

# Long-Term Outcomes of Corneal Collagen Cross-Linking: Results of 6-Years Follow-Up

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## Research article

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# Abstract

**Background:** Our aim was to evaluate the long-term effects of conventional epithelium-off corneal cross-linking performed on patients with progressive keratoconus.

**Methods:** A retrospective analysis was performed on 34 eyes of 34 patients with progressive keratoconus underwent conventional cross-linking using Pentacam HR Scheimpflug camera. Visual acuity, spherical equivalent, keratometry, pachymetry and corneal topographic indices were analysed preoperatively and at 1, 3, and 6 years after the surgery.

**Results:** Statistically significant decrease was detected at 1 year in spherical equivalent ( $p = 0.022$ ), with no significant changes afterward ( $p = 0.616$ ). Uncorrected and best corrected distance visual acuity improved significantly in the first postoperative year ( $p = 0.017$  and  $p = 0.003$ , respectively), and remained stable with no significant changes at further visits ( $p = 0.203$  and  $p = 0.336$ , respectively). Significant decrease of central corneal thickness and thinnest corneal thickness was observed at 1 year (both  $p < 0.001$ ), with additional thinning of thinnest corneal pachymetry up to 3 years ( $p = 0.01$ ). Maximum keratometry and mean keratometry showed significant, continuous improvement between all consecutive visits over the whole follow-up period (all  $p$ -values  $< 0.05$ ). Significant improvement was found in the following 5 topographic indices at 1 year: ISV ( $p = 0.001$ ), IVA ( $p = 0.028$ ), KI ( $p = 0.002$ ), CKI ( $p < 0.001$ ) and  $R_{\min}$  ( $p < 0.001$ ), with further improvement up to 3 years in ISV ( $p = 0.007$ ), in CKI ( $p = 0.019$ ) and in  $R_{\min}$  ( $p = 0.015$ ).  $R_{\min}$  showed more improvement up to the end of follow-up ( $p < 0.001$ ).

**Conclusions:** Conventional epithelium-off corneal cross-linking is effective in halting the progression of keratoconus and in regularization of the anterior corneal surface over a long-term follow-up period up to 6 years.

## Background

Cross-linking (CXL) is a minimal-invasive surgical therapy of ectatic corneal disorders such as keratoconus or postrefractive keratectasia. Results of the first human clinical study reported by Wollensak et al. in 2003 presented conventional CXL as a new treatment possibility to stop the progression of keratoconus [1]. Afterwards, CXL became the primary option for surgical management of keratoconus, radically reducing the number of more invasive interventions such as penetrating keratoplasty [2, 3].

A number of research groups have demonstrated that CXL significantly improves corneal biomechanical properties [4–6]. Increased corneal stiffness and improved resistance to enzymatic degradation have been reported in several in vitro studies [7–11]. This is believed to be achieved by combined use of photosensitizer riboflavin and UV-A light that induces photochemical covalent bonds between collagen fibers. Development of cross-links strengthens intermolecular cohesion and modify the underlying pathophysiology of keratoconus.

Successful of standard epithelium-off CXL in slowing down or halting the deterioration of keratoconus have been confirmed by various clinical studies [12–16]. Recent data supports that CXL is effective in the management of early and advanced keratoconus as well [12]. It has been proven that CXL causes significant changes on both anterior and posterior corneal surface [17, 18]. Flattening of the cornea, reduction of astigmatic power and wavefront aberrations have been reported [19, 20]. Uncorrected and best corrected visual acuity also seemed to be improved compared to untreated keratoconic eyes [21, 22].

Currently, rotating Scheimpflug photography is the most prevalent imaging technique in the diagnosis, staging and follow-up of patients with keratoconus. This technique allows rapid and noncontact measurement of the anterior segment parameters. Comprehensive assessment of both anterior and posterior corneal surface, thus, ectatic changes can be identified in early stages. Pentacam system provides evaluation of corneal topographic indices, which can reflect optical properties and pathological alterations in the curvature of the anterior shape.

However, several studies investigate corneal changes after CXL, most have reported results with a relatively short follow-up period within two years, thus, available data about long-term results is limited. The aim of this study was to evaluate the long-term outcomes of conventional epi-off CXL for progressive keratoconus by using Scheimpflug topographic and tomographic parameters and analyzing clinical results.

