Original Article

Effects of collagen cross-linking on corneal topographic characteristics in the patients with keratoconus

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Abstract

Background: Keratoconus is a bilateral, non-inflammatory, progressive disorder characterized by corneal thinning and protrusion, progressive myopia, and irregular astigmatism. Available treatment for keratoconus is the use of spectacles, soft contact lenses, rigid or gas permeable contact lens, collagen cross-linking, intracorneal ring segment implantation using laser or mechanical channel creation, keratoplasty either penetrating or deep anterior lamellar for severe disease. Collagen cross linking is the treatment of choice for primary Keratoconus of progressive variety. It halts progression of Keratoconus and later improves patient's vision. **Objectives:** To evaluate effect of Corneal Collagen Cross Linking (C_xL) on Corneal Topographic characteristics (K_1, K_2, Kapex, corneal thickness). **Methodology:** This prospective observational study was conducted in the department of Cornea, National Institute of Ophthalmology and Hospital, Dhaka from January 2019 to April 2020 on 60 eyes of 60 patients of keratoconus. Patients were selected purposively based on specific selection criteria. Corneal Collagen cross-linking(C_xL) were done in all the selected patients by a single competent cornea specialist. They were followed up on 1 month, 3 months and 6 months after procedure. K_1, K_2 and Kapex and corneal thickness were assessed in each follow-up. All the relevant data were recorded in a pre-designed data collection sheet. Data were analyzed by using window software SPSS ver. 21. Ethical approval was taken from ethical review committee of National Institute of Ophthalmology and Hospital, Dhaka prior to commencement of the study. **Results:** The study comprised participants aged predominantly between 20 to 30 years (45%), with more males (66.7%) than females (33.3%). Post collagen cross-linking (C_xL) treatment, significant reductions were observed in flat keratometry (K_1), steep keratometry (K_2), steepest keratometry (Kapex), and central corneal thickness (CCT) across all assessment periods (1, 3, and 6 months). Notably, K_1 decreased from 45.66±3.43 diopters at baseline to 43.29±3.29 diopters at 6 months, K_2 decreased from 50.22±5.93 diopters to 47.12±4.48 diopters, Kapex decreased from 54.50±7.38 diopters to 51.32±5.13 diopters, and CCT decreased from 467.53±37.38 micrometers to 425.03±26.41 micrometers ($p<0.001$ for all). **Conclusion:** Analytical findings of this study show that keratometric values as well as central corneal thickness improve after C_xL.

Key words: Collagen cross-linking, Corneal topography, Keratoconus, Corneal ectasia, Visual acuity

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Introduction

Keratoconus is a progressive, bilateral, and asymmetric degenerative disease of the cornea, characterized by central or inferotemporal thinning, and occasionally superior thinning. It is the leading cause of corneal ectasia, resulting in a conical cornea that leads to high myopia, irregular astigmatism, and impaired vision. Typically emerging during puberty, the disease progresses until the fourth decade of life.[1,2,3]

Keratoconus has a prevalence of 5 to 23 per 10,000 and an incidence of 4.5 per 10,000, with variation due to differing diagnostic criteria across studies.[1,2,3] It affects all races and shows mixed gender predominance in various studies.[4-7] Symptoms and ocular signs vary with disease severity, with progression leading to severe, irreversible vision loss. Irregular astigmatism can be indicated by a "scissors-like" reflex in

retinoscopy. Moderate to advanced stages often show Fleischer's ring due to iron accumulation from corneal curvature changes.[8] Munson's sign, Rizzuti's sign, and Descemet's membrane rupture, leading to sudden vision loss and pain, are observed in advanced keratoconus.[9]

Corneal topography images the cornea by projecting concentric rings of light, creating a Placido image, which is analyzed to produce a detailed surface map.[10] This technique provides information on anterior and posterior corneal curvature, corneal thickness, anterior chamber depth, and details of the iris and lens.[11-12] It is essential for detecting, monitoring, and managing corneal ectasia, especially keratoconus, and for measuring corneal thickness.[13] Corneal topography is particularly useful in screening for subclinical keratoconus in candidates for refractive surgery, as it can detect subtle posterior corneal changes that precede anterior steepening.

