BMC Ophthalmology

RESEARCH

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Corneal cross-linking effects on ocular surface parameters and corneal topographic and optical characteristics in progressive keratoconus cases: a prospective single-arm study

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Abstract

Objective This study aims to evaluate the effects of epithelial-off corneal cross-linking (CXL) on the ocular surface and corneal topographic and optical parameters in progressive keratoconus (KCN) cases.

Study design Prospective single-arm interventional study.

Methods Thirty eyes of 25 progressive KCN cases needing corneal CXL entered the study. All the included eyes underwent an epi-off corneal CXl procedure following the Dresden protocol. The ocular surface parameters, including tear break-up time (TBUT), Schirmer I test, and Ocular surface disease index (OSDI), were evaluated at baseline, one and 6 months after the procedure. The corneal imaging with Pentacam (Oculus Inc.) was conducted at these visits, measuring topographic parameters (e.g., K_{max}, K_1, K_2, and corneal thickness), indices (e.g., ISV, IVA, KI IHA), and aberrations.

Results The median age of the patients was 24.0 (IQR:21.0–26.5) with a baseline BCVA of 0.045 LogMAR (IQR:0.000–0.301). The BCVA had no significant change in the last follow-up (p:1.000). The baseline median values for TBUT, Schirmer test, and OSDI were 11.0s, 13.0mm, and 28.12, demonstrating a significant ocular surface malfunction. These ocular surface parameters showed no significant change 6 months after CXL (p: 0.662, 0.534, and 0.372, respectively). The K_1 and K_2 values decreased significantly at the last follow-up compared to the baseline (44.4 vs. 45.6 (p:0.019) and 48.0 vs. 48.1 (p:0.008), respectively). The only topographic indices that improved 6 months after CXL was the index of surface variance (ISV) (70.50 vs. 61.70, p:0.036). The corneal front surface higher-order aberrations, including spherical aberration, coma, and trefoil, showed no significant change 6 months after CXL.

Conclusion Progressive KCN cases cope with some ocular surface problems, such as dry eye, but the corneal CXL is safe for these cases without causing any deterioration in the ocular surface problems. The corneal CXL might not improve the topographic indices and corneal aberrations 6 months after the procedure.

Keywords Keratoconus, Cross-linking, CXL, Ocular surface, Topographic indices, Aberration

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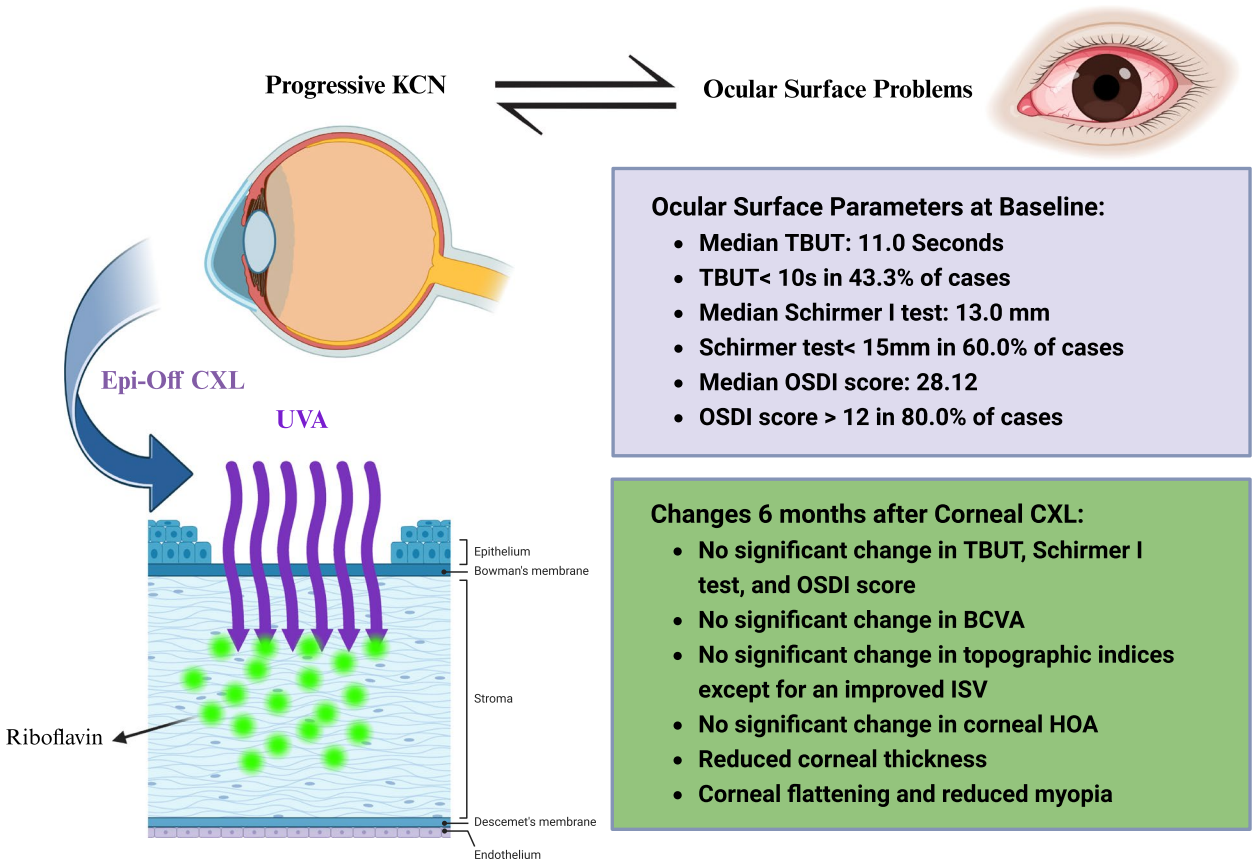
Graphical Abstract