## Methods

This retrospective study was conducted on a group of 34 eyes from 34 patients with progressive keratoconus underwent conventional collagen cross-linking. All patients were examined and treated at the Department of Ophthalmology, Semmelweis University. The protocol of the study was approved by the Semmelweis University Regional and Institutional Committee of Sciences and Research Ethics, and was performed in accordance with the Declaration of Helsinki. Patients with corneal thickness below 400  $\mu\text{m}$ , preoperative corneal scarring, prior keratitis, history of any eye injury were excluded.

Conventional epithelium-off corneal CXL was performed by the same surgeon (Z.Zs.N.) following the standard Dresden protocol [1]. The surgical treatment was performed under sterile conditions in the operating room. Under topical anesthesia with oxybuprocaine eye drops (Benoxi®, Unimed Pharma, Bratislava, Slovakia), the epithelial layer in a central diameter of 8 mm was manually removed. Then, 0.1% riboflavin droplets (Medio-Haus Medizinprodukte GmbH, Rostock, Germany) were instilled in every 2 minutes for 30 minutes before irradiation. The central cornea was exposed to UV-A light with a wavelength of  $370 \pm 5$  nm (CSO Vega CMB X Linker, CSO Scandicci, Firenze, Italy) at an irradiance of  $3 \text{ mW/cm}^2$  intensity for the next 30 minutes. During irradiation, instillation of riboflavin in every 2 minutes was continued. At the end of the treatment, topical antibiotic drops were administered and a bandage was applied. On the first postoperative day, the bandage was removed. Antibiotic eyedrops (5 mg/ml levofloxacin) were prescribed to be instilled five times per day for one week postoperatively. After

complete corneal reepithelization, topical corticosteroid (1 mg/ml fluorometholone) was administered four times daily within the following one month.

All patients were examined preoperatively and postoperatively at 1, 3 and 6 years after CXL procedure. Ophthalmological examinations included manifest refraction, uncorrected (UCDVA) and best corrected distance visual acuity (BCDVA) assessment (tested with Snellen charts and converted to logMAR values), slit-lamp biomicroscopy of the anterior segment and Scheimpflug imaging with Pentacam HR (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany). The following pachymetric and topographic values were recorded and analyzed: central corneal thickness (CCT), thinnest corneal thickness (ThCT), maximum keratometry ( $K_{max}$ ) and mean keratometry ( $K_{mean}$ ), index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central keratoconus index (CKI), index of height asymmetry (IHA), index of height decentration (IHD) and minimum radius of curvature ( $R_{min}$ ).

Statistical analysis was performed using IBM® SPSS® Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). Normality of the variables was assessed using Kolmogorov-Smirnov test. Differences were assessed by paired t-test for parametric values, and by Wilcoxon rank-sum test for nonparametric data. To present the tendencies in evolution of measured data, preoperative to 1 year, 1 year to 3 years and 3 years to 6 years values were compared. *P* value of < 0.05 was considered statistically significant.

## Results

Thirty-four eyes of 34 patients (24 men and 10 women) with progressive keratoconus underwent conventional CXL were included in our analysis. The mean age was  $27.79 \pm 7.8$  years (ranging between 14 and 48 years; 15% were between 10–19 years old; 47% were between 20–29 years old; 32% were between 30–39 years old and 6% were between 40–49 years old). Fifteen right eyes (44%) and nineteen left eyes (55%) were included. The cohort comprised 16 eyes (47.1%) in stage I, 23 eyes (44.1%) in stage II and 3 eyes (8.8%) in stage III according to Amsler-Krumeich classification of keratoconus severity [23]. All patients participated at all visits.

In Table 1, pre-, and postoperative outcomes of visual acuity and spherical equivalent are shown. Regarding SE, statistically significant decrease was detected at 1-year follow-up ( $p = 0.022$ ), with no significant changes between further subsequent examinations. The mean change in SE was  $+1.12 \pm 2.68$  D 6 years after CXL treatment. Both UCDVA and BCDVA improved significantly at 1 year after the treatment compared to baseline ( $p = 0.017$  and  $p = 0.003$ , respectively). After the first year, UCDVA and BCDVA remained stable with no significant changes between consecutive visits (Table 1). Overall, during the study period, 58.8% of treated eyes had at least 1-line gain both in UCDVA and in BCDVA (Fig. 1).

Table 1  
Pre-, and postoperative values of visual acuity, keratometry and corneal thickness.

