# Evaluation of tear film before and after corneal collagen crosslinking in patients with keratoconus

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**Short title:** Tear film before and after CXL in patients with keratoconus

**Abstract**

**Purpose:** This study aimed to evaluate tear film changes before and after corneal collagen cross-linking in patients with keratoconus.

**Methods**: This study included 60 eyes of 30 keratoconus patients who underwent corneal collagen cross-linking surgery at the outpatient clinic of the Mansoura Ophthalmic Center. Patients were evaluated using various methods, including personal history, refraction, slit-lamp examination, fundoscopy, and IOP measurement of ocular tension. Pentacam HR (Oculus, Inc., Wetzlar, Germany) was used to diagnose and assess the progression of keratoconus. The Media Works Dry Eye Diagnostic System (D130) was used to evaluate eight tear film parameters before and after surgery. The outcome measures were noninvasive break-up time (NIBUT), Hybrid break-up time (H-BUT), tear meniscus height, lipid layer, eyelid edge, meibomian gland, ocular surface staining, and eye redness analysis.

**Results:** The mean age was 22.03 years. There was a slight improvement in UCVA from the preoperative to 6th month follow-up, but the difference was not statistically significant. The BCVA remained the same from the preoperative to 6th month follow-up. Preoperatively, 52 eyes (86.7%) were refracted, increasing to 56 eyes (93.3%) at 6th month follow-up. The cylinder amount decreased from the preoperative to 6th month, but the difference was not statistically significant. Keratometry revealed a reduction in the mean values of K1, K2, and Kmax. Corneal thickness decreased slightly at the thinnest location, but the difference was not significant. There was a statistically significant improvement in the NIBUT and H-BUT 1st rupture time and average rupture time, and a significant improvement in their grades by the end of follow-up.

**Conclusion:** This study demonstrated that epi-off CXL treatment can control keratoconus progression and improve tear film parameters, reducing dry eye symptoms within six months in patients with keratoconus.

**Keywords:** dry eye disease, keratoconus, crosslinking, media works, dry eye diagnostic system.

## INTRODUCTION

Keratoconus is a progressive corneal disorder characterized by irregular astigmatism and corneal thinning, resulting in vision impairment[1]. The condition typically manifests in the second decade of life, progressing variably before stabilizing naturally around the fourth decade. While it affects all ethnicities and genders, it is more prevalent in Mediterranean countries[2].

Numerous clinical investigations have shown diminished tear quality in individuals with keratoconus, as indicated by shortened tear break-up time (TBUT) and increased corneal staining, which contribute to visual deterioration[3].

The choice of treatment depends on the severity of keratoconus, with the aim of enhancing vision and halting ectasia progression. In recent years, corneal collagen cross-linking (CXL) has emerged as the primary therapeutic approach for managing keratoconus progression[1].

Multiple studies have demonstrated that CXL is a safe and effective method for arresting keratoconus progression by increasing the number of covalent bonds in the corneal stroma, thereby enhancing the structural stability of the tissue[4].

During the CXL procedure, the removal of the corneal epithelium and exposure to ultraviolet A (UVA) radiation damages the subepithelial nerve plexus, leading to reduced corneal sensitivity. This loss of corneal sensation is expected to negatively affect the reflex that triggers blinking and basal tear production[5].

Various reports have highlighted the effect of CXL on normalizing the corneal surface, which is expected to improve tear film distribution and positively affect dry eye symptoms. However, there is limited research on tear function following CXL in patients with keratoconus. Therefore, this study aimed to investigate whether CXL can enhance tear film in eyes with keratoconus.

**PATIENTS AND METHODS:**

This prospective, uncontrolled, interventional study included 60 eyes of 30 keratoconus patients who underwent corneal collagen cross-linking surgery. Patients were selected from the outpatient clinic of Mansoura Ophthalmic Center between July 2022 and June 2023.

The study included Patients with progressive keratoconus aged between 18-35 years old and diagnosed according to these four indices: inferior steepening > 1.5 D, anterior elevation > 15 µm, posterior elevation >20 µm, and K2 > 46.5 D, associated with one clinical sign such as Rizutti's sign, Vogt's striae, Fleischer ring, and scissoring of the red reflex on retinoscopy. Progression was diagnosed if a reduction in corrected visual acuity of at least one line, an increase in maximum K > 1.0 D, and a 20 µm decrease in central corneal thickness occurred over 6 months. Exclusion criteria included eyes with corneal scarring, ocular surface diseases, systemic diseases, lid disorders, drug intake affecting tear production or stability, pregnant and lactating females, previous ocular or lid surgeries, ocular trauma, and contact lens use.