Introduction

Keratoconus (KCN) is a bilateral and asymmetric degeneration of the cornea, marked by localized thinning of the corneal tissue, resulting in the protrusion of the affected area. The corneal protrusion results in significant myopia and irregular astigmatism, compromising visual quality. Typically, it manifests itself during the second decade of life [1, 2]. The condition does not have merely a structural component, and inflammatory changes in the ocular surface have been demonstrated [3].

The management of KCN depends on the stage of ectasia and includes several types of interventions. Refractive correction is typically employed in mild cases, while moderate cases may necessitate wearing rigid contact lenses. Advanced cases may require surgical options, including the implantation of intracorneal ring segments or keratoplasty. Corneal collagen cross-linking (CXL) should also be considered in progressing cases [4]. The corneal CXL procedure causes chemical reactions, specifically free radical production, in the corneal stroma, leading to the formation of covalent bonds among collagen molecules, fibers, and microfibrils using riboflavin and ultraviolet A (UVA) radiations. The improvement of collagen bonding is believed to inhibit additional thinning and ectasia, ultimately decreasing or stopping the progression of keratoconus [5].

Dry eye disease (DED) covers a range of symptoms and signs linked to damaged ocular lubrication, characterized by diminished quality or quantity of tears on the ocular surface [6]. DED is considered a dysfunction of the integrated functional unit, including the lacrimal glands, ocular surface, eyelids, and sensory and motor nerves [7]. The results of studies conducted on keratoconus patients indicate a decrease in both the quantity and quality of the tear film in these patients [8, 9]. Besides, therapeutic approaches for KCN cases, such as contact lenses and corneal CXL, might exacerbate the condition of the ocular surface.

This study examines the corneal cross-linking procedure's impact on the cornea's topographic and optical

parameters, including topographic indices and aberrations beside the ocular surface parameters. By delving into these parameters, we seek to comprehensively understand how CXL influences dry eye syndrome and overall corneal structure in this condition. Also, the correlation between the ocular surface and corneal structural parameters is evaluated.

Methods

Participants

This prospective single-center, single-arm interventional study was performed in the Nikookari Eye Hospital in Tabriz, involving 30 eyes between August 2023 and September 2024. Eyes were included in the current study if corneal CXL was intended for treating progressive keratoconus and had no exclusion criteria. The progressive KCN was defined as having one of these changes 6 months after the previous ophthalmic evaluation: 1) a reduction of one line or more in best-corrected visual acuity (BCVA) based on E-Chart, 2) an increase of 1.0 diopters or more in maximum K-reading (K_{max}), or 3) a thinning equal or more than 2% of corneal thickness at its thinnest point. The exclusion criteria are extensively defined below.

Exclusion criteria

- History of any ocular surgery
- History of ocular surface injury, such as a scar-forming trauma or chemical burn
- History of other conditions affecting the cornea, such as infectious keratitis, corneal dystrophies, and degenerations
- History of other ocular diseases, such as glaucoma and uveitis
- History of using any eye drops or contact lenses in the past year
- History of systemic diseases such as atopic or autoimmune disorders
- Pregnant or breastfeeding patients during the study
- Lack of patient consent to participate in the study

Ocular examinations and outcome measurements

Each patient underwent four visits following their enrollment in the study: before corneal CXL, one week, one and 6 months after the procedure. Each visit included a comprehensive ophthalmological examination, fundoscopy using a slit lamp, objective and subjective refraction assessments, and an evaluation of the patient's BCVA. The ocular surface parameters and corneal topography were evaluated at the baseline, one and 6 months after the procedure.

The ocular surface condition of the patients was evaluated using the tear break-up time test (TBUT), Schirmer I test, and the Ocular surface disease index (OSDI) questionnaire. The TBUT was assessed with a fluorescein-impregnated strip moistened with a non-preserved saline solution applied in the tear film, and the patient was asked not to blink. The tear film was evaluated with cobalt blue light under the slit-lamp biomicroscopy. The duration from the fluorescein dye application to the appearance of the first dark spot or drying of the tear film was measured in seconds. The Schirmer I test involves inserting a paper test strip into the lateral third of the lower eyelid following the drying of the inferior fornix, with the length of the hydrated section of the strip observed after 5 min.