	Preoperative data	Postoperative outcomes			p values		
		1 year	3 years	6 years	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
UCDVA (logMAR)	0.58 ± 0.38	0.49 ± 0.35	0.48 ± 0.37	0.43 ± 0.37	0.017	0.203	0.312
BCDVA (logMAR)	0.21 ± 0.25	0.17 ± 0.21	0.14 ± 0.18	0.09 ± 0.12	0.003	0.336	0.058
SE (D)	-2.90 ± 2.46	-2.42 ± 1.81	-2.33 ± 2.23	-1.90 ± 2.44	0.022	0.616	0.140
CCT (µm)	486.68 ± 34.43	466.85 ± 37.68	463.32 ± 40.64	462.53 ± 44.17	< 0.001	0.123	0.645
ThCT (µm)	466.68 ± 35.61	447.71 ± 40.61	439.53 ± 40.53	440.97 ± 44.88	< 0.001	0.01	0.539
K <sub>max</sub> (D)	56.43 ± 4.88	55.14 ± 4.84	54.17 ± 4.67	53.54 ± 4.56	< 0.001	0.011	0.001
K <sub>mean</sub> (D)	48.07 ± 2.94	47.01 ± 3.01	46.58 ± 3.02	45.93 ± 2.90	< 0.001	0.004	< 0.001
<p>The preoperative and postoperative data (mean ± SD) of visual acuity (uncorrected (UCDVA) and best corrected distance visual acuity (BCDVA) in logMAR), spherical equivalent (SE; in diopters (D)), pachymetry (central corneal thickness (CCT) and thinnest corneal thickness (ThCT) in µm) and keratometry (maximum (K<sub>max</sub>) and mean keratometry (K<sub>mean</sub>) in diopters (D)) is shown. <i>P</i> &lt; 0.05 was considered statistically significant.</p>							
<p>p<sub>1</sub>: level of significance in comparison of 1 year results to preoperative values</p>							
<p>p<sub>2</sub>: level of significance in comparison of 3 years results to 1 year results</p>							
<p>p<sub>3</sub>: level of significance in comparison of 6 years results to 3 year results</p>							

Thickness of the central cornea (CCT) decreased between baseline and 1 year (mean change was -19.82 ± 19.26 µm, *p* < 0.001), and was stabilized thereafter up to 3 years and to 6 years (*p* = 0.123 and *p* = 0.645, respectively). A significant decrease was found in thinnest pachymetry at 1 year compared to baseline with a mean change of -18.97 ± 19.5 µm (*p* < 0.001), which was followed by further -8.18 ± 17.43 µm thinning up to 3 years (*p* = 0.01). Afterwards, ThCT remained stable (*p* = 0.539). The mean change in CCT was -24.15 ± 23.47 µm and was -25.71 ± 25.61 µm in ThCT 6 years after the treatment.

As show in Table 1, keratometry readings showed significant, continuous improvement between consecutive visits over the entire follow-up time (Table 1). Evolution of K<sub>max</sub> showed significant improvement with flattening effect from 56.43 ± 4.88 D to 55.14 ± 4.84 D in the first postoperative year (*p*

< 0.001), with an additional significant decrease to  $54.17 \pm 4.67$  D at 3 years postoperatively ( $p = 0.011$ ). Significant flattening was continued to  $53.54 \pm 4.56$  D thereafter ( $p = 0.001$ ). For  $K_{\text{mean}}$ , difference was statistically significant at 1 year compared to the baseline with a decrease from  $48.07 \pm 2.94$  D to  $47.01 \pm 3.01$  D ( $p < 0.001$ ). Significant flattening was recorded after the first year as well to  $46.58 \pm 3.02$  D and further to  $45.93 \pm 2.90$  D at the end of the follow-up time ( $p = 0.004$  and  $p < 0.001$ , respectively). At the end of study period, the mean change in  $K_{\text{max}}$  was  $-2.89 \pm 2.78$  D and was  $-2.14 \pm 1.59$  D in  $K_{\text{mean}}$  compared to baseline (Fig. 2).