This study followed the tenets of the Declaration of Helsinki and was approved by the International Research Board (IRB) NO: MS:22.11.2195, Faculty of Medicine, Mansoura University. Verbal consent was obtained from the participants after explaining the aims, methods, and anticipated benefits.

The patients were evaluated through comprehensive history taking, which encompassed personal history, including age, sex, and occupation. The ocular history was assessed by focusing on ocular allergy, eye rubbing, ocular surgery, and ocular trauma. Systemic history was obtained, with particular attention paid to autoimmune diseases and diabetes mellitus. Drug intake was also recorded and a family history of keratoconus was documented.

Ophthalmic examination was performed, including preoperative visual acuity measurement, both uncorrected and best-corrected visual acuity (UCVA and BCVA), using a standard Landolt chart, and then transformed into logMAR for statistical analysis, refraction measurements, slit-lamp examination, fundoscopy, and IOP measurement using applanation tonometry.

Pentacam HR is a non-contact method used to assess the anterior segment of the eye, providing accurate data on corneal contour, pachymetry, anterior chamber depth, and pupil diameter. Different corneal maps were obtained, including curvature maps for K1, K2, and Kmax; anterior and posterior elevation maps; and pachymetric maps for corneal thickness at the pupil center and thinnest location.

The tear film and ocular surface were evaluated using the Media Works Dry Eye Diagnostic System (D130). It is a noninvasive test that allows precise and repeatable assessment of the tear film, which is preferable to invasive techniques, as there is no contact between the measuring instrument and the eye or eyelids. The examination started with data entry, including patient name, ID, and date of birth. Subsequently, 130 software systems were selected, and the data were recorded. Eight tear film parameters were assessed.

The non-invasive breakup time (NIBUT) automatically acquires the first and average breakup times. The examination scope was 8 mm to bring a more comprehensive diagnosis outcome (Use Placido ring, magnification x10, and the patient was asked to blink once, keep the eye open, and stop shooting after 20s. The grading of NIBUT was as follows: grade 0 (normal), first rupture time: 10 s, average rupture time: 14 s; Grade I (warning), first rupture time: 6-9 s, average rupture time: 7-13 s, Grade II (dry eye), first rupture time: 5 s; and average, rupture time: 7 s.

Tear meniscus height (TMH) was measured automatically or manually with a normal value of ≥0.2 mm.

Next, the lipid layer thickness was assessed using a white ring projection system (magnification x10, the patient was asked to blink every 2s, and the software stopped shooting after 10s. Grading was performed by comparing the results with the standard grading template, Grade I: <30 (unit nm), Grade II: 30 – 60 (unit nm), Grade III: 60 – 80 (unit nm), and Grade IV: > 80 (unit nm).

Subsequently, meibomian glands (MG) were assessed using a built-in infrared lighting system that expands the image scope of glands, with adjustable depth of field making the glands more prominent and distinguishable against the background (dry eye module were removed, magnification x6, images were taken for upper and lower MG, which were analyzed automatically (Grading of MG was as follows: grade 0, No MG Loss, Grade I: MG Loss < 1/3; grade II: MG Loss 1/3 to 2/3; and Grade III: MG Loss > 2/3).

Next, eyelid margins were evaluated using the optical system of Media Works (magnification x10, focus on eyelid, and images were taken for upper and lower eyelid margins). Grade I: Normal (bright, transparent); Grade II: Mild (gland cap crown-glandular prominent); Grade III: Moderate (glandular fat plug - disappearance of the marginal mucosa, hyperkeratosis); and Grade IV: Severe (uneven margins, disappearance of the meibomian glands, posterior margin blunt round, thickening, and new blood vessel).

Subsequently, conjunctival and ciliary congestion was evaluated, with a normal value of ≤2.