The patients underwent corneal imaging using the Pentacam (Oculus Inc.) device. The K_{max}, K_1, K_2, corneal astigmatism and corneal thickness at the thinnest point of the cornea were measured as the topographic characteristics of the cornea. The index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), index of height asymmetry (IHA), index of height decentration (IHD), and minimum radius of curvature (Rmin) were evaluated as topographic indices of the cornea. The total wavefront aberration (WFA), and front surface higher order aberration (HOA), spherical aberration (SA), vertical and horizontal coma, trefoil at 0 and 30 degrees were evaluated as the corneal amperometric parameters.

Corneal CXL procedure

The Dresden protocol was utilized to cross-link the patients in this investigation. Following topical anesthesia (Tetracaine hydrochloride 0.5% ophthalmic solution), the epithelium of the central 7 mm cornea is excised using 20% ethanol solution (applied for 15 s). The surface is subsequently treated with a riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 10 ml dextran 20% solution) every 5 min for 30 min before UVA irradiation. An irradiance of 3 mW/cm2 of UVA radiation with a wavelength of 370 nm was administered to the cornea at a distance of 1 cm for 30 min, resulting in a dose of 5.4 J/cm2. A bandage contact lens was placed on the cornea after the termination of the CXL procedure. The patients received topical preservative-free Levofloxacin ophthalmic solution (0.5%) and artificial tears (Sodium Hyaluronate 0.15%) Q6h for a week after the surgery. The betamethasone 0.1% ophthalmic solution was prescribed initially every 4 h and tapered and discontinued through 4 weeks. The bandage contact lens is removed one week after the procedure, which is when the epithelial repair process has been completed.

Statistical analysis

The quantitative data with normal distribution were compared between the visits using One-way Repeated Measures ANOVA (Post-Hoc: Bonferroni). For comparison between the baseline and the first follow-up (in case of *p*-value lower than 0.05 in ANOVA test), we used Paired-samples Students' T-Test due to loss to follow-up of some cases in the last visit. The Related-Samples Friedman's Two-Way Analysis of Variance by Ranks followed by Wilcoxon signed ranks Test (used for comparison of baseline and first follow-up) were used for quantitative data without normal distribution. To compare the qualitative data, we used the Chi-squared test. The Spearman correlation test evaluated the possible correlation between the variables. All the statistical analyses were conducted using IBM SPSS Statistics 27.0 software. The figures are created in BioRender.com.

Ethical considerations

This study adhered to the Declaration of Helsinki and received approval from the Tabriz University of Medical Sciences research ethics committee with the approval code of IR.TBZMED.REC.1403.061. Informed consent was obtained from all the included patients before entering the study.

Results

Patients

A total number of 30 eyes (15 OD, 15 OS) of 25 patients (12 Males, 13 Females) entered the study. The median age of the patients was 24.0 (IQR:21.0–26.5). All the patients came for the first follow-up visit, and out of 30 eyes, only three missed the second post-op visit. The mean interval between the first post-op visit and the CXL was 28.9 days (95%CI:26.8–31.1). This value for the second post-op visit was 169.1 days (95%CI:161.0–177.3).

Best corrected visual acuity

The median pre-op BCVA of the eyes was 0.045 LogMAR (IQR:0.000–0.301). The comparison of the BCVA on the follow-up visits with the baseline revealed a significant difference between them (p:0.019). The median BCVA was mildly worse on the first follow-up than the baseline. The values on the second follow-up showed no significant difference compared to the baseline and the first follow-up. The study's detailed findings regarding the BCVA can be found in Table 1.

Ocular surface parameters

On the baseline, the median TBUT was 11.00 s (IQR:7.75–15.50), and 13 (43.3%) eyes had TBUT shorter than 10 s. The TBUT showed a significant difference between the follow-up visits and the baseline (p:0.019). The pairwise comparison revealed no significant difference between the follow-ups and the baseline. Table 2 shows the detailed results of the study.

Table 1 The detailed data regarding the BCVA on baseline and follow-up visits

	Baseline (n:30)	1 Month (n:30)	5–6 Months (n:27)	*p*-value
Median BCVA (LogMAR) (IQR)	0.045 (0.000–0.301)	0.154 (0.000–0.265)	0.096 (0.000–0.301)	**0.019**^{F}
Comparison to baseline *p*-value	-	**0.008**^{W}	1.000^{F}	

F Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, *W* Wilcoxon signed ranks Test

The prevalence of abnormal TUBT was 23.3% and 44.4% in the first and second follow-up, respectively. Although the prevalence of the abnormal TBUT was lower on the first follow-up, it was not statistically significant compared to the baseline and the second follow-up (p:0.100 and 0.091, respectively). The statistically insignificant difference might be due to the limited number of studied cases.