Regarding topographic indices, significant improvement was observed in the first postoperative year in the following 5 indices: ISV (from  $88.82 \pm 30.89$  to  $82.71 \pm 31.91$ ,  $p = 0.001$ ), IVA (from  $0.98 \pm 0.39$  to  $0.92 \pm 0.43$ ,  $p = 0.028$ ), KI (from  $1.24 \pm 0.11$  to  $1.22 \pm 0.11$ ,  $p = 0.002$ ), CKI (from  $1.06 \pm 0.04$  to  $1.04 \pm 0.04$ ,  $p < 0.001$ ) and  $R_{\text{min}}$  (from  $6.02 \pm 0.53$  to  $6.19 \pm 0.54$ ,  $p < 0.001$ ). Further improvement up to 3 years was recorded in ISV (from  $82.71 \pm 31.91$  to  $79.09 \pm 32.16$ ,  $p = 0.007$ ), CKI ( $1.04 \pm 0.04$  to  $1.03 \pm 0.04$ ,  $p = 0.019$ ) and  $R_{\text{min}}$  (from  $6.19 \pm 0.54$  to  $6.27 \pm 0.56$ ,  $p = 0.015$ ). Furthermore,  $R_{\text{min}}$  showed more improvement until 6 years (from  $6.27 \pm 0.56$  to  $6.35 \pm 0.56$ ,  $p < 0.001$ ) (Fig. 3). No significant changes were observed in change of IHD and IHA during whole follow-up time ( $p$  value was  $> 0.05$  at all time points). Data of topographic indices measured at different visits are summarized in Table 2 (Table 2). None of the treated corneas showed increased keratometry readings or deteriorating topographic indices in our cohort after CXL.

Table 2  
Pre-, and postoperative data of topographic indices.

	Preoperative data	Postoperative outcomes			<i>p</i> values		
		1 year	3 years	6 years	<i>p</i> <sub>1</sub>	<i>p</i> <sub>2</sub>	<i>p</i> <sub>3</sub>
<b>ISV</b>	88.82 ± 30.89	82.71 ± 31.91	79.09 ± 32.16	78.85 ± 33.37	0.001	0.007	0.786
<b>IVA</b>	0.98 ± 0.39	0.92 ± 0.43	0.89 ± 0.43	0.88 ± 0.44	0.028	0.064	0.750
<b>KI</b>	1.24 ± 0.11	1.22 ± 0.11	1.21 ± 0.11	1.21 ± 0.12	0.002	0.241	0.361
<b>CKI</b>	1.06 ± 0.04	1.04 ± 0.04	1.03 ± 0.04	1.03 ± 0.04	< 0.001	0.019	0.096
<b>IHA</b>	32.52 ± 20.21	31.94 ± 16.42	31.56 ± 18.38	29.79 ± 16.88	0.959	0.263	0.567
<b>IHD</b>	0.11 ± 0.05	0.10 ± 0.05	0.10 ± 0.05	0.10 ± 0.05	0.074	0.986	0.963
<b>R<sub>min</sub></b>	6.02 ± 0.53	6.19 ± 0.54	6.27 ± 0.56	6.35 ± 0.56	< 0.001	0.015	< 0.001

Table 2 summarizes the preoperative and postoperative values (mean ± SD) of following topographic indices: index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central keratoconus index (CKI), index of height asymmetry (IHA), index of height decentration (IHD) and minimum radius of curvature (R<sub>min</sub>). *P* < 0.05 was considered statistically significant.

*p*<sub>1</sub>: level of significance in comparison of 1 year results to preoperative values

*p*<sub>2</sub>: level of significance in comparison of 3 years results to 1 year results

*p*<sub>3</sub>: level of significance in comparison of 6 years results to 3 year results

## Discussion

Over the past decade, treatment of corneal ectatic diseases has fundamentally changed due to the introduction of corneal cross-linking. A number of former studies presented the beneficial effects of CXL [20, 24, 25]. Based on these results, treating of keratoconus with standard epithelium-off cross-linking seems to be safe and effective surgical technique. However, most of the available research provides results within two or three years after treatment. Existing literature of longer outcomes of conventional CXL is still limited. The goal of this study was to assess visual outcomes and corneal changes 6 years after conventional corneal cross-linking in patients with progressive keratoconus.

In the present study, enrolled patients were followed by a relatively long period of time (6 years), allowing for a potentially valuable analysis of the outcomes of conventional cross-linking using UV-A light at 3 mW/cm<sup>2</sup> irradiance intensity with 370 ± 5 nm wavelength performed according to standard Dresden protocol.