Finally, the tear films were stained with fluorescein for topographical evaluation ( hybrid-BUT test), which automatically acquired the first and average breakup times. The test used a Placido ring and magnification x10, and standard fluorescein strips were applied to the inferotemporal conjunctival area. The patient blinks once and keeps the eyes open. The test recorded one video for 20s, and automatic hybrid breakup time results were obtained. The results were graded into three levels: Grade 0 (Normal): first rupture Time: 10 s, average rupture time: 14 s, Grade I (Warning): first rupture time: 6-9 s, average rupture time: 7-13 s, and Grade II (Dry eye): first rupture time: 5 s, average rupture time: 7 s. Corneal and epithelial staining was performed using a built-in yellow filter and a cobalt blue filter.

Finally, the Mediawork Dry Eye Diagnostic System provides a comprehensive report including the 8 measured parameter. Figure (1).

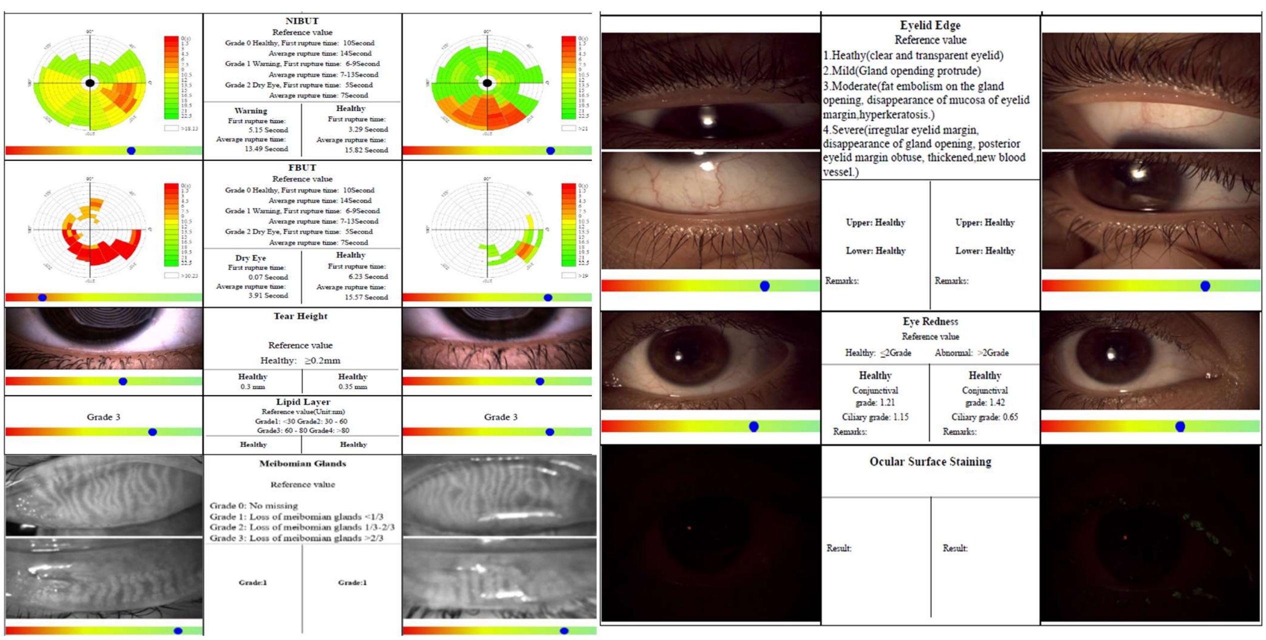


Figure I: Dry eye comprehensive evaluation report (A: NIBUT; B: H-BUT; C: TMH; D: lipid layer thickness; E: MG; F: eyelid margin; G: Conjunctival and ciliary congestion; H: Ocular surface staining).

The surgical technique of corneal collagen cross-linking involves using the epithelium-off accelerated technique performed under aseptic conditions and betadine 5%. Topical anesthesia was applied four times, and the epithelium was pretreated with ethyl alcohol and then removed by mechanical rubbing with a blunt spatula to debride the central 9 mm of the corneal epithelium. Riboflavin solution was instilled over the de-epithelized cornea four times every 2 min for 10 min until complete saturation was achieved. Exposure to ultraviolet A irradiation was performed for 10 min, while instilling the drops every 2 min. A bandage contact lens was applied until complete regeneration was achieved in three days.

