Original Article

The influence of corneal collagen cross-linking on anterior chamber in keratoconus

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Aims: This study aimed to evaluate the effect of the corneal changes following corneal cross-linking (CXL) on the anterior chamber in keratoconus patients. **Materials and Methods:** Forty-five eyes of 32 patients who had been diagnosed with progressive keratoconus and had undergone CXL were included in this retrospective study. The thinnest corneal thickness of the progressive keratoconus patients included in the study was >400 µ. The preoperative (T0), postoperative 6th month (T1), and postoperative 1st year (T2) anterior chamber volume (ACV), anterior chamber angle (ACA), and anterior chamber depth (ACD) scheimpflug imaging values were obtained for each eye. **Results:** The mean T0 ACV value was 182.79 ± 36.68 mm^3, while the T1 value was 201.25 ± 41.73 mm^3 and the T2 value was 208.40 ± 42.69 mm^3 with a statistically significant difference between the periods ($P = 0.001$). The mean T0 ACA value was 38.64° ±5.85°, increasing to 41.45° ±4.83° in the T1 and 42.10° ± 4.84° in the T2. The T0 value was significantly lower than the post-CXL values ($P = 0.003$). The mean ACD value was 3.73 ± 0.29 mm at the T0 and 3.82 ± 0.38 mm at the T1 and 3.84 ± 0.36 mm at the T2. The pre-CXL values were significantly lower than the post-CXL values ($P = 0.001$). **Conclusions:** The improvement of corneal parameters by CXL in keratoconus patients can have a positive effect on anterior chamber parameters as well. This effect becomes marked at the postoperative first 6-month evaluation.

Access this article online
Website: www.ijo.in
DOI: 10.4103/ijo.IJO_948_16
Quick Response Code:

Key words: Anterior chamber, cornea, cross-linking, keratoconus, Pentacam

Keratoconus is an ectatic corneal disorder characterized by corneal protrusion, irregular astigmatism, and decreased visual acuity caused by progressive corneal thinning.[1] Keratoconus leads to biomechanical changes in the cornea, and the definite cause is not yet known.

The biomechanical properties of the cornea are determined by its collagen structure, composition, and the bonds of the collagen fibrils. The cornea's resistance is mainly defined by the three-dimensional configuration of the collagen lamellae.[2] The changes in the corneal collagen structure and organization, extracellular matrix alterations, and keratocyte apoptosis in keratoconus are the main factors causing corneal biomechanical weakness.[3,4] Corneal cross-linking (CXL) has been used as an effective and safe treatment for keratoconus and other ectatic corneal disorders in the recent years.[5] Topical riboflavin is activated by ultraviolet A (UVA) light and used as a photosensitizer. This causes the production of oxygen radicals, leading to the development of strong chemical bonds between the collagen fibrils and corneal hardening.[6]

The anterior chamber parameters have been shown to be affected in addition to the corneal parameters by the progression in keratoconus.[7,8] Most of the studies on the effect of CXL in keratoconus have focused on the cornea. Cornea is one of the anterior chamber components. Strengthening the cornea with a CXL can also cause significant changes in the anterior chamber.

The Pentacam (Oculus Pentacam, Oculus Optikgerate GmbH, Germany) rotating Scheimpflug camera enables evaluation of the whole anterior segment, from the anterior corneal surface to the lens' posterior surface.[9]

The aim of this study was to evaluate the effect of the corneal changes following CXL on the anterior chamber in keratoconus patients using the Pentacam.

Materials and Methods

This retrospective study conformed to the Helsinki Declaration, and approval was obtained from the local Ethics Committee (reference number: 2015/5-19). The patients provided written informed consent. A total of 45 eyes of 32 patients who had been diagnosed with progressive keratoconus and had undergone CXL were included in the study. Patients with a thinnest corneal thickness (TCT) value >400 µ underwent the standard 1% riboflavin-UVA CXL procedure defined by Wollensak *et al*.[10] The patients who had TCT value <400 µ were excluded from the study. Patients with a history of corneal surgery or a corneal scar, those who had suffered from any intra- or post-operative complication, who were pregnant or nursing, or who had diabetes or collagen tissue disease were excluded from the study. The postoperative 1-year follow-up