In our study, SE, UCDVA and BCDVA improved significantly in the first postoperative year and remained stable without any further significant changes between the subsequent visits up to 6 years. Outcomes of our analysis confirmed the results of several long-term studies, which assumed that CXL improves visual acuity [26–28]. Although in these studies, values were compared between different timepoints and baseline examination, thus, it was not revealed whether there was any further significant change between consecutive visits. Based on detailed statistical analysis between each visits, both Shaheen et al. and O’Brart et al. stated that significant visual and refractive improvement can occur even after the first postoperative year after CXL [29, 30]. Improvement in SE and visual acuity is a consequence of more regularized corneal surface, which is indicated by reduced keratometry and improved topographic indices in our analysis. However, further continuous significant improvement was found in some of these latter parameters in our data, results suggest that the extent of changes in keratometry and topographic indices did not generate further improvement in refraction and visual acuity after the first postoperative year in our cohort. Thus, according to our findings, final visual and refractive outcomes can be achieved until the end of the first postoperative year. In some recent studies, authors found deterioration in a few percent of involved eyes [29, 31]. Similarly, 2.9% of treated eyes had more than two-line-loss 6 years after CXL in our series. However, severe corneal scarring was not detected in any patients, cellular changes in the corneal stroma may induce increased scattering and changes in transparency, which might be related to visual loss. Although, the greater percent of treated eyes showed stabilization or improvement of visual acuity, the possibility of visual deterioration after treatment confirms that corneal cross-linking should only be performed on patients with documented progression of keratoconus as recommended in the literature for this treatment [32]. Further studies are warranted to determine the expectable changes in visual acuity and find those patients who have increased risk for visual loss in long-term after CXL.

In our series, both central and thinnest corneal pachymetry showed the greatest reduction in the first postoperative year. Measured at thinnest point of the cornea, pachymetry showed further thinning up to 3 years. Cellular changes after CXL, i.e. more compacted structure of collagen fibrils have an impact on pachymetry and may result in corneal thinning [33]. Meanwhile, findings about the evolution of corneal thickness after cross-linking are controversial. Greenstein et al. found that corneal thickness decreases after treatment, but later it recovers to preoperative values [33]. In contrast, Vinciguerra et al. found significant decrease in corneal thickness after CXL, but no recovering tendency [21]. According to our results, pachymetry did not change after 3 years, suggesting that the structure of the corneal stroma is stabilized thereafter.

In agreement with the results of previous studies [24, 30, 34], significant decrease in keratometry readings was observed after the treatment in our analysis. Flattening effect of CXL was most pronounced in the first postoperative year, although it was found to be continued even after the third postoperative year up to 6 year. Nicula et al. observed progressive decrease in maximum and average keratometry up to 10 years postoperatively [27]. In an other previous long-term study, similar tendency in improvement of keratometry readings was also observed with significant decrease 1 year postoperatively, maintained up to 7 years [29]. The authors suggested that long-term topographic changes are not only due to CXL, but also increasing age-related corneal stiffness can modify corneal reshaping [29]. So far, the processes

influencing changes of the corneal structure after conventional CXL in long term are unclear, but it has been confirmed by our results as well that corneal curvature changes can occur even several years after therapy. This change in curvature should be taken into consideration even long time after CXL in patients who require contact lens fitting. In the current series, none of the eyes had increasing keratometry values over follow-up period, confirming the long-term stabilization effect of CXL.

Findings of our study showed significant improvement of ISV, IVA, KI, CKI and  $R_{\min}$  in the first postoperative year. Greentstein et al. observed very similar results demonstrating improvement in ISV, IVA, KI and  $R_{\min}$  with a follow up of 12 months [35]. Koller et. al found significant improvement in KI, CKI,  $R_{\min}$  and IHA during the same follow-up period [13]. According to the study of Toprak et al., ISV, CKI and  $R_{\min}$  improved after conventional cross-linking [36]. In spite of the different findings, improvement of these indices mirrors that the corneal front surface become more optically regular after CXL treatment. In addition, in this study, further improvement of ISV, CKI and  $R_{\min}$  was revealed up to 3 years. Moreover, the latter had additional improvement up to the end of the follow-up period, which is consistent with our findings of continued decrease of keratometry in long-term. Meanwhile, no significant changes were observed in the remained two indices, i.e. IHD and IHA, suggesting postoperative stabilization of these values. Topographic indices are elevated in keratoconic eyes (except for  $R_{\min}$ , which shows decreased values in ectatic disorders) [35]. Improvement of ISV means decrease in deviation of corneal radii from the median value, which represents a more regularized corneal surface. Improvement of IVA indicates more symmetrical shape of anterior corneal surface with respect to horizontal meridian. Decrease of KI and CKI is in strong relationship with decrease of keratometry, thus, represents the regularization of keratoconic topography and improvement of the asymmetry between central and peripheral parts. Finally, increase of  $R_{\min}$  is related to flattening of the maximum steepness of the cone. Overall, comprehensive analysis of topographic indices suggests an optically more regular and symmetric corneal surface with flattening of the cone. To the best of our knowledge, our study is the first in the literature that presents data of topographic indices measured by Pentacam with the long follow-up period.