The baseline median Schirmer I test was 13.00 mm (IQR:7.00–18.25), and the frequency of the values lower than 15 mm was 60.0% (n:18). The comparison of the Schirmer test results between the follow-up visits and the baseline showed no significant difference (p:0.534). The detailed results are provided in Table 2.

The frequency of the abnormal Schirmer test on the first and second follow-ups was 60.0% and 66.7%, respectively, without any significant difference compared to the baseline (p:1.000 and 0.602, respectively).

The median OSDI score on the baseline was 28.12 (IQR:14.06–41.60), and 80.0% (n:24) of the eyes had scores higher than 12, indicating an abnormal ocular surface. There was no statistical difference between the follow-up visits and the baseline regarding the OSDI score (p:0.372). The detailed results are available in Table 2.

80.0% and 81.5% of eyes on the first and second follow-up visits had OSDI scores higher than 12, which shows no significant difference from the baseline (p:1.000 and 0.887, respectively).

Considering the OSDI scores higher than 32 as an indicator of severe ocular surface disease, 36.7%, 30.0%, and 33.3% of the eyes on the baseline, first, and second follow-up visits meet this criteria. The prevalence

Table 2 The detailed data regarding the ocular surface parameters on baseline and follow-up visits

	Baseline (n:30)	1 Month (n:30)	5–6 Months (n:27)	*p*-value
Median TBUT (Seconds) (IQR)	11.00 (7.75–15.50)	12.00 (9.75–17.00)	11.00 (5.00–21.00)	**0.019**^{F}
Comparison to baseline *p*-value	-	0.101^{W}	0.662^{F}	
Median Schirmer I test (mm) (IQR)	13.00 (7.00–18.25)	14.00 (9.50–16.25)	12.00 (10.00–17.00)	0.534^{F}
Median OSDI score (IQR)	28.12 (14.06–41.60)	23.96 (12.50–41.60)	27.08 (12.50–37.50)	0.372^{F}

F Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, *W* Wilcoxon signed ranks Test

of this stage of ocular surface disease showed no significant difference between the various visits (p:0.860). Figure 1 demonstrates the case-based data on TBUT, Schirmer 1 test, and OSDI score during the follow-ups.

Corneal topographic parameters

The mean K_{max} was 53.0 D (95%CI:51.2–54.7) on the baseline. The comparison of the baseline and the follow-up visits was statistically significant (p:0.016). The pairwise comparison showed a significantly lower K_{max} on the second follow-up than on the first follow-up (p:0.022). However, the follow-up values showed no statistical difference from the baseline. Although the *p*-value for the comparison of the second follow-up and the baseline was insignificant, it had a borderline value, and the mean K_{max} seems lower on the second follow-up than the baseline. The detailed results of topographic evaluations are available in Table 3.

The K_1 and K_2 values on the second follow-up were significantly lower than the baseline and the first follow-up (p:0.019 and 0.008, respectively). The baseline and the first follow-up values on the table are provided for all the cases (n:30), and the three cases that missed the last follow-up had lower values of K_1 and K_2. However, the last follow-up was compared to the baseline using data from 27 eyes, which completed all the visits. The mean K_1 of the 27 eyes at the baseline was 45.6 (95%CI:44.4–46.8), and the value for the last follow-up was 44.4 (95%CI:43.3–45.6). The median K_2 of the 27 eyes at the baseline was 48.1 (IQR:46.6–50.8), and the correspondence value at the last follow-up was 48.0 (IQR:45.5–50.1). On the other hand, the Astigmatism did not show any significant difference between the various visits (p:0.712).

As expected, The mean corneal thickness at the thinnest point of the cornea was significantly lower on the first and second follow-ups than the baseline. There was no significant difference between the follow-ups (p:1.000).

Corneal aberrations

The comparison of corneal aberration parameters in the follow-up visits to the baseline showed no significant difference except for the median total aberration. The median total corneal aberration was significantly lower in the 5–6 months follow-up compared to the baseline and the first follow-up (p:0.043 and 0.013, respectively). However, the difference does not seem clinically significant and might be due to changes in lower-order aberrations. Although the median HOA, SA, and vertical Coma seem to be lower in the last follow-up compared to the baseline, it was statistically insignificant. Table 4 shows the detailed results of the study.