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Manuscript received: 12.12.16; Revision accepted: 18.03.17

Cite this article as: Polat N, Gunduz A, Colak C. The influence of corneal collagen cross-linking on anterior chamber in keratoconus. Indian J Ophthalmol 2017;65:271-5.

results of patients with progression on preoperative repeated Scheimpflug images taken over a period of at least a year and who had undergone CXL afterward were evaluated. All patients received a detailed ophthalmic examination that included slit-lamp biomicroscopy examination, applanation tonometry, and dilated fundus examination. Refractive measurements of the patients were measured with an auto kerato-refractometer (KR-8900; Topcon Co., Tokyo, Japan). All examinations were performed by the same physician. Scheimpflug ocular imaging was performed on undilated eyes under scotopic conditions by the same experienced technician, and values were obtained for each eye as follows: the flat meridian of the anterior corneal surface (K1), steep meridian of the anterior corneal surface (K2), mean anterior corneal curvature (Km), TCT, corneal volume (CV), anterior chamber volume (ACV), anterior chamber angle (ACA), and anterior chamber depth (ACD). The preoperative, postoperative 6th month, and postoperative 1st year spherical equivalent (SphEq), cylinder (Cyl) results, and the Scheimpflug imaging parameters were compared retrospectively.

Statistical analysis

The variables of the groups were presented as mean ± standard deviation. The IBM SPSS Statistics soft ware, version 22.0 for Windows (Chicago, IL., USA) was used for statistical analyses. Normality was assessed using Shapiro–Wilks test. The repeated-measures analysis of variance was performed for repeated measurements. $P < 0.05$ was considered statistically significant.

Results

There were 17 male and 15 female patients with a mean age of 23.35 ± 7.50 years. The 45 eyes consisted of 24 right and 21 left eyes. All patients were followed up for at least 1 year postoperatively. Table 1 presents the pre-CXL and post-CXL K1, K2, Km, SphEq, Cyl, TCT, CV, ACV, ACA, and ACD values.

The mean pre-CXL K1 value of the study patients was 46.36 ± 2.75 D. The mean post-CXL K1 value was 45.88 ± 2.95 D at the 6th month and 45.02 ± 3.05 D at the 1st year with a statistically significant decrease at the 1st year (P = 0.001). The mean pre-CXL K2 value was 50.60 ± 3.64 D, changing to 49.70 ± 3.55 D 6 months after CXL and 48.70 ± 3.64 D 1 year after CXL with a statistically significant difference between the periods (P = 0.001). The mean Km value was 48.36 ± 2.95 D before CXL, 47.65 ± 3.55 D 6 months after CXL, and 46.64 ± 3.40 D 1 year after CXL, with a statistically significant difference between the periods (P = 0.001). The mean SphEq value was − 6.25 ± 2.25 D at preoperative, −5.75 ± 3.00 D at the 6th month, and − 5.25 ± 2.50 D at the 1st year with a statistically significant decrease at the 1st year (P = 0.003). The mean Cyl value was − 4.50 ± 2.50 D at preoperative, −4.15 ± 2.25 D at the 6th month, and − 3.65 ± 2.50 D at the 1st year, with a statistically significant decrease at the 1st year (P = 0.002) [Fig. 1].

The mean pre-CXL TCT value was 436.20 ± 32.15 μm, changing to 430.10 ± 40.01 μm 6 months after CXL and 454.10 ± 45.70 μm 1 year after CXL, with a statistically significant increase in the 1st year (P = 0.001). The initial mean CV value was 55.10 ± 4.25 mm^3, changing to 55.15 ± 5.35 mm^3 6 months after CXL and 57.27 ± 3.65 mm^3 1 year after CXL, with a statistically significant increase in the 1st year (P = 0.001) [Fig. 1].

