Risk Factors For Progression Following Corneal Collagen Crosslinking In Keratoconus

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Research Article

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Abstract

Purpose: To assess risk factors for progression following corneal collagen crosslinking (CXL) in eyes with keratoconus.

Methods: Charts of patients who developed progression following conventional CXL treatment (Dresden protocol) were retrospectively evaluated in two centers (Center 1, and Center 2). 871 eyes of a total of 676 patients were analyzed. Progression was defined as >1 diopter (D) increase in maximum keratometry (Kmax) readings compared to baseline.

Results: Progression was noted in 20 eyes of 20 patients (progression rate 3%). The mean age of the patients was 17.65 ± 5.76 (11–34) years and the mean follow-up following CXL was 36.70 ± 25.72 (12–84) months. The gender distribution was 13 (65%) females, and seven (35%) males. Four eyes (20%) had mild, 13 eyes (65%) had moderate, and three eyes (15%) had severe keratoconus at baseline. Fifteen eyes (75%) had allergic conjunctivitis and 20 eyes (100%) reported eye-rubbing. Cone location was central in 17 (85%) eyes and peripheral in 3 (15%) eyes. A mean of 2.21 ± 1.30 D (1.00 – 5.30 D) steepening was determined at Kmax 6 to 82 months following CXL treatment.

Conclusions: Progression rate was found to be higher in the patients under the age of 17 years, female gender, allergic conjunctivitis, high preoperative Kmax (>57 D), thin corneas (<430 μm) . The majority of progressive patients were central cone and moderate keratoconus.

Introduction

Keratoconus is a bilateral noninflammatory ectasia of the cornea characterized by progressive corneal thinning leading to irregular astigmatism, progressive myopia, and corneal scarring [1]. It varies with environmental, genetic and ethnic factors, and prevalence rates differ in different races [2]. Corneal collagen cross-linking (CXL) treatment is a procedure that uses ultraviolet A irradiation (UVA) and riboflavin to induce cross-links between the collagen fibers in the corneal stroma to increase the rigidity of the cornea [3]. It has been shown to slow down or halt keratoconus progression, with favorable clinical and topographic results [4–6]. The initiation of CXL treatment has led to a marked decrease in the need for corneal transplant surgery in patients with progressive keratoconus [7]. However, it is also known that not all keratoconus cases progress at the same rate [8]. Systematic analysis of the rate of change in disease progression is a sensitive tool for defining the treatment efficacy of CXL in preventing keratoconus progression [9, 10].

In this study, we examined the prognostic parameters potentially responsible for progression before CXL treatment in rare keratoconus patients who developed CXL and then progressed.

Methods

This retrospective study is part of an ongoing longitudinal study to evaluate CXL treatment outcomes in patients with keratoconus. Between December 2010 and May 2020, 871 eyes of 676 keratoconus patients treated with standard CXL in the Cornea Department of Harran University, School of Medicine (Center 1) and Ankara University, School of Medicine, Cornea Department (Center 2), were included in the study. The same parameters were obtained from both centers. Approval for the study was given by the local ethics committee (Ethics acceptance number: HRU / 20.19.2) and all transactions were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before the study.

Patients with a diagnosis of keratoconus, with tomography findings such as asymmetric bow tie pattern, inferior-superior (IS) asymmetry obtained by high-resolution Scheimpflug imaging (Pentacam HR; Oculus GmbH, Wetzlar, Germany) and with clinical signs such as stromal thinning, Fleischer ring, or Vogt stria after CXL treatment were evaluated for progression over at least a 12-month follow-up period. Progression was defined as a $\geq$ 1 diopter (D) increase in maximum keratometry (Kmax) readings compared to baseline levels. Three consecutive measurements were made by the same technician; data with an error-free status ('OK' as indicated by the technician) were evaluated in the study. Additionally, patients who used contact lenses before and after CXL treatment did not wear their contact lenses for at least one week prior to the examination. Those who had had ocular surgery other than CXL, those who developed corneal infection or scarring after treatment, those with autoimmune disease, and women who were pregnant or lactating were excluded from the study.