In the present study, we assessed refractive and visual outcomes, keratometry, pachymetry and topographic indices after conventional corneal cross-linking. However, our study has some main limitations. A prospective study with larger number of involved patients could provide more accurate results regarding data. Furthermore, detailed long-term evaluation also of the features of the posterior corneal surface and corneal densitometry would specify corneal changes after CXL more precisely. In addition, estimation of potential long-term visual outcomes and corneal flattening based on preoperative parameters would provide useful information for clinicians in predicting postoperative outcomes, therefore further studies are warranted.

## Conclusion

In brief, according to our findings, it can be stated that conventional epithelium-off corneal cross-linking is able to prevent the progression of keratoconus, and regularization of the anterior corneal surface can be

achieved by the treatment in long-term. Both UDVA and BCDVA, keratometry and topographic indices of ISV, IVA, KI, CKI and  $R_{\min}$  showed improving tendency after the treatment. Corneal reshaping is most pronounced in the first postoperative year and the process may continue further up to 6 years postoperatively.

## Declarations

### Ethics approval and consent to participate

This study was carried out with the approval of the Semmelweis University Regional and Institutional Committee of Sciences and Research Ethics, and followed the tenets of Declaration of Helsinki. This was a retrospective study, hence, informed consent was not required.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no financial interests to declare related to the study.

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### Authors' contributions

ACs: reviewed the literature, collected data, performed the statistical analysis and wrote the manuscript. HK: participated in study concept and design. KK: helped in formatting and language, critical revision of the manuscript. ZZsN: contributed to the critical reading of the manuscript, provided equipment and facilities. All authors read and approved the final manuscript.