The mean pre-CXL ACV value was 182.79 ± 36.68 mm^3, while the post-CXL 6th month value was 201.25 ± 41.73 mm^3 and the post-CLX 1st year value was 208.40 ± 42.69 mm^3, with a statistically significant difference between the periods (P = 0.001). The mean pre-CXL ACA value was 38.64° ± 5.85°, increasing after CXL to 41.45° ±4.83° in the 6th month and 42.10° ±4.84° in the 1st year. The pre-CXL values were significantly lower than the post-CXL values (P = 0.003). The mean ACD value was 3.73 ± 0.29 mm before the CXL procedure and 3.82 ± 0.38 mm at the 6th month and 3.84 ± 0.36 mm at the 1st year after the procedure. The pre-CXL values were significantly lower than the post-CXL values (P = 0.001) [Fig. 2].

Table 1: Statistical analysis of variables according to periods

Variables	Periods (mean±SD)			P
	Preoperative	Postoperative 6th month	Postoperative 1st year	
K1 (D)	46.36±2.75	45.88±2.95†	45.02±3.05*,‡	0.001
K2 (D)	50.60±3.64	49.70±3.55*,†	48.70±3.64*,‡	0.001
Km (D)	48.36±2.95	47.65±3.55*,†	46.64±3.40*,‡	0.001
SphEq (D)	6.25±2.25	5.75±3.00	5.25±2.50*	0.003
Cyl (D)	4.50±2.50	4.15±2.25	3.65±2.50*	0.002
TCT (μm)	436.20±32.15	430.10±40.01†	454.10±45.70*,‡	0.001
CV (mm^3)	55.10±4.25	55.15±5.35†	57.27±3.65*,‡	0.001
ACV (mm^3)	182.79±36.68	201.25±41.73*,†	208.40±42.69*,‡	0.001
ACA (°)	38.64±5.85	41.45±4.83*	42.10±4.84*	0.003
ACD (mm)	3.73±0.29	3.82±0.38*	3.84±0.36*	0.001

*Statistically significant change compared with preoperative measurements, †Statistically significant change compared with postoperative 1st year measurements, ‡Statistically significant change compared with postoperative 6th month measurements. K1: Flat meridian of the anterior corneal surface, K2: Steep meridian of the anterior corneal surface, Km: Mean anterior corneal curvature, SphEq: Spherical equivalent, Cyl: Cylinder, TCT: Thinnest corneal thickness, CV: Corneal volume, ACV: Anterior chamber volume, ACA: Anterior chamber angle, ACD: Anterior chamber depth

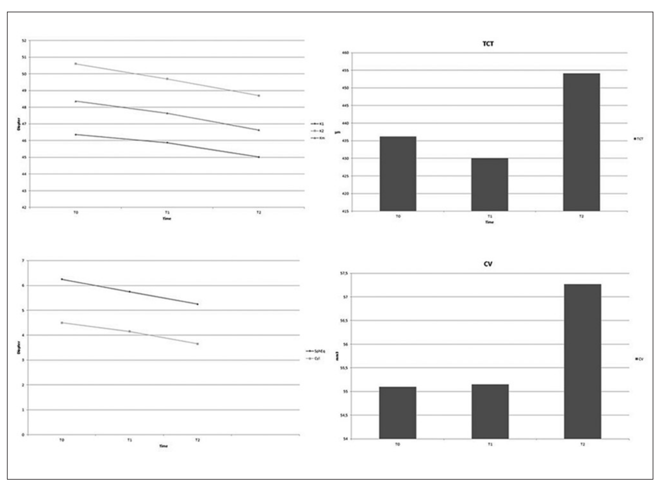

Figure 1: Graphs for changes in the K, refractive results, thinnest corneal thickness, and corneal volume according to time

