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Epithelial thickness and tomographic characteristics in central keratoconus: A comparative analysis of cross-linked and untreated eyes

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Abstract

Purpose: To evaluate epithelial thickness (ET) and corneal tomographic parameters in early-stage keratoconus (KC) patients with central cones, comparing eyes with and without a history of corneal collagen cross-linking (CXL).

Methods: This retrospective cross-sectional study included patients with early-stage keratoconus (Grade 1–2) and central cone localization diagnosed between 2020 and 2024. Central cones were defined by a maximum keratometry value within the central 3 mm zone, and one eye per patient was randomly selected. Eyes were classified as cross-linked (CXL+) or untreated (CXL−), with all treated eyes demonstrating clinical stability. Corneal tomography and epithelial thickness mapping were performed using Scheimpflug imaging and spectral-domain anterior segment optical coherence tomography.

Results: Group 1 ($n = 30$ eyes) had a mean age of 24.6 ± 5.7 years, significantly younger than Group 2 ($n = 33$ eyes, 35.9 ± 9.0 years, $p < 0.05$). The mean interval since CXL was 4.8 ± 3.2 years. Gender distribution did not differ significantly between groups. Among epithelial parameters, central ET was significantly thinner in CXL-treated eyes ($p = 0.014$), whereas peripheral ET values showed no significant differences. Tomographic comparison revealed a significant reduction in front apex thickness in Group 1 ($p = 0.018$), while other indices remained comparable.

Conclusion: In early-stage central keratoconus, CXL-treated eyes demonstrated thinner central epithelial thickness compared to untreated eyes in a cross-sectional comparison. These findings suggest that epithelial remodeling may serve as a long-term biomarker of biomechanical stabilization after CXL, highlighting the clinical utility of epithelial mapping in the follow-up of keratoconus patients.

Keywords

Corneal collagen crosslinking, keratoconus, corneal epithelial thickness profile, pachymetry maps

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Introduction

Keratoconus (KC) is a progressive, non-inflammatory ectatic disorder of the cornea characterized by stromal thinning, protrusion, and irregular astigmatism, ultimately leading to visual deterioration if left untreated.[1,2] The reported incidence and prevalence of KC have been rising in recent decades, partly due to advances in corneal imaging technologies, with younger age at diagnosis remaining a major concern because of the higher risk of rapid progression.[3,4]

The corneal collagen crosslinking (CXL) has emerged as the only established treatment proven to halt or slow KC progression by increasing the biomechanical rigidity of the corneal stroma.[5–7] The clinical outcomes following CXL are influenced by several factors including baseline corneal thickness, disease severity, and particularly cone localization.[8–10] Central cone localization has been associated with more pronounced higher-order aberrations and reduced visual quality, but its relationship with long-term remodeling after CXL remains an area of uninvestigated.[11,12]

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In recent years, anterior segment optical coherence tomography (AS-OCT) has enabled high-resolution mapping of the corneal epithelium, providing a new dimension in understanding KC pathophysiology.[13–15] The epithelium is known to remodel by thinning over the cone apex and thickening in surrounding areas, thereby masking stromal irregularities.[16–19] Following CXL, several studies have demonstrated alterations in epithelial thickness (ET), suggesting that epithelial remodeling may serve as a surrogate marker of both biomechanical stabilization and disease activity.[20] However, most available data focus on comparisons between KC and normal eyes, while fewer studies have specifically addressed how epithelial thickness profiles differ between CXL-treated and untreated KC eyes.[5,18]

Given the increasing clinical reliance on epithelial mapping as a biomarker for KC progression and treatment response, understanding post-CXL epithelial remodeling is of particular clinical importance. In this study, we aimed to investigate epithelial thickness and tomographic indices in early-stage keratoconus patients with central cones, comparing eyes with and without prior CXL treatment. By focusing on this subgroup, we aimed to elucidate whether persistent epithelial alterations could reflect the long-term structural effects of CXL.

Methods

This study was designed as a retrospective, cross-sectional observational analysis. The study adhered to the tenets of the Declaration of Helsinki, and it was approved by the ethics board (Registration Number and Date : 2023/5/49 and 17/08/2023). A written informed consent was obtained from the patients or their kin. In this study, the keratoconus patients who were diagnosed at Department of Ophthalmology, Balıkesir University between 2020 and 2024 were retrospectively evaluated. The keratoconus patients who have central cone localization with Grade 1–2 KC according to Krumeich classification. If the maximum keratometry (*K*max) was located within the central 3 mm, the cone was considered central.[9,11,12] To avoid intra-subject correlation, only one eye per patient was randomly selected for statistical analysis. The exclusion criteria were severe/advanced keratoconus (Grade 3–4), postoperative complications following CXL—including keratitis, central corneal scarring, and delayed epithelial healing—as well as corneal opacities, epi-on CXL, history of prior ocular surgeries like refractive surgery, ocular conditions such as glaucoma, retinal disorders, herpetic keratitis, and others, along with those with autoimmune diseases, systemic connective tissue disorders, lack of data from the files.