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## Figures

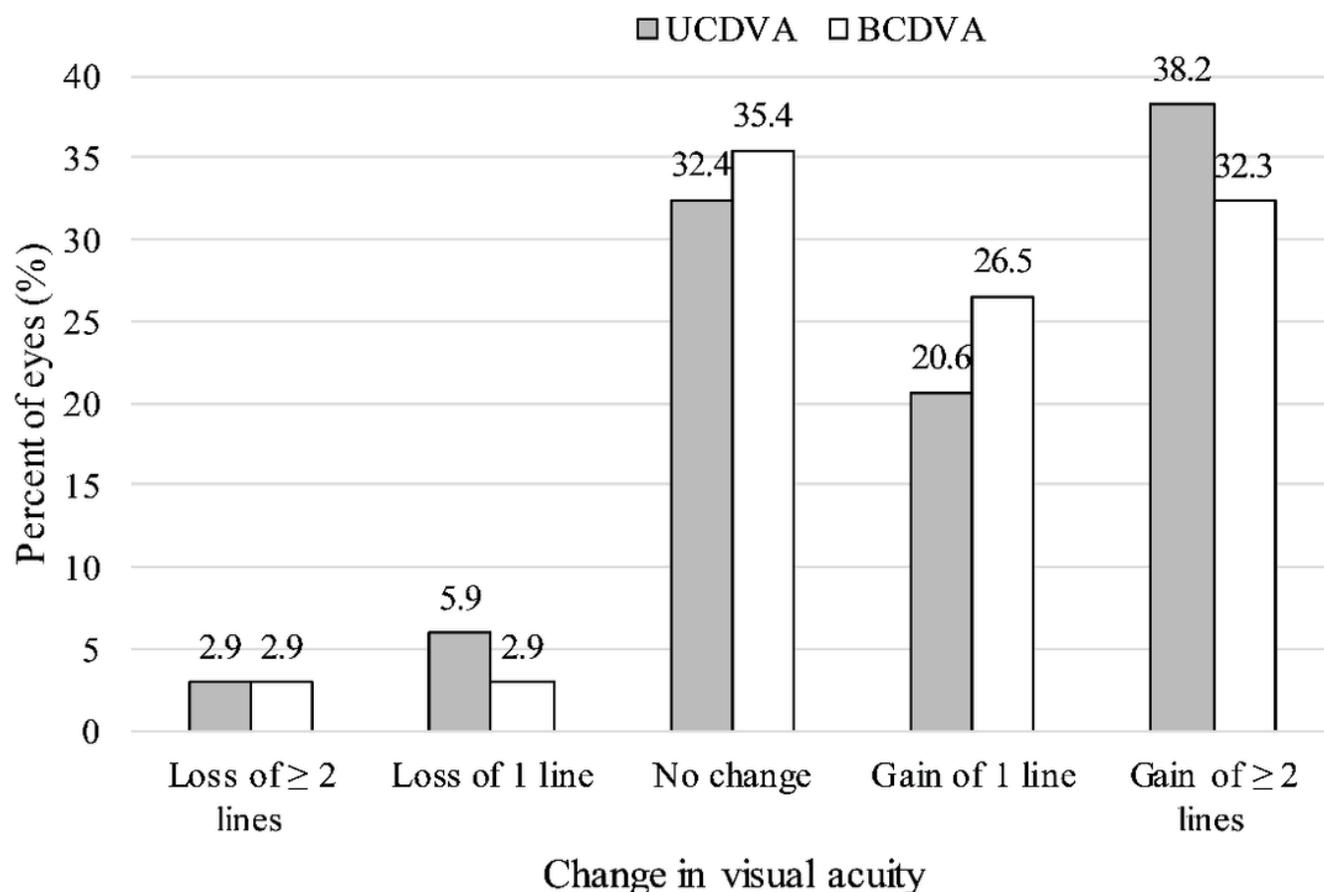
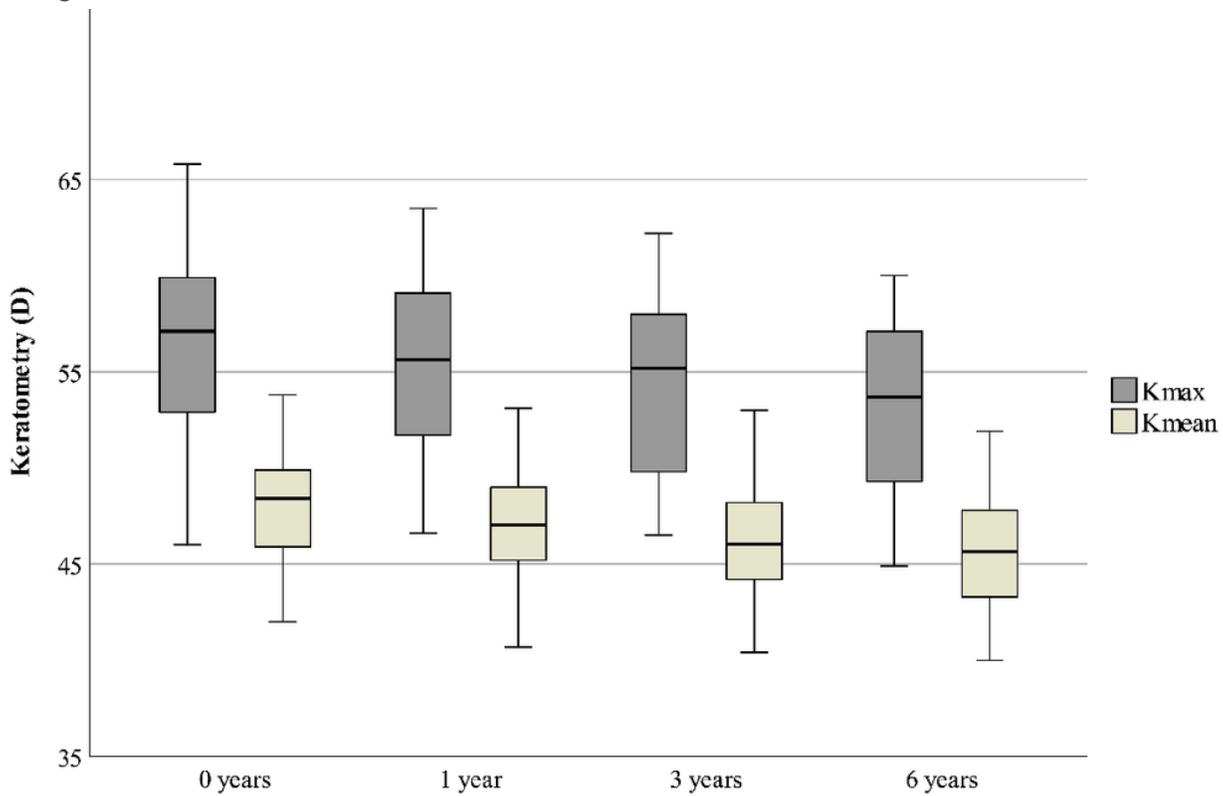