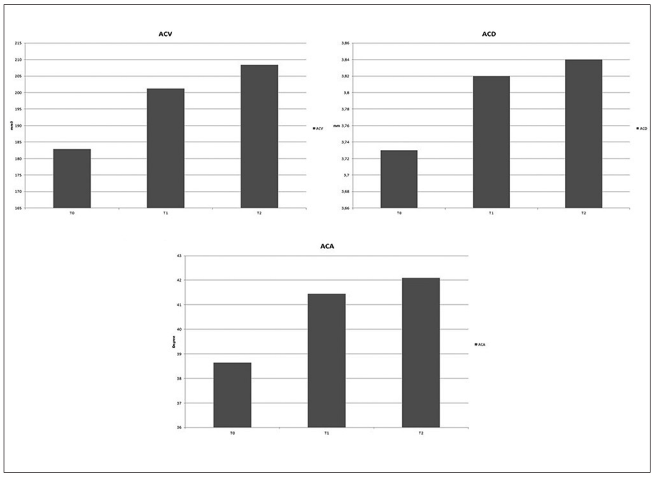

Figure 2: Graphs for changes in the anterior chamber volume, anterior chamber angle, and anterior chamber depth according to time

Discussion

We evaluated the 1-year follow-up results in our study, as it has previously been reported that the maximum corneal curvature regression following CXL is seen in the 1st postoperative year.[11]

There are variable results about corneal curvature regression following CXL.[5,10-12] We found an approximate 0.5 D K1 decrease in the postoperative 6th month and an approximate 0.85 D additional decrease in the postoperative 1st year. For K2, there was an approximate 0.9 D K2 decrease in the postoperative 6th month and approximately 1 D additional decrease in the postoperative 1st year. There was an approximate 0.7 D Km decrease in the postoperative 6th month and an approximate 1 D additional decrease in the postoperative 1st year. Comparing the results of our 1-year study with the above long-term studies reveals that the corneal curvatures were stabilized in the first 6 month and the largest corneal curvature regression after CXL was in the second 6 month, but this needs to be supported with meta-analysis studies.

The studies about refractive change after CXL suggest different results. Sharma *et al*.[13] found significant decrease in Cyl at postoperative 6th month but not in SphEq. They limited their study with 6 months. Ghanem *et al*.[14] reported that Sph Eq and Cyl did not change at postoperative 6th month. They also found significant decrease in SphEq at postoperative 1st year, but this significant change was not in Cyl. The mean SphEq and Cyl of our patients decreased at postoperative 6th month but not in statistically significant manner. There was a statistically significant decrease of these results at postoperative 1st year. We think that these results may be related to the fact that the main regression in the corneal curvatures is at the postoperative 1st year. We also believe that significant decrease in refractive results could be related to the improved corneal symmetry indices due to a smaller difference between the superior and inferior corneal hemimeridians (flattest vs. steepest).[12] We did not evaluate the corneal symmetry indices in our study. However, our finding that the regression in the steep meridian was larger than in the flat meridian supports this notion in the postoperative second 6 months.

Many studies reported the corneal thickening after CXL, followed by thinning.[5,15-17] There are various explanations for thinning at the postoperative period. Toprak and Yildirim[18] reported a thinning of the cornea compared to the preoperative period with 6 months of follow-up and they suggested the potential cause as corneal tissue loss in the early postoperative period. Some other studies have reported that the demarcation line and haze developing after CXL can cause erroneous results with the optic pachymetry method.[11,19] Gutiérrez *et al*.[20] revealed with the Pentacam densitometry that the corneal density increased in the first 3 months following CXL, but then decreased and returned to the baseline value at 1 year. We also agree with all these points, and therefore believe that these issues should be taken into account when evaluating early postoperative results. There are also some studies that report increase or no change in the corneal thickness at the postoperative 1st year.[6,21,22] Our results showed that TCT decreased at the 6th month but not in a statistically significant manner, while increased significantly at the postoperative 1st year. We believe that these changes were due to corneal tissue loss in the early postoperative period and the remodeling in the second 6 months caused by CXL in the cornea. Wollensak *et al*.[23] have shown with histopathological evaluation that the collagen fiber diameter increases following CXL. Mazzotta *et al*.[24] stated that the collagen lamellae reconstruction following CXL could continue for years, again supporting our results.