Demographic features including age, sex, ocular and systemic anamnesis, best-corrected visual acuity (BCVA) at last visit, the presence of CXL history, the duration from CXL if performed were obtained. The decision for CXL was the age under 25, or the presence of progression by a consistent change in at least two of the following parameters: steepening of the anterior corneal surface, steepening of the posterior corneal surface, and thinning and/or thinning or changes in the pachymetric rate of change.[8]

The whole cases underwent epi-off CXL with standardized protocol as 9 min Ultraviolet A (UV-A) irradiance at 10 mW/cm2. The corneal topographic (CSO Sirius, Florence, Italy) parameters including average anterior K, posterior K1, posterior K2, average posterior K, front apex thickness, front apex curve, central corneal thickness, anterior chamber deep, thinnest corneal thickness, corneal diameter, surface irregularity factor (SIF), symmetry index of the bow-tie (SIB), total corneal astigmatism, anterior cornea asphericity in 8 mm, posterior corneal asphericity in 8 mm, best-fit sphere elevation at the front cornea (BCeVf) and best-fit sphere elevation at the back cornea (BCVb) through were recorded. To assess corneal epithelial thickness, a spectral-domain OCT (Optovue, Fremont, CA, USA) device with a scan rate of 26,000 axial scans per second, an axial resolution of 5 μm, a transverse resolution of 15 μm, and an add-on lens (CAM) was used, and assessed the regional corneal architecture and epithelial thickness profile in KC. Corneal epithelial thickness was assessed using spectral-domain AS-OCT (Optovue, Fremont, CA, USA) with a scan diameter of 6 mm centered on the corneal apex. Regional epithelial thickness values were obtained for the central, superior, inferior, nasal, and temporal zones as provided by the device's automated segmentation software. Corneal epithelial map values including Central ET, Superior-ET, Inferior -ET, Nasal-ET, Temporal -ET through OCT were recorded from the files of patients. The patients were divided into two groups according to the CXL history: Group 1 (CXL+) and Group 2 (CXL-). All eyes in the CXL-treated group demonstrated clinical and tomographic stability during follow-up, with no evidence of progression based on standard clinical criteria. The obtained data were statistically analysed.

Statistical analysis

SPSS V25 (IBM, Chicago, IL, USA) was used to perform the statistical analysis. The data were checked using histograms and the Shapiro–Wilks test to determine if they followed a normal distribution. Continuous variables were expressed as mean ± standard deviation (SD). The independent samples t-test was employed to compare means between two independent groups. Qualitative variables were analyzed using the $\chi 2$ test and reported as frequency and percentage (%). A p value less than 0.05 (two-tailed) was considered statistically significant.

Results

The medical records of 236 patients who diagnosed with keratoconus were systematically reviewed, and 46 eyes of

Table 1. Comparison of epithelial thickness parameters between groups.

	Group 1 ($n=30$)		Group 2 ($n=33$)	
ET Parameters(μm)	Mean	P value	Mean	P value
Central ET	49.8 ± 5.0	0.014 *	53.1 ± 5.0	0.014 *
Superior-ET	48.2 ± 5.7	0.683	47.7 ± 3.8	0.683
Inferior -ET	56.3 ± 4.2	0.957	56.2 ± 4.6	0.957
Nasal-ET	54.9 ± 3.8	0.292	55.9 ± 4.1	0.292
Temporal -ET	53.7 ± 3.7	0.970	53.6 ± 3.9	0.970

*ET: Epithelial Thickness, μm: Micrometer, * $p < 0.05$, statistically significant.*

46 patients were identified as providing the predefined eligibility criteria for inclusion. The mean age patients was 24.6 ± 5.7 years in Group 1 ($n=30$) and 35.9 ± 9.0 years in Group 2 ($n=33$). CXL + cases were significantly younger than CXL- group ($p=0.008$) There was no significant difference in gender distribution among groups ($p=0.942$). The mean duration from CXL was 4.8 ± 3.2 years in Group 1.