Treatment options for keratoconus include spectacles, soft and rigid gas permeable contact lenses, intracorneal ring segment implantation, collagen cross-linking, and keratoplasty (penetrating or deep anterior lamellar) for severe cases.[14] Corneal collagen cross-linking (C_xL), introduced by Wollensak et al.[15,16] stabilizes progressive keratoconus and reduces the need for penetrating keratoplasty by increasing corneal biomechanical strength by 300%. This is achieved through the combined action of riboflavin and UV light, creating additional chemical bonds in the anterior corneal stroma with minimal exposure to surrounding eye structures.[15,17,18,19] Post-treatment, corneal topography improves, indicating increased stability and reduced curvature.[20] C_xL was introduced in Bangladesh's private hospitals in 2011 and in the National Institute of Ophthalmology in 2019, supervised by expert cornea specialists.

Decreased corneal stability contributes to the progressive protrusion seen in keratoconus, leading to impaired vision due to irregular astigmatism, myopia, corneal thinning, and scarring. Collagen cross-linking, a major advancement in keratoconus treatment, stabilizes the condition, enhances corneal strength, and flattens the cornea as shown by corneal topography. There is limited data on collagen cross-linking outcomes in Bangladesh. This study, conducted at a tertiary eye care center in Bangladesh, aims to assist cornea specialists in planning effective treatments for keratoconus patients.

Methods

This prospective observational study was conducted at the Department of Cornea, National Institute of Ophthalmology and Hospital, Dhaka, from January 2019 to April 2020. The study included 60 eyes of keratoconus patients selected purposively based on specific inclusion and exclusion criteria. Patients with progressive moderate keratoconus were included, while those with other ocular or systemic conditions affecting the cornea, history of recent ocular trauma or surgery, and non-compliance to follow-up were excluded. Collagen cross-linking (C_xL) procedures were performed by a single cornea specialist, with follow-up assessments at 1,3 and 6 months post-procedure. Key variables measured included K_1 (flat keratometry), K_2 (steep keratometry), Kapex (steepest keratometry), and corneal thickness. Data were collected using a pre-designed sheet and analyzed with SPSS ver.[21], employing descriptive and inferential statistics. Ethical approval was obtained, and patient confidentiality and informed consent were ensured. Quality assurance included using sophisticated instruments for assessments and regular supervision checks.

Collagen cross-linking (C_xL) using riboflavin and ultraviolet A radiation was performed under sterile conditions. Riboflavin 0.1% solution was instilled every 10 minutes for 2 hours, followed by topical anesthesia with oxybuprocaine 0.4% eye drops every 5 minutes for 15 minutes. Pilocarpine 1% was then instilled to constrict the pupil. Riboflavin was subsequently applied over the cornea every 3 minutes for 15 minutes, and ultraviolet A irradiation was administered using a calibrated device for 30 minutes to the central 9 mm of the cornea, with riboflavin instillation every 5 minutes. Postoperatively, a bandage contact lens was worn for 5 days, along with dexamethasone and moxifloxacin eye drops for 2 weeks, artificial tears for 4 weeks, and flurometholone eye drops from the 3rd to the 4th week. Follow-up visits were scheduled at specific intervals.

Results

Table-1: Demographic characteristics of the subjects (n=60)

Variables	Frequency	Percentage (%)
Age group		
10-20 years	16	26.67
20-30 years	27	45
30-40 years	17	28.33
Mean±SD	22.7±7.10	
Gender		
Male	40	66.7
Female	20	33.3

The majority of participants were aged between 20 to 30 years (45%), followed by those aged 10 to 20 years (26.67%) and 30 to 40 years (28.33%), with a mean age of 22.7±7.10 years. In terms of gender distribution, there were more male subjects (66.7%) compared to females (33.3%).