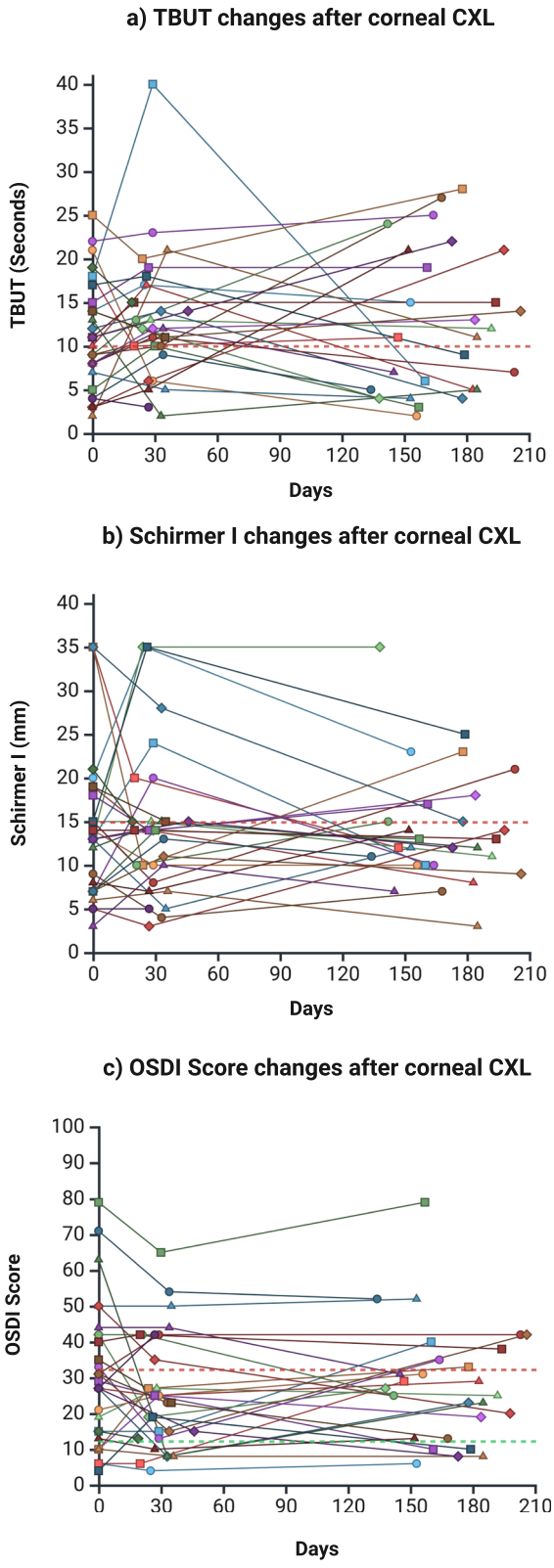
Pentacam corneal topographic indices

The evaluation of the corneal topographic indices after the CXL procedure showed no significant changes except for the ISV. The index of surface variance was significantly lower in the 5–6 months follow-up compared to the baseline and the first-month follow-up (p:0.036 and 0.040, respectively). The ISV values were 7.81 (95%CI: 0.41–15.21) and 8.14 (95%CI: 0.30–15.99) lower in the last follow-up than the baseline and the first follow-up. Table 5 shows the detailed results of the study.

Refractive error

The mean spherical equivalence of the refractive error on the baseline was −5.62 D (95%CI:((−4.60)-(−6.65)). The intervisit comparisons showed a significant difference (p: < 0.001). The myopia was less on the second follow-up compared to the baseline and the first follow-up (p:0.056 and < 0.001, respectively). However, the *p*-value for the comparison with the baseline was borderline. In addition, the median cylinder values were significantly lower on the second follow-up compared to the baseline and the first follow-up (p:0.019 and 0.002, respectively). The detailed results are provided in Table 6.

The comparison between the cylinder values of the corneal topography and autorefraction was made. The results showed that the values of the auto refractometer were significantly higher than the topography findings



◄ **Fig. 1** Detailed case-based data on TBUT, Schirmer I test, and OSDI scores before and after corneal CXL. Each symbol and its related line represents a case. **a** shows the TBUT changes after corneal CXL, and the red dashed line shows the threshold for abnormal TBUT (10 s). **b** shows the Schirmer I test changes after corneal CXL, and the red dashed line shows the threshold for abnormal Schirmer I test (15 mm). **c** shows the OSDI score changes after corneal CXL, the green dashed line shows the threshold for abnormal OSDI score (12), and the red dashed line indicates the threshold for severe ocular surface disease (32). As demonstrated, most cases had a baseline abnormal TBUT, Schirmer I test, and OSDI scores with no significant change after corneal CXL

on the baseline and the first follow-up visit (p:0.002 and 0.003, respectively). However, the results of the second follow-up showed no significant difference between the two devices (p:0.173).

Correlations

We performed a Spearman's correlation test to evaluate the possible correlation between the corneal topographic features and the ocular surface findings of patients at the baseline. The results are provided in Table 7 in detail. As declared in the table, the only statistically significant correlation was between the IHD and TBUT measurements; the higher the IHD, the lower the TBUT.