The corneal epithelial thickness values were summarized in Table 1. There was only significant difference in terms of central ET ($p=0.014$). Mean central corneal thickness was greater in group 1 (478.7 mm) than in group 2. However, this difference was not statistically significant ($p=0.057$). The thinnest corneal thickness was 459.2 mm in group 1 and 440.7 mm in group 2 ($p=0.156$). Total corneal astigmatism was lower in group 1 than in group 2 (−3.48, −3.79 mm, respectively) ($p=0.724$).There was only significant difference in terms of front apex thickness among groups ($p=0.018$). A detailed comparison of tomography indices is summarized in Table 2.

Discussion

This study compared corneal ET and tomographic indices in KC patients with central cones, stratified by CXL status. The principal findings were that CXL-treated eyes exhibited significantly thinner central ET and reduced front apex thickness compared to untreated eyes, while other epithelial and tomographic indices did not differ. These results underscore the importance of epithelial mapping as a biomarker for long-term corneal remodeling following CXL.

Our cohort demonstrated a significantly younger age profile among CXL-treated patients, which is consistent with established clinical protocols favoring early intervention in younger individuals at higher risk of progression.[7,8,21] This demographic trend reflects the global consensus that progression is most aggressive during the second and third decades of life and that timely CXL is essential to prevent irreversible visual decline.[8] The mean follow-up interval exceeding four years in the treated group also provides robust evidence of long-term epithelial remodeling after stabilization.

The corneal epithelium is increasingly recognized as an active participant in KC pathophysiology, rather than merely a passive covering layer. In untreated KC, the epithelium thins over the cone apex and compensates with thickening in the paracentral and peripheral zones, creating a smoothing effect that partially masks stromal irregularity.[11,14,15] Reinstein et al.[14] and Kanellopoulos &

Table 2. Statistical comparison of corneal topographic parameters between groups.

	Group 1 ($n=30$)		Group 2 ($n=33$)	
Topographic Parameters	Mean	P value	Mean	P value
Average anterior K	45.6 ± 2.6	0,211	46.4 ± 2.4	0,211
Posterior K1	44.6 ± 2.6	0,376	45.27 ± 2.8	0,376
Posterior K2	48.2 ± 4.4	0,130	49.94 ± 4.5	0,130
Average Posterior K	46.3 ± 3.3	0,196	47.4 ± 3.3	0,196
Front Apex Thickness(μm)	501.2 ± 76.7	0,018	462.8 ± 45.4	0,018
Front Apex Curve(D)	53.8 ± 9.9	0,684	53.0 ± 5.0	0,684
Central Corneal Thickness(μm)	478.7 ± 48.9	0,057	453.8 ± 52.4	0,057
Anterior Chamber Deep(mm)	4.2 ± 5.0	0,291	3.25 ± 0.3	0,291
Thinnest Corneal Thickness(μm)	459.2 ± 48.0	0,156	440.7 ± 53.1	0,156
Corneal Diameter(mm)	12.0 ± 0.4	0,577	12.1 ± 0.4	0,577
Sıf	4.7 ± 3.7	0,372	3.9 ± 3.4	0,372
Sıb(diopter)	1.4 ± 0.9	0,466	1.2 ± 0.9	0,466
Total Corneal Astigmatism	−3.48 ± 4.21	0,724	−3.79 ± 2.49	0,724
Anterior Cornea Asphericity İn 8 mm(Q)	4.79 ± 3.78	0,357	3.94 ± 3.48	0,357
Posterior Corneal Asphericity İn 8 mm(Q)	1.35 ± 0.90	0,629	1.24 ± 0.91	0,629
BCVf(μm)	2.39 ± 1.75	0,628	2.18 ± 1.58	0,628
BCVb(μm)	2.60 ± 1.68	0,998	2.61 ± 2.00	0,998

K: Keratometry, μm: Micrometer, D: Diopter, mm: Milimeter, Q:Corneal Asphericity, BceVf:Best-fit Sphere, Elevation at the Front Cornea, BCVb:Best-fit Sphere Elevation at the Back Cornea.

* $p < 0.05$, statistically significant.

Asimellis[19] highlighted the diagnostic potential of epithelial mapping, demonstrating that localized epithelial thinning may precede detectable topographic changes . Our finding of persistently reduced central ET in CXL + eyes suggests that while CXL halts biomechanical progression, it does not reverse epithelial remodeling once established, but may instead "lock in" a stable pattern. The persistence of central epithelial thinning in CXL-treated eyes may not merely represent residual disease morphology, but rather reflect the new biomechanical equilibrium achieved after cross-linking.