Table-2: Distribution of mean value of flat keratometry (K_1) reading in diopter in different assessment periods

Assessment periods	Diopteric value	*p*-value
Baseline	45.66±3.43(SD)	p-value
1 month after C_xL	45.55±3.41(SD)	<0.001s
3 months after C_xL	44.35±3.35(SD)	<0.001s
6 months after C_xL	43.29±3.29(SD)	<0.001s

s=significant, p value obtained by paired t test

Table-2 shows the mean values of flat keratometry (K_1) readings in diopters across various assessment periods post collagen cross-linking (C_xL) treatment. Initially, at baseline, the mean K_1 value stood at 45.66±3.43 diopters. Significant reductions were observed at both the 1-month (45.55±3.41 diopters) and 3 months (44.35±3.35 diopters) follow-up, with a further significant decrease noted at 6 months post-C_xL (43.29±3.29 diopters).

Table-3: Distribution of mean value of steep keratometry (K_2) reading in diopter in different assessment periods

Assessment periods	Diopteric value	p-value
Baseline	50.22±5.93(SD)	-
1 month after C_xL	48.41±5.17 (SD)	<0.001s
3 months after C_xL	47.87±4.81 (SD)	<0.001s
6 months after C_xL	47.12±4.48 (SD)	<0.001s

s=significant, p value obtained by paired t test

Table 3 shows the mean values of steep keratometry (K_2) readings in diopters across different assessment periods post collagen cross-linking (C_xL) treatment. Initially, at baseline, the mean K_2 value was 50.22±5.93 diopters. Subsequent assessments at 1, 3, and 6 months post-C_xL reveal a consistent decrease in K_2 values. Significant reductions were observed at all follow-up intervals: 1 month (48.41±5.17 diopters), 3 months (47.87±4.81 diopters), and 6 months (47.12±4.48 diopters) post-C_xL treatment ($p<0.001$).

Table-4: Distribution of mean value of steepest keratometry (Kapex) reading in diopter in different assessment periods

Assessment periods	Diopteric value	*p*-value
Baseline	54.50±7.38(SD)	-
1 month after C_xL	53.12±6.93 (SD)	<0.001s
3 months after C_xL	52.41±5.77 (SD)	<0.001s
6 months after C_xL	51.32±5.13 (SD)	<0.001s

s=significant, p value obtained by paired t test

Table 4 shows the mean values of steepest keratometry (Kapex) readings in diopters across different assessment periods following collagen cross-linking (C_xL) treatment. Initially, at baseline, the mean Kapex value was 54.50±7.38 diopters. Subsequent assessments at 1, 3, and 6 months post-C_xL show a consistent decrease in Kapex values, indicating a progressive flattening of the cornea. Significant reductions were observed at all follow-up intervals: 1 month (53.12±6.93 diopters), 3 months (52.41±5.77 diopters), and 6 months (51.32±5.13 diopters) post-C_xL treatment ($p<0.001$).

Table-5: Distribution of mean value of central corneal thickness (CCT) in micro-meter in different assessment periods

Assessment periods	Value (µm)	*p*-value
Baseline	467.53±37.38(SD)	-
1 month after C_xL	442.22±34.47 (SD)	<0.001s
3 months after C_xL	430.42±27.82 (SD)	<0.001s
6 months after C_xL	425.03±26.41 (SD)	<0.001s

s=significant, p value obtained by paired t test

Table 5 shows the mean values of central corneal thickness (CCT) in micrometers across different assessment periods following collagen cross-linking (C_xL) treatment. Initially, at baseline, the mean CCT was 467.53±37.38 micrometers. Subsequent assessments at 1, 3, and 6 months post-CxL demonstrate a consistent decrease in CCT values. Significant reductions were observed at all follow-up intervals: 1 month (442.22±34.47 micrometers), 3 months (430.42±27.82 micrometers), and 6 months (425.03±26.41 micrometers) post-C_xL treatment ($p<0.001$).