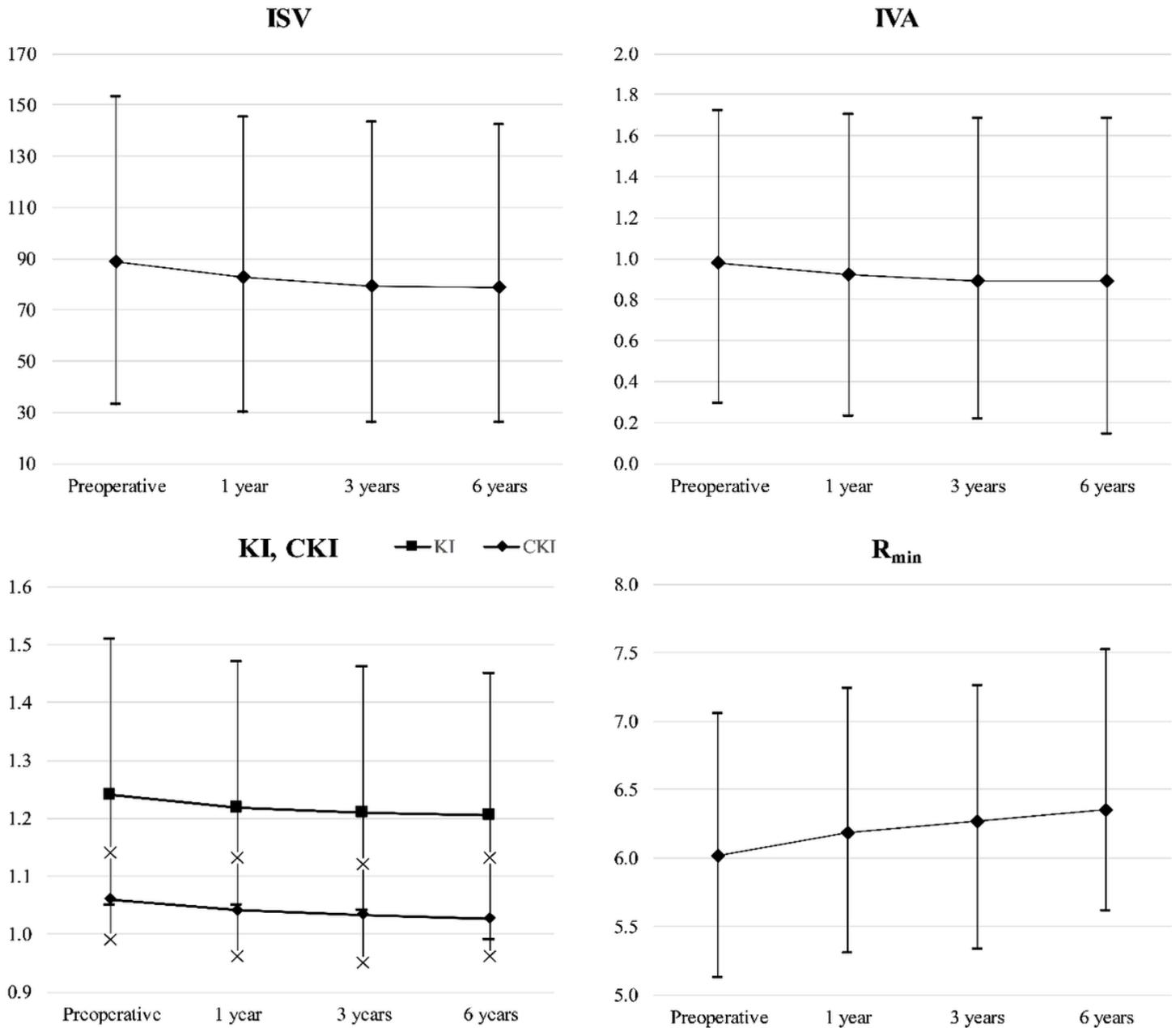
Figure 1

Changes in uncorrected- (UCDVA), and best corrected distance visual acuity (BCDVA) 6 years after cross-linking.



**Figure 2**

Evolution of keratometry values in diopters (D). Significant flattening was observed between consecutive visits up to 6 years postoperatively in maximum keratometry (Kmax) and in mean keratometry (Kmean) readings.



**Figure 3**

Changes in topographic indices. Figure 3 shows the evolution of ISV (index of surface variance), IVA (index of vertical asymmetry), KI (keratoconus index), CKI (central keratoconus index) and R<sub>min</sub> (radius of minimum curvature). Significant improvement was found all of these 5 indices in the first postoperative year. Improvement in ISV, CKI and R<sub>min</sub> was found up to 3 years. R<sub>min</sub> showed further increase 6 years after CXL.