Discussion

In our prospective study, we evaluated the effects of conventional epi-off CXL on the subjective and objective parameters of ocular surface condition, corneal topographic parameters, indices, and corneal aberrations. BCVA and ocular surface parameters, including TBUT, Schirmer test, and OSDI score, showed no significant difference 5–6 months after CXL. It is worth mentioning that more than 80% of patients had an abnormal OSDI score throughout the study.). The K1 and K2 values decreased significantly at the last follow-up compared to the baseline. The corneal topographic indices showed no significant change after CXL, except for the ISV, which was reduced 5–6 months after CXL. Regarding the corneal aberrations, only total corneal aberration showed a minor reduction 5–6 months after CXL, which might not be clinically significant.

Keratoconus is not merely a structural disease of the cornea; it has an inflammatory compartment affecting the ocular surface and tear film. It has been shown that various inflammatory cytokines such as IL-1β, IL-6, IL-17A, TNFα, and TGFβ have higher levels in patients' tear film with KCN [3]. Compared to the controls, it has been shown that the proteomic profile of the tear film is different in keratoconus cases. Proteins such as Proline-rich protein 27 (PRR27), Immunoglobulin heavy variable

Table 3 The detailed data regarding the Corneal Topographic Parameters on baseline and follow-up visits

	Baseline (n:30)	1 Month (n:30)	5–6 Months (n:27)	*p*-value
Mean K_{max} (D) (95%CI)	53.0 (51.2–54.7)	52.9 (51.1–54.7)	51.7 (50.1–53.2)	**0.016**^{A}
Comparison to baseline *p*-value	-	0.834^{T}	0.051^{A}	
Mean K_1 (D) (95%CI)	45.5 (44.4–46.7)	45.0 (43.9–46.1)	44.4 (43.3–45.6)	**0.004**^{A}
Comparison to baseline *p*-value	-	0.082^{T}	**0.010**^{A}	
Median K_2 (D) (IQR)	47.9 (46.0–50.5)	47.7 (46.2–51.5)	48.0 (45.5–50.1)	**0.004**^{F}
Comparison to baseline *p*-value	-	0.811^{W}	**0.019**^{F}	
Mean Astigmatism (D) (95%CI)	3.24 (2.76–3.73)	3.29 (2.77–3.81)	3.32 (2.81–3.83)	0.712^{A}
Mean Corneal Thickness (μm) (95%CI)	451.2 (437.1–465.3)	412.9 (398.2–427.5)	410.0 (394.4–425.6)	**< 0.001**^{A}
Comparison to baseline *p*-value	-	**< 0.001**^{T}	**< 0.001**^{A}	

F Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, *A* One-way Repeated Measures ANOVA (Post-Hoc: Bonferroni), *T* Paired-samples Students' T-Test, *W* Wilcoxon signed ranks Test

Table 4 The detailed data regarding the Corneal aberrations on baseline and follow-up visits

	Baseline (n:30)	1 Month (n:30)	5–6 Months (n:27)	*p*-value
Median Total Aberration (μm) (IQR)	187.45 (177.89–198.45)	187.88 (174.60–202.72)	185.82 (174.37–200.03)	**0.008**^{F}
Comparison to baseline *p*-value	-	0.396^{T}	**0.043**^{F}	
Corneal Front Surface Aberrations				
Median Higher Order Aberrations (μm) (IQR)	5.342 (3.239–7.449)	5.370 (3.524–7.092)	5.131 (3.550–7.274)	0.553^{F}
Median Spherical Aberration (μm) (IQR)	−0.501 ((−0.878)-(−0.196))	−0.478 ((−1.103)-(−0.279))	−0.340 ((−0.800)-(0.030))	0.459^{F}
Median Vertical Coma (μm) (IQR)	−1.454 ((−2.363)-(−0.736))	−1.328 ((−1.915)-(−0.840))	−1.027 ((−2.133)-(−0.650))	0.772^{F}
Mean Horizental Coma (μm) (95%CI)	0.057 ((−0.411)-(0.527))	−0.028 ((−0.404)-(0.348)	0.217 ((−0.286)-(0.720))	0.176^{A}
Median Trefoil 30° (μm) (IQR)	0.200 ((−0.091)-(0.303))	0.172 ((−0.084)-(0.357))	0.157 ((−0.060)-(0.388))	0.236^{F}
Mean Trefoil 0° (μm) (95%CI)	0.005 ((−0.128)-(0.140))	−0.076 ((−0.228)-(0.075))	−0.025 ((−0.149)-(0.099))	0.139^{A}

F Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, *A* One-way Repeated Measures ANOVA (Post-Hoc: Bonferroni), *T* Paired-samples Students' T-Test

5–51 (IGHV5-51), and Keratin type I cytoskeletal 13 (KRT13) are increased in KCN cases tear film, which might play as a diagnostic tool in the future [10]. Interestingly, it has been suggested that tear film microbiome also may play a role in the keratoconus. The Pelomonas and Ralstonia genera are shown to be unique for the tear film of KCN cases compared to the controls [11]. In addition to these laboratory findings regarding the tear film differences in KCN cases, there are clinical findings, too.