Patients were evaluated according to preoperative age, gender, spherical equivalent (SE), Kmax, cone location, keratoconus stage, endothelial cell count (ECC), and several prognostic parameters such as allergic conjunctivitis. The presence of tarsal papillae and conjunctival hyperemia were evaluated in all patients on slit lamp examination. Those with signs of allergic conjunctivitis were separated from the others. The Collaborative Longitudinal Evaluation of Keratoconus study [11] was used to stage the progression of keratoconus (Table 1). Axial topography maps for each eye were analyzed to determine the cone position. Cone location was examined for each eye to denote a central or peripheral location. In all patient eyes, the endothelium was photographed and evaluated using a Topcon SP-1P non-contact autofocus specular microscope (Topcon Corp, Tokyo, Japan). Images of the central corneal window were analyzed and manually corrected, and three ECC measurements were averaged.

Table 1
Collaborative Longitudinal Evaluation of Keratoconus Study classification of keratoconus using the steepest K-reading.

Staging of Keratoconus	K-Readings (using the steepest K)
Mild	≤ 45.00 D
Moderate	45.00–52.00 D
Advanced	≥ 52.00 D
Source: Zadnik K, Barr J, Edrington T, et al. Baseline findings in the collaborative longitudinal evaluation of keratoconus (CLEK) study. Invest Ophthalmol Vis Sci. 1998;39:2537–2546.	

Surgical Technique

The standard technique (Dresden Protocol) CXL treatment was used in both centers [3]. It was confirmed from the file data that the surgical procedure and duration were the same for all patients. Ocular anesthesia was provided using 0.5% proparacaine ophthalmic solution. After the surgical drape, an area of 9.0 mm was scraped from the corneal epithelium using a crescent knife. This was followed by the topical dropwise application of a 0.1% riboflavin solution with 20% dextran (MedioCROSS D, Peschke Meditrade, Germany) every 2 min for a total of 30 min over the course of the procedure. Intraoperative corneal thickness was measured using ultrasonic pachymetry (DGH 500, DGH Technology, Exton, Pennsylvania, USA). The cornea was irradiated with 365-nm UVA light using a LightLink-CXL system (LIGHTMED, Taiwan) in Center 1 or a CCL-Vario system (Peschke Trade, Hünenberg, Switzerland) in Center 2 over the 30-min period; the irradiation diameter was 8.0 mm and the irradiance was 3.0 mW/cm^2. After irradiation, the corneal surface was washed thoroughly with a balanced salt solution. At the end of the procedure, a bandage contact lens was placed on the cornea. Oral analgesic was given to all patients for 3–5 days postoperatively. Topical 0.5% levofloxacin was used four times a day for 1 week. After the healing of the corneal epithelial defect, 0.1% fluorometholone was started four times a day. Corticosteroid eye drops were gradually reduced over a 4-week period postoperatively. The patients were followed up on postoperative days 1, 3, and 7. Refractive and topographic controls were performed at 1 and 3 months postoperatively and then every 3 months thereafter.

Statistical Analysis

The data obtained in the study were analyzed statistically using SPSS for Windows version 22.0 software (IBM SPSS Inc, Chicago, IL, USA). The compliance of the data to normal distribution was evaluated using the Shapiro-Wilk test. The correlation between prognostic factors and the change in Kmax after CXL treatment (ΔKmax) was examined. The patient data of both centers were examined separately and a comparison was made on mean values. A p value of < 0.05 was considered statistically significant.

Results

In both centers, follow-ups were analyzed retrospectively from the patients' data. Four hundred one eyes of 295 patients from center 1, and 470 eyes of 381 patients from center 2 were analysed.The total number of patients who developed post-CXL progression from the two centers was 20 (progression rate 3%). Twelve (60%) of these cases were obtained from Center 1, and eight (40%) were from Center 2. The mean age of the patients was 17.65 ± 5.76 (11–34) years, and the mean follow-up following CXL was 36.70 ± 25.72 (12–84) months. The gender distribution was 13 (65%) females, and seven (35%) males. During the follow-up period, the mean time before the onset of post CXL progression was 31.35 ± 24.78 (6–82) months, and the median time to progression was 20.50 months.