Postoperative treatment included topical antibiotics, artificial tears, and cycloplegic eye drops until complete re-epithelialization. After re-epithelization, the contact lens was removed, and combined antibiotic and steroid eye drops were administered four times daily for one week with gradual withdrawal until the end of the first month.

Postoperative follow-up examinations were conducted on 1st, 3rd, 7th day to assess complete epithelialization, followed by additional check-ups at 1, 3, and 6 months. The examination included visual acuity measurement, refraction measurements, slit-lamp biomicroscopic examination, Pentacam evaluation, and tear film analysis using the Mediawork Dry Eye Diagnostic System.

**Statistical analysis:**

Data was collected, revised, and analyzed using Statistical Package for the Social Sciences software (version 25.0; SPSS, Inc., Chicago, IL, USA). Data are presented as median, mean, and standard deviation (SD) for all quantitative values, or as several cases (percentage) for qualitative values.

The distributions of the tested variables were examined using the SK test for normality. The differences between continuous variables were determined using an independent sample test for parameters within or maldistributed and the Mann-Whitney test for non-normally distributed variables, as appropriate. Chi-square or Fisher 's exact tests were used to compare qualitative variables as appropriate. One-way analysis of variance (ANOVA) was used to examine the mean differences between more than two normally distributed groups. Statistical significance was set at $P < 0.05$.

**RESULTS**:

In this study, the mean age of the study group was (22.03±5.7 years); 50% of patients were male, and most of the patients were students. The details of the demographic data are shown in Table (1).

**Table 1.:** Demographic data of study groups.

| | **Study group N=60 eyes** |
|---|---|
| **Age (years)** Mean± SD | 22.03±5.7 |
| **Sex** | |
| Male | 15 (50%) |
| Female | 15 (50%) |
| **Occupation** | |
| Student | 24 (80%) |
| House wife | 3 (10%) |
| Doctor | 1 (3.3%) |
| Worker | 1 (3.3%) |
| Engineer | 1 (3.3%) |

SD: Standard Deviation.

There was a slight improvement in uncorrected visual acuity (UCVA) from the preoperative period to the 6-month follow-up, but this was not statistically significant. Best-corrected visual acuity was consistent. Throughout the follow-up period, the number of eyes that could be refracted increased from 86.7% to 93.3% at 6-month follow-up. The cylindrical power decreased from the preoperative period to the 6-month follow-up, but the difference was not statistically significant. The detailed visual acuity and refraction data are presented in Table (2).

**Table 2:** Visual acuity measurement and refraction at interval time in the study group.

| | Preoperative | 1 month | 3 months | 6 months | P value |
|---|---|---|---|---|---|
| **UCVA** (logMAR) | 0.82±0.52 | 0.78±0.48 | 0.8±0.49 | 0.78±0.51 | 0.96 |
| **BCVA** (logMAR) | 0.53±0.4 | 0.52±0.4 | 0.51±0.39 | 0.51±0.41 | 0.99 |
| **Refract ability** | 52 (86.7%) | 56 (93.3%) | 56 (93.3%) | 56 (93.3%) | 0.72 |
| **Cylinder** | −4.6±2.4 | –4.4±2.2 | –4.3±2.1 | –4.1±2.3 | 0.67 |

P value <0.05 is statistically significant, p<0.001 was considered highly significant. UCVA, uncorrected visual acuity; BCVA, best-corrected visual acuity.

Regarding keratometry, there was a statistically significant reduction in the mean values of reduction in K1, K2, and Kmax were statistically significant from the preoperative to 6th month follow-up (P=0.04, P= 0.03, and P =0.04, respectively). Regarding corneal thickness, there was a slight decrease in the corneal thickness of the thinnest location from the preoperative period to the 6th month, but the difference was not statistically significant. Details of keratometry values and corneal thickness are illustrated in Table (3).