Several studies have described post-CXL alterations in epithelial architecture. Farouk et al. conducted an AS-OCT evaluation of changes in the corneal epithelial thickness following collagen cross-linking (CXL), and reported that epithelial remodeling occurs after CXL in the areas of protrusion and thinning while the thickness of the epithelium was greatest at the cone's base and diminishes as one moves away from it.[22] Bagheri et al. demonstrated that CXL decreased corneal epithelial thickness decreased in all sectors.[23] Rocha et al.[5] further documented both epithelial and stromal remodeling after CXL, suggesting a coordinated structural response to enhanced biomechanical rigidity. Our findings are in line with this literature, providing evidence that central epithelial thinning may persist for years after treatment, potentially reflecting the long-term stabilization of the cone apex.

Interestingly, our study found no significant differences between groups in global tomographic indices, except for front apex thickness. This discrepancy highlights the complementary role of epithelial mapping in disease monitoring. While tomography primarily reflects stromal architecture, epithelial thickness mapping captures subtle surface remodeling that may be overlooked by pachymetry or curvature analyses alone. This is consistent with Besek et al.,[12] who emphasized the disproportionate influence of cone localization on central optical quality, rather than on global topographic parameters. Thus, epithelial mapping may serve as a more sensitive indicator of localized biomechanical stress and long-term treatment effects. Kanellopoulos and Asimellis further suggested that epithelial remodeling patterns could serve as an adjunct to tomography in early KC detection. Our findings extend this concept to the post-CXL setting, implying that stable epithelial configurations may signal long-term treatment success.[19]

The clinical relevance of our findings lies in the potential use of ET mapping as a non-invasive biomarker for long-term monitoring after CXL. Persistent central epithelial thinning in stable CXL eyes could signify effective biomechanical stabilization, distinguishing treated stability from untreated progression. In clinical practice, incorporating ET analysis into follow-up protocols may improve the detection of subtle progression and guide individualized retreatment decisions. Moreover, as emerging techniques such as transepithelial CXL and customized protocols gain traction, epithelial mapping may become indispensable in assessing their efficacy relative to standard epithelium-off approaches.

This study has several limitations. Its retrospective design and relatively small sample size limit the generalizability of our findings. The central cone localization was defined as *K*max located within the central 3 mm zone, consistent with previous reports.[9,11,12] Although alternative metrics such as mean Kmax within the central 3 mm may offer additional insight, these parameters were not uniformly available in this retrospective dataset. Additionally, the absence of longitudinal pre- and post-CXL epithelial data prevents us from characterizing the dynamic trajectory of epithelial remodeling. Given the cross-sectional nature of the study and the absence of pre-CXL baseline epithelial data, the observed differences in epithelial thickness between groups should be interpreted cautiously. These findings do not allow conclusions regarding longitudinal epithelial remodeling or treatment-induced changes but rather represent structural differences observed at a single time point. Future prospective studies with serial OCT imaging would help clarify the temporal evolution of ET changes after CXL. Recent studies have proposed advanced epithelial and tomographic indices to further refine keratoconus characterization and treatment monitoring.[24,25] Although such parameters could not be evaluated in the present retrospective cohort due to data availability, our findings support the concept that epithelial thickness metrics provide complementary information to conventional tomography, particularly in centrally located cones. Future prospective studies incorporating these novel indices may further enhance the clinical utility of epithelial mapping after CXL. Moreover, integrating epithelial mapping with biomechanical assessments, such as corneal hysteresis or Brillouin microscopy, may yield a more comprehensive understanding of treatment effects. Finally, exploring correlations between ET changes and visual quality metrics, including higher-order aberrations, could provide clinically meaningful insights into functional outcomes.

Conclusion

In summary, this study demonstrates that central epithelial thickness and front apex thickness differ significantly between CXL-treated and untreated KC eyes with central cones, even years after intervention. These findings reinforce the role of epithelial remodeling as a persistent marker of biomechanical stabilization following CXL and highlight the added value of epithelial mapping in the longitudinal monitoring of keratoconus. By incorporating ET assessment into clinical practice, clinicians may enhance the precision of disease staging, progression detection, and treatment evaluation in keratoconus management.

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Ethical considerations

The study adhered to the tenets of the Declaration of Helsinki, and it was approved by the Balikesir University Clinical Studies Ethical Committee (Registration Number and Date : 2023/5/49 and 17/08/2023).

Consent to participate

A written informed consent was obtained from the patients or their kin for participation.

Consent for publication

A written informed consent was obtained from the patients or their kin for publication.

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Declaration of conflicting interests

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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