It has also been found that KCN cases have lower corneal sensitivity and Schirmer test values, besides the loss of conjunctival goblet cells [12]. Dienes et al. showed that cases with KCN have lower sensitivity to mechanical, chemical, and thermal stimulations than the controls. However, they reported a high mean OSDI score for KCN cases compared to controls (26.8 vs. 8.1), comparable to our results (28.12). They suggested that the abnormal corneal sensory responses to the stimulations might be an underlying reason for the higher OSDI score and discomfort in the KCN cases [13]. Németh et al. also had higher OSDI scores for KCN cases than the controls (31.4 vs. 17.5) correlated with surface asymmetry index (SAI) and surface regularity index (SRI) [14]. Besides the nature of the KCN, therapeutic approaches such as contact lens use might affect the ocular surface parameters of these patients.

Table 5 The detailed data regarding the Corneal topography indices on baseline and follow-up visits

	Baseline (n:30)	1 Month (n:30)	5–6 Months (n:27)	*p*-value
Mean ISV (95%CI)	70.50 (61.40–79.60)	70.87 (61.64–80.09)	61.70 (52.79–70.62)	**0.012**^{A}
Comparison to baseline *p*-value	-	0.897^{T}	**0.036**^{A}	
Median IVA (IQR)	0.680 (0.452–0.880)	0.700 (0.465–0.922)	0.660 (0.490–0.870)	0.618^{F}
Median KI (IQR)	1.160 (1.107–1.235)	1.180 (1.107–1.257)	1.140 (1.090–1.240)	0.162^{F}
Mean IHA (95%CI)	31.43 (26.15–36.71)	28.18 (22.88–33.48)	28.41 (22.46–34.37)	0.267^{A}
Median IHD (IQR)	0.093 (0.068–0.126)	0.082 (0.062–0.122)	0.072 (0.052–0.113)	0.495^{F}
Median Rmin (IQR)	6.225 (6.052–6.800)	6.305 (6.077–6.800)	6.450 (6.200–6.930)	0.335^{F}

ISV Index of surface variance, *IVA* Index of vertical asymmetry, *KI* Keratoconus index, *IHA* Index of height asymmetry, *IHD* Index of height decentration, *Rmin* Minimum radius of curvature, *F* Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, *A* One-way Repeated Measures ANOVA (Post-Hoc: Bonferroni), *T* Paired-samples Students'T-Test

Table 6 The detailed data regarding the refractive error on baseline and follow-up visits

	Baseline (n:30)	1 Month (n:30)	5–6 Months (n:27)	*p*-value
Mean SE (D) (95%CI)	−5.62 ((−4.60)-(−6.65))	−6.00 ((−5.00)-(−6.98))	−4.95 ((−3.84)-(−6.05))	**< 0.001**^{A}
Comparison to baseline *p*-value	-	0.099^{T}	0.056^{A}	
Median Cylinder (D) (IQR)	4.00 (2.00–5.25)	4.37 (2.18–5.31)	4.00 (2.00–4.75)	**< 0.001**^{F}
Comparison to baseline *p*-value	-	0.752^{W}	**0.019**^{F}	

F Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, *A* One-way Repeated Measures ANOVA (Post-Hoc: Bonferroni), *T* Paired-samples Students'T-Test, *W* Wilcoxon signed ranks Test

Table 7 The detailed data regarding the correlation analysis between the corneal topographic findings and the ocular surface parameters

	TBUT (CC, *p*-value)	Schirmer Test (CC, *p*-value)	OSDI (CC, *p*-value)
K_{max}	−0.060, 0.754	−0.002, 0.991	0.094, 0.622
Corneal Thickness	0.318, 0.087	−0.001, 0.998	−0.172, 0.363
ISV	−0.091, 0.633	−0.073, 0.702	0.137, 0.471
IVA	−0.076, 0.689	0.009, 0.962	0.218, 0.247
KI	0.038, 0.840	0.090, 0.637	0.110, 0.563
IHA	−0.184, 0.330	−0.007, 0.970	0.257, 0.170
IHD	**−0.393, 0.032**	−0.137, 0.472	−0.180, 0.342
Rmin	0.020, 0.916	−0.042, 0.826	−0.51, 0.788

CC Correlation coefficient, *ISV* Index of surface variance, *IVA* Index of vertical asymmetry, *KI* Keratoconus index, *IHA* Index of height asymmetry, *IHD* Index of height decentration, *Rmin* Minimum radius of curvature

Corneal surgeries such as refractive ones could induce post-operative dry eye symptoms via various mechanisms, such as corneal innervation damage leading to dysesthesia, reduced tear film stability, and tear secretion deficiency [15]. On the other hand, the corneal CXL might induce changes in the ocular surface due to oxidative stress and free radical production after UVA irradiation, in addition to the mentioned mechanisms [16].

