
<tr>
<td>Sphere (D)</td>
<td>–2.55±3.21</td>
<td>–1.48±2.39‡</td>
<td>–1.35±2.06</td>
</tr>
<tr>
<td>Cylinder (D)</td>
<td>–3.49±2.45</td>
<td>–3.00±2.25</td>
<td>–2.15±2.12</td>
</tr>
<tr>
<td>K1 (D)</td>
<td>45.06±4.55</td>
<td>43.51±4.67‡</td>
<td>44.51±2.05</td>
</tr>
<tr>
<td>K2 (D)</td>
<td>48.39±5.41</td>
<td>46.71±5.62‡</td>
<td>46.37±2.60</td>
</tr>
<tr>
<td>ThCT (µm)</td>
<td>472±33</td>
<td>441±39‡</td>
<td>489±26</td>
</tr>
<tr>
<td>PE (µm)</td>
<td>68.33±28.69</td>
<td>22.67±16.21‡</td>
<td>16.93±41.19</td>
</tr>
</tbody>
</table>

CXL = corneal cross-linking, UDVA = uncorrected distance visual acuity, CDVA = corrected distance visual acuity, K = keratometry, ThCT = thinnest corneal thickness, PE = posterior elevation

*Holladay equivalent keratometry readings in the flat (K1) and steep (K2) meridian, corneal thickness at thinnest pachymetry, and posterior elevation at minimum pachymetry at baseline and 1 year after treatment.

†Difference between groups.

‡$P < .05$ change between baseline and 1 year in the same group using Student $t$ test for paired samples.

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**Figure 1.** Receiver operator characteristic curve analysis determined change in posterior elevation (PE) as the most sensitive variable to differentiate corneal cross-linking cases from controls. The evaluated variables were change in Holladay equivalent keratometry (K) readings in the flat (K1) and steep (K2) meridians and change in PE at minimum pachymetry between baseline and 1 year.
Scheimpflug imaging with a concomitant improvement in visual function after the procedure. Although this flattening effect of CXL has already been reported by previous studies evaluating the anterior surface of the cornea,\textsuperscript{11-13} this is the first study to demonstrate corneal flattening of both the anterior and posterior corneal surfaces based on analysis of detailed corneal elevation maps of Scheimpflug imaging.

Corneal thickness at minimum pachymetry decreased significantly 1 year after CXL in accordance with previously reported results.\textsuperscript{12,13} Although the pathophysioloogy of these alterations are not explored in detail, postoperative keratocyte apoptosis and structural changes in corneal collagen fibrils and extracellular matrix may play a pivotal role in corneal thinning after CXL.\textsuperscript{8,9,12}

Both the statistically significant decrease in posterior elevation and the parallel decrease in Holladay equivalent keratometry values\textsuperscript{24} in the CXL group indicate flattening of the cornea after CXL (Table 1). According to ROC curve analysis, change in posterior elevation proved to be the most sensitive parameter to detect CXL effect on corneal shape, followed by changes in steep and flat keratometry values.

Although flattening of the cornea may result in alteration of the radius of the best fit toric ellipsoid reference surface, in this study, best fit toric ellipsoid reference surface was used as it was proven to be the most sensitive reference body to detect local, subtle elevation changes in keratoconus.\textsuperscript{23}

We analyzed the influence of corneal thickness on the effect of CXL measured by changes in posterior elevation. The multivariable regression model showed that apart from CXL, initial corneal thickness also had a significant influence on changes of posterior elevation. Moreover, in this regression model, we found a significant negative interaction between CXL and initial corneal thickness, indicating that in eyes with thinner corneas the flattening effect of CXL is augmented. In our study, a standardized and widely used protocol was applied during CXL, providing nearly equal penetration depth of riboflavin and UVA. Supposing approximately equal penetration depth in all eyes, CXL may affect deeper stromal tissues of thinner corneas compared to less advanced cases with thicker corneas. These findings suggest that the thicker portion of the stromal tissue is affected by CXL, the more pronounced local flattening effect can be measured after the procedure.

Cross-linking has already proven to be effective in stabilizing corneal ectasia in progressive keratoconus. With the advent of the most modern diagnostic tools, early detection of forme fruste cases has become possible. Currently, applying this therapeutic approach is widely recommended in progressive keratoconus to preserve good visual function and relatively regular corneal shape.\textsuperscript{3-6} The results of this study demonstrate that posterior elevation measured by Pentacam is a highly sensitive parameter to monitor corneal flattening after CXL. Current clinical recommendations propose early treatment of progressive keratoconus to prevent deterioration of visual quality. However, our results have shown that in advanced cases with thinner corneas, CXL has even more detectable beneficial effect on corneal protrusion, suggesting its consideration as a therapeutic method of advanced keratoconus as well. This observation should be considered in the surgical planning of simultaneous topography-guided refractive laser surgery and CXL.

**AUTHOR CONTRIBUTIONS**

Study concept and design (K.K., I.K., K.M., J.N., Z.Z.N.); data collection (K.K., G.L.S.); analysis and interpretation of data (K.K., I.K., K.M., M.C.K.); drafting of the manuscript (K.K., I.K.); critical revision...

REFERENCES