The CV results of our study correlated with the TCT results. However, our postoperative CV results contradict the study of Toprak and Yildirim[18] with decreased CV results at the 6th month, and with the Vinciguerra *et al's*.[21] study reporting low CV values at the 1st year. De Bernardo *et al*.[25] reported that a statistically significant decrease in CV 1 month after treatment tends to increase during the 24-month follow-up. Our results are partially consistent with that of De Bernardo *et al*.[25] Our results showed a significant increase in the period of 6 months to 1 year, but their results were not significant. We think that the increase in our results is due to the continuation of remodeling.[24] Evaluation of our TCT and CV results together indicate that the main corneal remodeling and healing after CXL occurs from the postoperative 6th month to the 1st year.

The changes in all the parameters above indicate that the most important period for monitoring the post-CXL changes of the main anterior chamber parameters of our study (ACV, ACA, and ACD) is the 1st year. These parameters have previously been shown to be affected in keratoconus patients.[7,8] Emre *et al*.[7] studied 216 previously untreated keratoconus patients and found that the ACD showed a significant increase with increasing keratoconus stage, and that this increase could be due to anterior protrusion of the cornea. They found that the ACA showed a significant decrease and stated that this could be due to the compensatory flattening of the peripheral cornea. There was also an increase in ACV, but this was not statistically significant and could have been due to the ACD increase.[7] Abolbashari *et al*.[26] reported a correlation between corneal curvatures and anterior segment parameters in keratoconus patients with peripheral ACD, usually being related to the anterior corneal curvature. Smolek and Klyce[27] provided a reason for this, explaining that the corneal curvature is increasing in the central cone area, and it is being compensated by peripheral corneal flattening, leading to a low ACA. We are aware of only a few studies evaluating post-CXL anterior chamber parameters in keratoconus patients. The most comprehensive study on the anterior chamber parameters of ACV, ACA, and ACD is that of Toprak and Yildirim[18] who evaluated 47 keratoconic eyes during a 6-month period following CXL. They reported no significant change in these values. We found that the main change in these parameters was in the postoperative 6th month. Toprak and Yildirim's study results contradict our study that was conducted with almost the same number of patients and using the same measurement method. The reason may be the much higher mean K values in their study group, indicating that their patients mostly had progressive keratoconus, while the mean K values were lower in our patients, indicating early-stage keratoconus patients. Another study conducted by De Bernardo *et al*.[25] reported that ACD and ACV values did not change. They said that the stability of the ACV and ACD was associated with increase of axial length (AL). Their interpretation is contradictory with their results because their AL measurements were stable at postoperative 6th month and 1st year. Our results indicate that the improvement in anterior chamber parameters following CXL became apparent in the postoperative 6th month, and this improvement in ACA and ACD values was maintained until the postoperative 1st year but not statistically significant while the statistically significant increase in ACV values continued. Biomechanical stabilization of the cornea after CXL was reported previously.[28] On this basis, we believe that the stabilized cornea may have changed the anterior chamber parameters by corneal shrinking and the indirect pressure on the iris–lens diaphragm. The shrunken cornea due to the CXL effect may have reversed the peripheral corneal flattening as previously mentioned in keratoconus patients by Smolek and Klyce,[27] caused peripheral corneal steepening, and therefore increased ACA values. We also believe that the pressure caused on the anterior chamber by the cornea that was hardened due to the effect of CXL could shift the iris–lens diaphragm backward and therefore increase both the ACA and ACD values. New studies measuring the pre- and post-CXL iris–lens diaphragm positions and changes can clarify the matter. We believe the ACV value increase could be due to increases in ACA and ACD values.

Therefore, according to all these points, we believe that monitoring of the effect of CXL can be done by anterior chamber parameters, especially in the postoperative first 6 months.

The lack of a control group to avoid the ethical problems that would be caused by monitoring KC patients without treatment is a limitation of our study.

Conclusions

The improvement in and stabilization of corneal parameters by CXL in keratoconus patients can have a positive effect on anterior chamber parameters as well. This effect becomes marked at the postoperative first 6-month evaluation. It is possible that the anterior chamber parameter changes play a role in the visual acuity improvement in keratoconus patients following CXL. These CXL-related anterior chamber changes could be important in any refractive surgery or cataract surgery that may be required in keratoconus patients. New studies that objectively evaluate the iris–lens diaphragm position before and after CXL are required to elucidate these anterior chamber changes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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