Before CXL treatment, the mean SE value was − 5.83 ± 3.71 (− 15.0 to − 1.0) D. Fifteen eyes (75%) had allergic conjunctivitis and 20 eyes (100%) reported eye-rubbing. Keratoconus staging was as follows: four (20%) cases with mild, 13 (65%) cases with moderate, and three (15%) cases with severe. The mean Kmax obtained with the Scheimpflug camera was 57.26 ± 4.95 (47.30–66.20) D, and the mean thinnest corneal thickness was 442.25 ± 45.18 (515–361) µm. Three (15%) cases had peripheral cone localization, and 17 (85%) cases had a central cone. The mean ECC obtained from noncontact specular microscope measurements was 2611.85 ± 433.22 (3256–1562) cells/mm^2. The data of all patients before CXL treatment are shown in Table 2. No significant correlation was found between the variables in the correlation analysis performed for prognostic factors effective in progression ($p > 0.05$).

Table 2
The datas of different groups.

	Center 1 (n:12)		Center 2 (n:8)		Δ Kmax > 2.21 D (n:7)		All Patients (n:20)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	16.00	2.26	18.87	7.98	16.14	2.67	17.65	5.76
Follow-up (months)	17.75	6.06	61.87	22.79	18.00	5.41	36.70	25.72
Prog Date(months)	13.25	5.77	55.12	22.82	14.14	6.93	31.35	24.78
SE (D)	-7.09	4.58	-4.21	2.92	-7.35	4.22	-5.83	3.71
Kmax (D)	57.90	5.55	55.95	5.44	56.91	4.94	57.26	4.95
Δ Kmax (D)	3.07	1.57	1.56	0.46	3.65	1.09	2.21	1.30
TCT (μm)	426.25	45.97	463.75	39.98	430	47.34	442.25	45.18
ECC (cell/mm^2)	2843.12	315.07	2346	446.5	2708.14	390.82	2611.85	433.22
	Count	**Ratio**	**Count**	**Ratio**	**Count**	**Ratio**	**Count**	**Ratio**
Mild KC	3	25%	1	12%	3	42%	4	20%
Moderate KC	6	50%	7	88%	2	29%	13	65%
Advanced KC	3	25%	0	0%	2	29%	3	15%
AC	11	92%	7	88%	5	86%	15	75%
Central Cone	11	92%	6	75%	5	86%	17	85%
Peripheral Cone	1	8%	2	25%	1	14%	3	15%

AC: allergic conjunctivitis; Δ Kmax: the change in the maximum keratometry after CXL treatment; ECC: endothelial cell count; KC: keratoconus; Kmax: maximum keratometry; Prog Date: progression start date; SD: standard deviation; SE: spherical equivalent; TCT: thinnest corneal thickness.

Figure 1 shows the ΔKmax and the dates of progression onset. According to the monthly variation in Kmax, seven cases showed an increase in ΔKmax above the mean value (2.21 D), as indicated in the graph of Fig. 1. All of these cases included patients from Center 1, specifically, three males and four females with a mean age of 16.14 ± 2.67 (12–20) years. Two cases (29%) had severe keratoconus, two cases (29%) moderate, and three cases (42%) mild. Five of the seven patients had allergic conjunctivitis

(vernal limbal conjunctivitis), whereas the conus was centrally located in six cases and was inferior in one case. The mean SE was − 7.35 ± 4.22 (− 15.0 to − 2.50) D, the mean Kmax was 56.91 ± 4.94 D, the thinnest pachymetry value was 430.0 ± 47.34 (361–483) µm, and the mean ECC was 2708.14 ± 390.82 (2212–3256) cells/mm^2.

Data Of Study Centers

Center 1

The mean age of the patients was 16.00 ± 2.26 (12–20) years, the mean follow-up period was 17.75 ± 6.06 (12–25) months, and the mean post-CXL progression time was 13.25 ± 5.77 (6–22) months. Before CXL treatment, the mean SE value was − 7.09 ± 4.58 D, while AK staging indicated three cases as mild, six cases as moderate, and three cases as severe keratoconus. Allergic conjunctivitis was detected in 11 (92%) of the cases. In the imaging performed with the Scheimpflug camera, the central cone was present in 11 cases; in one case, the cone was located peripherally. Kmax was 57.9 ± 5.55 D, the thinnest pachymeter was 426.25 ± 45.97 µm, and the ECC was 2843.12 ± 315.07 cells/mm^2. ΔKmax after CXL treatment was 3.07 ± 1.57 D. Bilateral progression was observed in one case who reported excessive eye-rubbing. In Center 1, a LightLink-CXL (LIGHTMED, Taiwan) device was used for UVA application. (Table 2)