**Table 3:** Keratometry and thinnest corneal location thickness at interval time in the study group.

| | Preoperative | 1 month | 3 months | 6 months | P value |
|---|---|---|---|---|---|
| **K1** | | | | | |
| Mean± SD | 48.02±3.67 | 47.52±3.45 | 47.52±3.4 | 47.22±3.13 | P=0.04*<br>P1= 0.26<br>P2= 0.26<br>P3= 0.03* |
| **K2** | | | | | |
| Mean± SD | 51.23±4.43 | 50.83±4.2 | 50.8±4.14 | 50.08±3.94 | P= 0.03*<br>P1= 0.39<br>P2= 0.39<br>P3=0.04* |
| **K max** | | | | | |
| Mean± SD | 54.85±6.22 | 54.4±6.14 | 54.05±6.07 | 53.65±5.2 | P= 0.04*<br>P1= 0.29<br>P2= 0.30<br>P3 =0.048* |
| **Thinnest Location** | | | | | |
| Mean± SD | 471.68±54.53 | 472.25±52.88 | 468.51±51.94 | 467.33±52.58 | 0.94 |

P value <0.05 is statistically significant, p<0.001 is highly significant, p= total p-value, p1= preoperative vs. 1 month, p2= preoperative vs. 3 months, and p3= preoperative vs. 6 months.

Regarding the results of the dry eye diagnostic system, the study found significant improvements in the first rupture time and average rupture time of NIBUT and H-BUT from the preoperative period to the 6th month, as well as in the NIBUT grade by the end of the follow-up at the 6th month. Additionally, there was a significant improvement in the H-BUT grade by the end of the follow-up at the 6th month. Details of NIBUT 1st rupture time& average rupture time & H-BUT 1st rupture time& average rupture time shown in Table (4).

**Table 4:** Noninvasive tear film break-up time assessment (NIBUT) and hybrid break-up time assessment (H-BUT) at interval time in the study group.

| | Preoperative | 1 month | 3 months | 6 months | P value |
|---|---|---|---|---|---|
| **NIBUT 1st rupture time (sec)** | | | | | |
| Mean± SD | 8.6±8.1 | 9.08±7.6 | 12.9±7.3 | 14.3±6.2 | P=0.006*<br>P1=0.99<br>P2=0.1<br>P3=0.01* |
| **NIBUT Avg. rupture time (sec)** | | | | | |
| Mean± SD | 11.4±6.3 | 12.4±5.7 | 15.3±5.8 | 16.2±4.8 | P=0.003*<br>P1=0.9<br>P2=0.04*<br>P3=0.007* |
| **H-BUT 1st rupture time (sec)** | | | | | |
| Mean± SD | 10.8±7.1 | 12.3±6.7 | 13.41±7.02 | 15.05±6.31 | P=0.006*<br>P1=0.87<br>P2=0.1<br>P3=0.01* |
| **H-BUT Avg. rupture time (sec)** | | | | | |
| Mean± SD | 13.01±4.96 | 14.2±5.3 | 15.39±5.07 | 16.7±4.87 | P=0.03*<br>P1=0.7<br>P2=0.2<br>P3=0.02* |

P value <0.05 is statistically significant, P<0.001 is highly significant, P= total p-value, P1= preoperative vs. 1 month, P2= preoperative vs. 3 months, and P3= preoperative vs. 6 months. NIBUT, noninvasive tear film break-up time; H-BUT = Hybrid break-up time assessment.

The study found that the tear meniscus height (TMH) was similar preoperatively and at the 6th month follow-up. Fifty-eight eyes (96.7%) had a healthy lipid layer, and no significant differences were found in the lipid layer and MG analysis in the 6th month. However, there was a significant difference in the degree of eye redness. Details of the tear meniscus height and lipid layer, MG analysis, eyelid edge, Eye Redness and Ocular Surface Staining are shown in Table (5).

**Table 5:** Distribution of Tear meniscus height and lipid layer grade and meibomian gland analysis and eyelid edge, Eye Redness grading, and Ocular Surface Staining at interval time in the study group.

| | Preoperative | 1 month | 3 months | 6 months | P value |
|---|---|---|---|---|---|
| **Tear meniscus Height (mm)** | | | | | |
| Mean± SD | 0.21±0.03 | 0.23±0.05 | 0.21±0.03 | 0.2±0.03 | P=0.01* P1=0.1 P2=1 P3=0.7 |
| **Lipid layer Grade** | | | | | |
| Grade 2 | 2 (3.3%) | 4 (6.7%) | 2 (3.3%) | 2 (3.3%) | 0.06* |
| Grade 3 | 18 (30%) | 28 (46.7%) | 40 (66.7%) | 40 (66.7%) | |
| Grade 4 | 40 (66.7%) | 28 (46.7%) | 18 (30%) | 18 (30%) | |
| **Meibomian gland** | | | | | |
| Grade 1 | 54 (90%) | 54 (90%) | 54 (90%) | 54 (90%) | 1 |
| Grade 2 | 6 (10%) | 6 (10%) | 6 (10%) | 6 (10%) | |
| **Eyelid edge** | | | | | |
| Healthy | 58 (96.7%) | 54 (90%) | 60 (100%) | 60 (100%) | 0.101 |
| Mild | 2 (3.3%) | 6 (10%) | 0 (0.00%) | 0 (0.00%) | |
| **Eye Redness** | | | | | |
| Normal | 55 (91.7%) | 56 (93.3%) | 60 (100%) | 60 (100%) | 0.02* |
| **Ocular Surface Staining** | | | | | |
| Normal | 60 (100%) | 60 (100%) | 60 (100%) | 60 (100%) | 1.00 |