A prospective study with a one-year follow-up on 24 KCN cases demonstrated no significant changes in subjective or objective parameters of ocular surface such as OSDI score, TBUT, Schirmer test, and tear film osmolarity after epi-off CXL [17]. Another study on the effect of accelerated CXL on the ocular surface parameters showed no significant change except for increased metaplastic changes and reduced goblet cells in conjunctiva 3 months after the procedure [18]. Our results were coherent with the aforementioned studies. The stability of ocular surface parameters after the corneal CXL procedure might be related to the temporary effect of UVA radiations on the conjunctiva and tear film. The UVA is applied only for a limited duration with controlled power, and the field is restricted to the central cornea, so long-term changes in the ocular surface might not be expected after the CXl procedure, as our results show.

Nevertheless, Uysal et al. declared an increased TBUT 18 months after CXL compared to the baseline. They showed that the improvement in the TBUT values is correlated with the decrease in keratometry values (K_1 and K_2), suggesting that the smoother and flatter the corneal surface, the more stable the tear film [19]. Besides the possible effects of corneal CXL on the ocular surface, its main impact is on the corneal structure and topography.

Some corneal topographic indices have been reported to improve in one-year follow-up after the CXL procedure, including ISV, IVA, KI, and R_{min} [20]. However, in our study, the ISV index only showed a significant change 5–6 months after CXL. The difference between our results and the aforementioned study might be related to the severity of the KCN in included cases. The baseline topographic indices in the study of Greenstein et al. remarkably indicated more advanced stages of KCN than ours. On the other hand, another study with baseline topographic indices similar to ours showed a significant improvement in ISV, CKI, and R_{min} [21]. Although the changes in R_{min} in our study were not statistically significant, the median was improved in the second follow-up compared to the baseline. These findings suggest that the corneal CXL's effect on the topographic indices might be related to the staging of the KCN; the more advanced the KCN stage, the more indices get improved significantly.

The effect of corneal CXl on corneal wavefront aberrations has been evaluated using various devices with heterogeneous results. Greenstein et al., similar to our methodology, used a Pentacam device (Oculus Inc.) to evaluate and estimate the corneal aberrations. They demonstrated a significant reduction in total HOA, SA, and Coma induced by anterior cornea 1 year after CXL in KCN cases [22]. However, we failed to show such an improvement in our cases 5–6 months after CXL. Another study evaluating corneal aberrations with the iTrace device showed a significant HOA, SA, and Coma reduction 6 months after CXL in KCN cases [23]. However, Moramarco et al. showed that the anterior corneal wavefront aberration did not change after accelerated corneal CXL except for SA and trefoil at 0°, which showed a reduction 24 months after the procedure [24].

Regarding the literature review, our study is unique due to its comprehensive evaluation of the KCN cases concerning the ocular surface and corneal topographic and aberrometric characteristics after the corneal CXL procedure. The results show that progressive KCN cases have a significant problem with their ocular surface objective parameters and subjectively experience disturbing symptoms. However, these ocular surface problems are not correlated with the severity of corneal ectasia, except for a correlation between the IHD and TBUT. This correlation might be due to the corneal apex's inferior displacement in higher IHD levels, which could mechanically induce an earlier tear film break-up. In addition, our study emphasizes the corneal CXL's safety regarding patients' ocular surface issues. On the other hand, it shows that CXL could mildly flatten the cornea and reduce the myopia in progressive KCN cases. However, we failed to show such a significant improvement in corneal topographic indices and higher-order aberrations 6 months after CXL.

Although our study was comprehensive, it had some limitations. The study's sample size was limited, and the follow-up period was not extended. The Scheimpflug imaging used in the Pentacam device does not directly evaluate the corneal aberrations, and its measurements mainly estimate the reality. So, the corneal aberration measurements might not be as accurate as wavefront aberometry devices.

Conclusion

Although progressive KCN cases experience various ocular surface signs and symptoms, the corneal CXL could be safely applied in these patients without concerns about the deterioration of their symptoms. The corneal CXL could flatten the cornea and reduce myopia; however, the procedure might not improve the corneal topographic indices and higher-order aberrations in 6 months follow-up.

Acknowledgements
Not applicable.

Authors' contributions
All authors contributed to the study's conception and design. N.T., A.L., and S.N. performed clinical evaluations and surgical procedures. S.N., A.T., P.G., and T.A. performed the para-clinical evaluations and data collection. A.A. performed the data analysis and wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding
This study has received no funding from any institution.

Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study adhered to the Declaration of Helsinki and received approval from the Tabriz University of Medical Sciences research ethics committee with the approval code of IR.TBZMED.REC.1403.061. Informed consent was obtained from all the included patients before entering the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 19 January 2025 Accepted: 6 March 2025
Published online: 18 March 2025

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