Discussion

Keratoconus, a degenerative non-inflammatory condition, distorts the cornea, leading to a protruding cone shape, thinning, and scarring.[21] Corneal collagen cross-linking (C_xL) is the sole therapeutic approach capable of arresting keratoconus progression by strengthening the corneal collagen matrix through riboflavin photosensitization and UVA irradiation at 370 nm. This study, conducted at the National Institute of Ophthalmology and Hospital in Dhaka from January 2019 to April 2020, aimed to precisely assess keratometric alterations post-C_xL treatment in keratoconus patients.

In present study showed the majority of participants were aged between 20 to 30 years (45%), followed by those aged 10 to 20 years (26.67%) and 30 to 40 years (28.33%), with a mean age of 22.7±7.10 years. In terms of gender distribution, there were more male subjects (66.7%) compared to females (33.3%). This aligns closely with findings from Siddiqui and Shafique[21] study, which reported a similar mean age of 21 years. Likewise, Bozkurt et al.[22] found a mean age of 23.87±5.07 years, and Ahmet et al.[23] reported a mean age of 26±5 years, both studies showing a concentration of patients in

their twenties. Tiveron et al.[24] observed a mean age of 19.9±5.61 years, with a range from 12 to 30 years, mirroring the age distribution pattern in our study. These findings collectively indicate a trend where the majority of keratoconus patients seek treatment after entering their second decade of life. This demographic similarity across studies underscores the relevance of addressing visual health concerns, particularly keratoconus, among the economically active population, which typically begins after the second decade of life in the context of Bangladesh.

In the current study, 66.67% of the participants were male, while 33.33% were female. This closely resembles findings from Tiveron et al.[24], where 66.6% were male and 33.4% were female. Ahmet et al.[23] also reported a similar distribution, with 65.0% male and 35.0% female participants. These studies demonstrate consistency with the gender distribution observed in our study. Conversely, Erc Ument Bozkurt et al.[22] found a slightly different pattern, with 55% male and 45% female patients. However, all studies indicate a predominance of male patients seeking treatment for keratoconus.

In our present study, the mean values of flat keratometry (K_1) readings in diopters exhibited a consistent decrease across various assessment periods following collagen cross-linking (C_xL) treatment. Initially, at baseline, the mean K_1 value was 45.66±3.43 diopters. Significant reductions were observed at both the 1 month (45.55±3.41 diopters) and 3-month (44.35±3.35 diopters) follow-ups, with a further notable decrease noted at 6 months post-CxL (43.29±3.29 diopters). These findings echo results from numerous studies conducted worldwide. For instance, Bikbova and Bikbov[25] reported a decrease in K_1 from 44.6±1.12 diopters before C_xL to 42.38±1.75 diopters after 6 months of C_xL, showing similar trends as our study. Conversely, Ahmet et al.[23] observed diminished K_1 readings following C_xL, with values decreasing from 45.50±2.84 diopters before C_xL to 43.32±2.25 diopters after 6 months. Similarly, Filippello et al.[26] reported a reduction in K_1 from 45.13±0.97 diopters before C_xL to 44.57±1.11 diopters after 6 months of treatment, consistent with our findings. Additionally, Tian et al.[27] and Tiveron et al.[24] also observed reductions in K_1 readings 6 months after C_xL, aligning closely with our study results. These similarities across studies underscore the effectiveness of C_xL in reducing K_1 readings and stabilizing keratoconus progression. However, there may be slight variations in outcomes due to differences in patient demographics, treatment protocols, or other factors.

In current present study, the mean values of steep keratometry (K_2) readings in diopters demonstrated a consistent decrease across various assessment periods following collagen cross-linking (C_xL) treatment. Initially, at baseline, the mean K_2 value was 50.22±5.93 diopters. Subsequent assessments at 1, 3, and 6 months post-C_xL revealed significant reductions in K_2 values: 48.41±5.17 diopters at 1 month, 47.87±4.81 diopters at 3 months, and 47.12±4.48 diopters at 6 months ($p<0.001$). These findings are consistent with results from other studies. For example, Filippello et al.[26] reported similar outcomes, with a decrease in K_2 from 51.02±1.10 diopters before C_xL to 47.82±0.78 diopters after 6 months of treatment, aligning closely with our study. Likewise, Bikbova and Bikbov[25] observed reduced K_2 values from 47.80±2.23 diopters to 45.78±2.01 diopters post-C_xL, indicating a similar trend. Ahmet et al.[23] also reported diminished K_2 readings after 6 months of C_xL, with values decreasing from 48.72±3.08 diopters to 46.81±3.00 diopters. Additionally, Tian et al.[27] and Tiveron et al.[24] studies demonstrated reductions in K_2 readings 6 months after C_xL, further supporting the consistency of our findings. These similarities across studies underscore the effectiveness of C_xL in reducing K_2 values and stabilizing keratoconus progression. However, variations in outcomes may arise due to differences in patient characteristics, treatment protocols, or other factors.