Center 2

The mean age of the patients was 18.87 ± 7.98 (12–34) years, the mean follow-up period was 61.87 ± 22.79 (18–84) months, and the mean onset time of progression post-CXL was 55.12 ± 22.82 (12–82) months. Before CXL treatment, the mean SE value was − 4.21 ± 2.92 D. AK staging showed one case at mild, and seven cases as moderate keratoconus. Allergic conjunctivitis was detected in seven (88%) of the cases. In imaging performed with a Scheimpflug camera, there was a central cone in six cases, whereas the cone was located peripherally in two cases. Kmax was 55.95 ± 5.44 D, the thinnest pachymeter was 463.75 ± 39.98 µm, and the ECC was 2346 ± 446.5 cells/mm^2. ΔKmax after CXL treatment was 1.56 ± 0.46 D. In Center 2, a CCL-Vario, (Peschke Trade, Hünenberg, Switzerland) device was used for UVA application. (Table 2)

Discussion

In our study, we investigated the general prognostic features that potentially contribute to failed standard CXL treatment. In the literature, CXL treatment results have been reported from several long-term studies [5, 6, 12–14]. Based on the findings from these earlier studies, we now know that the standard CXL protocol is not worse than other protocols in stopping progression. However, in patients in whom the condition progresses despite standard CXL treatment, the factors affecting this condition have yet to be fully clarified. In this context, the results of our study provide additional insight into this progression.

In a meta-analysis [15] of the natural progression of patients with untreated keratoconus, the results showed that patients under 17 years of age and with a Kmax steeper than 55.0 D face a high risk of progression. Middle Eastern populations show a significantly greater increase in Kmax than Europeans

and East Asians. Our study was conducted with data from two centers. The mean Kmax values were greater than 55.0 D for both centers. In addition, Center 1 consisted of patients who were slightly younger and who had slightly greater preoperative Kmax values than the other center. There was also a sharper increase in the Kmax values of patients from Center 1 after CXL treatment.

Due to the nature of keratoconus disease, some groups of patients may progress despite CXL treatment. This is important, as emphasized by Koller et al [16], in that changing the inclusion criteria in CXL therapy could significantly reduce the complications and failures of CXL treatment. Cone location is known to be mostly central in all stages of keratoconus [17]. In our study, the data overwhelmingly indicated a central cone location in patients from both centers. Because having a central cone is a common condition in keratoconic eyes, it may not be an effective factor with respect to the development of progression. Of the patients included in our study, 65% were female. Studies show that gender is not a clear factor in patient selection for CXL [18]. Especially in Center 1, the female gender percentage was 75%, and in Center 2 it was 50%. Allergic conjunctivitis was present in 75% of the cases. In Center 1, this rate reached 92%, and in Center 2 it reached 88%. Bilateral progression was observed in one patient with excessive tear scratching. The relationship between eye scratching and keratoconus progression is a well-known association. The presence of allergic conjunctivitis may be a good indicator for progression.

Preoperative corneal thickness in Center 1 was evaluated as being ~ 40 µm thinner, and the SE and Kmax values were 3 D and 2 D higher, respectively (Table 2). We were unable to obtain any data showing that the preoperative ECC affects the progression of keratoconus. In our study, the ECC was higher in Center 1. The fact that patients with advanced and endothelial damage were not included in the study when selecting patients for CXL treatment may have been effective.

The surgical technique used in both centers was the same standard protocol; however, the UVA devices used were different. Here, the calibration error of the devices and care in administering the UVA radiation should be examined carefully, even if the standard protocol was applied in both centers.

With respect to the cause of keratoconus progression, patients with a high preoperative Kmax (> 57.0 D), thin corneal thickness (< 430 µm), presence of allergic conjunctivitis, female gender, and those under 17 years of age may show a more aggressive condition and early progression. The longer follow-up periods of the centers provide more stable results with regard to our analysis. However, it seems that progression may develop after a long follow-up, especially in those who are younger. Providing an effective strategy for preventing the development of aggressive progression is the main contribution of this study.

Declarations

Competing Interests:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-

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All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Ayhan Sağlık], [Gökçen Özcan] and [Ömür Uçakhan]. The first draft of the manuscript was written by [Ayhan Sağlık] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval:

Approval for the study was given by the local ethics committee (Ethics acceptance number: HRU / 20.19.2) and all transactions were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before the study.