P value <0.05 is statistically significant, p<0.001 is highly significant, p= total p-value, p1= preoperative vs. 1 month, p2= preoperative vs. 3 months, and p3= preoperative vs. 6 months.

**DISCUSSION:**

Keratoconus is a progressive and often asymmetric disorder characterized by gradual thinning and irregular steepening of the cornea. The irregular shape of the cornea in keratoconus can disrupt tear film distribution, affecting its stability and quality. KC is known to be associated with dry eyes; both conditions involve inflammatory processes that can exacerbate each other. Considering the ocular morbidity that dry eye can cause, therapeutic approaches for managing keratoconus should not worsen any underlying dry eye[7].

Corneal collagen cross-linking (CXL) is the standard method for stabilizing the cornea in keratoconus, enhancing biomechanical stability, and halting disease progression through the formation of new chemical bonds in the corneal stroma[8,21]. In the context of dry eye, crosslinking has demonstrated potential for enhancing tear film stability and alleviating ocular surface inflammation. Several studies have reported improvements in tear film parameters and ocular surface health after CXL[5]. Conversely, other studies reported no significant alterations in tear film parameters after CXL[28].

Our prospective, interventional, uncontrolled study was conducted to assess changes in the tear film before and after CXL using an epithelium-off accelerated technique.

The mean age of participants in the study was 22.03±5.7 years, which aligns closely with findings from Wang *et al*. (2022)[1] and Li *et al*. (2004)[13]. Keratoconus typically affects younger individuals, often starting in puberty and progressing until their 30s or 40s, which can influence tear film function[9].

The current study found no significant differences in uncorrected visual acuity (UCVA) or best-corrected visual acuity (BCVA) at various postoperative intervals. Although there was a slight improvement in UCVA from the preoperative to 6th month follow-up. Some studies have reported an increased BCVA after CXL[11,12], whereas others have indicated no change[14,15].

Wang *et al*. (2022)[1] also observed that while BCVA improved at most follow-up points, there were no statistically significant differences across the follow-up periods. In contrast, Zarei-Ghanavati *et al*. (2017)[16] reported a significant decline in UCVA over time with notable changes in BCVA.

Wittig-Silva *et al*. (2014)[17] demonstrated significant improvements in UCVA and BCVA over 36 months in a randomized controlled trial of CXL for progressive keratoconus, and Wisse *et al*. (2016) also noted significant increases in BCVA.

The study found no significant changes in refraction and cylinder measurements at different time points; however, refractable eyes increased by 6.6% at 6th month follow-up, and the amount of cylinder decreased from the preoperative to 6th month follow-up, consistent with Wittig-Silva *et al*. (2014)[17]. Similar to our results, some studies have reported changes in spherical equivalent values post-CXL[18]. Taşçı *et al*. (2020)[9] further supported that the epi-off CXL method can flatten the corneal surface and improve cylindrical refraction.

In this study, there was a notable decrease in K1, K2, and Kmax in the 1st, 3rd, and 6th months postoperatively compared with the preoperative levels. While some studies reported a significant reduction in Kmax following corneal cross-linking (CXL), others indicated stability in keratometry measurements. Zarei-Ghanavati *et al*. (2017) found a significant decrease in Kmax, suggesting a flattening effect from CXL, and Taşçı *et al*. (2020) also noted a significant reduction in K apex values at 6 months post-surgery[19,20,15,22,23,16,9].