In present study, the mean values of steepest keratometry (Kapex) readings in diopters exhibited a consistent decrease across various assessment periods following collagen cross-linking (C_xL) treatment. Initially, at baseline, the mean Kapex value was 54.50±7.38 diopters. Subsequent assessments at 1, 3, and 6 months post-C_xL revealed significant reductions in Kapex values: 53.12±6.93 diopters at 1 month, 52.41±5.77 diopters at 3 months, and 51.32±5.13 diopters at 6 months ($p<0.001$), indicating a progressive flattening of the cornea. These

findings align with those of Ahmet et al.[23], which demonstrated diminished Kapex readings after 6 months of CxL, decreasing from 54.90 ± 4.81 diopters to 51.98 ± 5.00 diopters. Similarly, Tian et al.[27] and Tiveron et al.[24] also reported reductions in Kapex readings 6 months after CxL, consistent with our study results. The consistent decrease in Kapex values observed across studies underscores the effectiveness of CxL in halting the progression of keratoconus. The strengthening of bonds between collagen fibers, facilitated by the application of ultraviolet light and riboflavin, is likely responsible for this outcome. While our study findings are in line with previous research, variations in treatment protocols or patient characteristics may account for slight differences in outcomes.

In our present study, we examined the mean values of central corneal thickness (CCT) in micrometers across different assessment periods following collagen cross-linking (CxL) treatment. Initially, at baseline, the mean CCT was 467.53±37.38 micrometers. Subsequent assessments at 1, 3, and 6 months post-CxL revealed a consistent decrease in CCT values, with significant reductions observed at all follow-up intervals: 442.22±34.47 micrometers at 1 month, 430.42±27.82 micrometers at 3 months, and 425.03±26.41 micrometers at 6 months post-CxL treatment ($p<0.001$). These findings are in line with those of Ahmet et al.[23], which demonstrated diminished corneal thickness after 6 months of CxL, decreasing from 470±32 micrometers to 404±47.11 micrometers. Similarly, Shetty et al.[28] reported similar results, showing a reduction in corneal thickness 6 months after CxL. The consistent decrease in CCT values observed across studies underscores the effectiveness of CxL in modifying corneal biomechanics and halting the progression of keratoconus.

This study sheds light on the effectiveness of collagen cross-linking (CxL) treatment in keratoconus patients within the context of a government hospital setup in Bangladesh. Our findings demonstrate consistent reductions in diopteric values of keratometric readings and central corneal thickness following CxL, aligning with established evidence from global studies. By providing evidence of the efficacy of CxL in halting the progression of keratoconus and improving visual outcomes, this study underscores the importance of implementing this treatment modality in the management of keratoconus in Bangladesh. These findings have significant implications for improving the quality of life and socioeconomic prospects of individuals affected by keratoconus in the country.

Conclusion:

The quantitative analysis conducted in this study underscores a statistically significant reduction in keratometric readings (K_1, K_2, Kapex) and central corneal thickness (CCT) following collagen cross-linking (CxL) treatment in keratoconus patients. However, several limitations were noted, including the absence of long-term follow-up data, restricted patient selection criteria, and the lack of correlation analysis between keratoconus severity and reduction in parameters. To address these limitations, future research should focus on studying the long-term effects of CxL, conducting multicenter studies for broader evaluation, and ensuring the availability of necessary equipment and skilled personnel in eye care centers.

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