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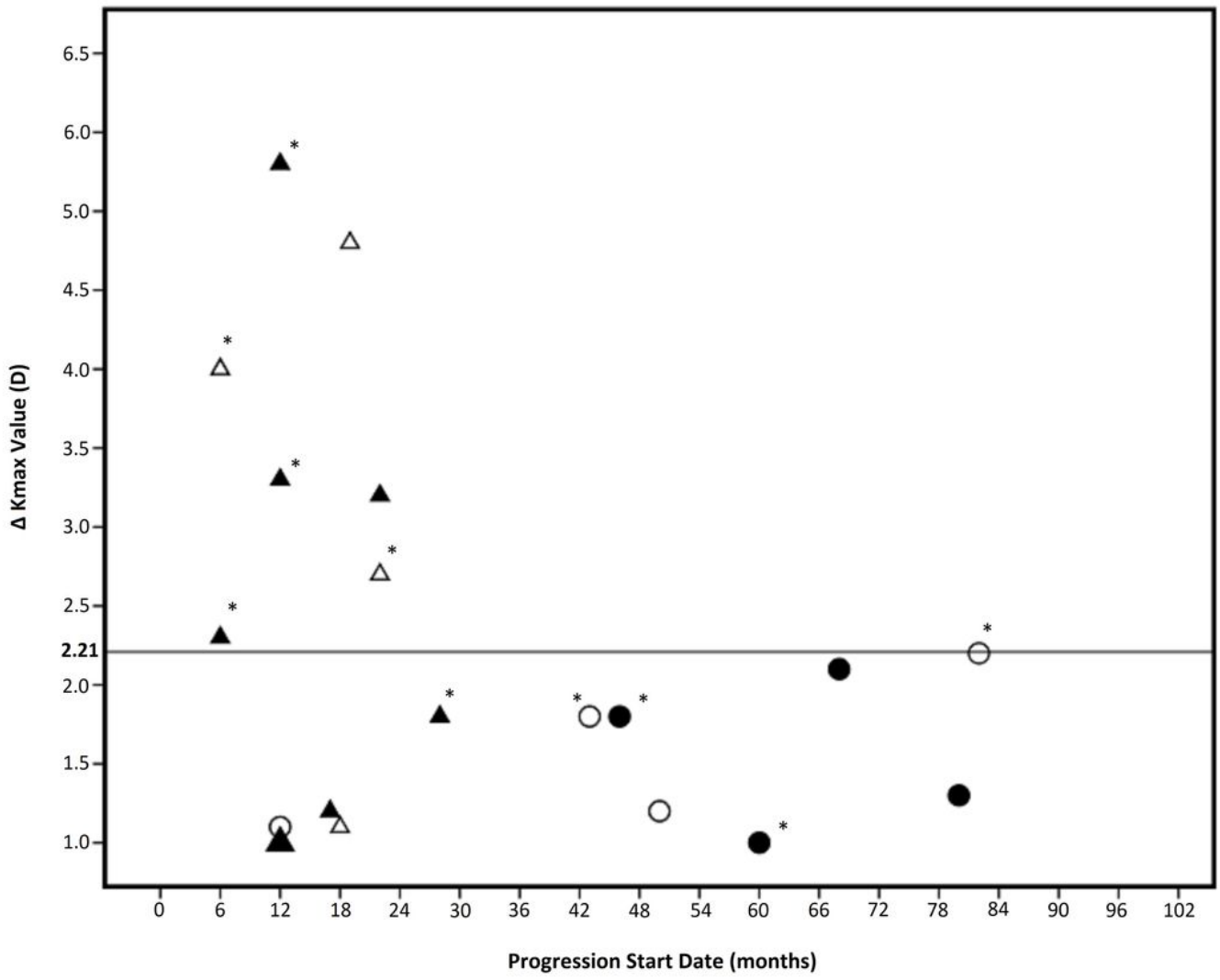
Figures



Kmax: maximum keratometry; D: diopter. * : preoperative age <17 years.

△ : Center 1 patients, preoperative mean Kmax < 57 D

▲ : Center 1 patients, preoperative mean Kmax > 57 D

○ : Center 2 patients, preoperative mean Kmax < 57 D

● : Center 2 patients, preoperative mean Kmax > 57 D

Figure 1

The patients data, the change in the Kmax (Δ Kmax) after CXL treatment and the progression starting time.