Wang *et al*. (2022) reported a reduction in Kmax at multiple postoperative intervals, with a significant decrease observed at 6th months. They identified a negative correlation between best-corrected visual acuity (BCVA) and Kmax, indicating that improvements in visual acuity were associated with decreases in Kmax after CXL[1].

Wittig-Silva *et al*. (2014) conducted a 36-month follow-up in a randomized controlled trial and demonstrated significant improvements in Kmax in the treated eyes, consistent with the findings of this study[17].

Uysal *et al*. (2020) observed significant improvements in median maximum keratometry and mean keratometry readings 18 months after CXL, whereas Kobashi *et al*. (2018) found that epioff CXL resulted in better Kmax values, suggesting that a flatter postoperative cornea aids in tear film stability[5,24].

The study found no significant differences in corneal thickness at various time points (preoperative, 1 month, 3 months, and 6 months) with respect to the thinnest location. The impact of corneal cross-linking (CXL) on thickness remains unclear, with immediate thinning post-CXL attributed to factors such as stromal compaction, dehydration, and changes in epithelial healing[10].

In contrast, Balıkçı and Ulutaş (2023) reported significant differences in apex, central, and thinnest corneal thicknesses[25].

The current study found a significant increase in NIBUT and H-BUTs at various postoperative intervals (1st, 3rd, and 6th month) compared with the preoperative values. This aligns with the findings of Wang *et al*. (2022), who reported a notable increase in average NIBUT at 12 months postoperatively, particularly in the epi-off group, indicating enhanced tear film stability postoperatively[1].

Mazzotta *et al*. (2008) demonstrated that corneal cross-linking (CXL) leads to corneal flattening and improved epithelial health, resulting in better tear mucin production and stable TBUT levels. This finding supports the conclusion that CXL enhances tear film stability, which is consistent with our findings. Uysal *et al*. (2020) also noted improvements in TBUT in keratoconic eyes 18 months after CXL, which was attributed to reduced corneal irregularity[26,5].

Corneal fluorescein staining is a critical diagnostic tool for dry eye disease, although results can vary based on the grade[27].

In this study, we re-evaluated changes in the tear film stained with fluorescein using the topographical method. Topographic evaluation of tears stained with fluorescein is called the Hybrid- BUT (H-BUT) test[6]. In our study, there was a statistically significant improvement between preoperative, 1st month, 3rd month, and 6th month regarding the H-BUT 1st rupture time and H-BUT Avg. rupture time and H-BUT grade.

In this study, there was no statistically significant difference in tear meniscus height measured preoperatively and at 1, 3, and 6 months postoperatively. This finding aligns with those of Zarei-Ghanavati *et al*. (2017) and Taneri *et al*. (2013), who also reported no significant changes in tear meniscus height after A-CXL treatment[16,28].

The results indicated no statistically significant differences in lipid layer grade and meibomian gland status between the preoperative period and the follow-up periods of 1 month, 3 months, and 6 months. This is consistent with Balıkçı and Ulutaş (2023), who found no significant changes in the meiboscore and meibomian gland loss after CXL. Additionally, no morphological changes in the meibomian glands were detected after treatment[25].

Similarly, no statistically significant differences were observed in eyelid edge or ocular surface staining across the same time intervals. Akgöz *et al.* (2023) also reported no significant differences in ocular surface staining between pre-treatment and 3 months postoperatively[29].

In contrast, the study found a statistically significant difference in eye redness, with findings similar to those of Wang *et al*. (2022), who noted significant reductions in bulbar redness scores in the epi-off group 12 months postoperatively. Uysal *et al*. (2020) also observed improvements in conjunctival health and tear film stability, suggesting that CXL does not exacerbate inflammation, and may positively influence bulbar redness[1,5].

The study acknowledges limitations, including a small sample size and short follow-up duration, suggesting the need for future studies including a larger sample size with different age groups and the use of different CXL techniques to confirm the impact of CXL on the ocular surface in patients with keratoconus.

## CONCLUSION:

Epi-off CXL treatment has been shown to control the progression of keratoconus and improve tear film parameters, reducing dry eye in patients with keratoconus. The results showed an improvement in tear film function within six months after CXL.

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**Data Availability:** The authors declare that all data supporting the findings of this study are available within the article and its supplementary information file.

**Competing interests:** The authors declare no competing interests.

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**Conflict of interest statement**

The authors declare that they have no conflict of interest.

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