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Epithelial Thickness Profile Change After Corneal Crosslinking: A Retrospective Research

Korneal Çapraz Bağlama Tedavisi Sonrası Epitel Kalınlığın Değişimi: Retrospektif Bir Araştırma

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ABSTRACT Objective: To assess the corneal epithelial remodeling after corneal crosslinking (CXL) and to investigate the relation between topographic parameters and epithelial thickness change. **Material and Methods:** Sixty-three eyes of 43 keratoconus patients were included in this retrospective study. Keratometry (K) and elevation data were assessed by Scheimpflug topography and corneal and epithelial thickness profile was obtained by anterior segment spectral-domain optical coherence tomography pre-operatively and at the 1st, 6th and 12th months after CXL. **Results:** Significant decreases were observed in mean K (p=0.014), maximum K (p=0.049), and mean central corneal thickness (p<0.007) after CXL. Superior corneal epithelial thickness was significantly thinner (p<0.001) and the difference between the minimum and maximum epithelial thickness was less at the post-operative first month and didn't change significantly afterwards. Standard deviation of epithelial thickness across the central 5 mm region statistically decreased in the follow-up period (p=0.008). **Conclusion:** Significant regularization of the epithelial thickness profile was seen in one year after epithelium-off CXL. Demonstrating the normalization of the corneal epithelium and understanding its impact on the post-operative healing process might contribute to the optimization of treatment protocols.

Keywords: Cross-linking, cornea; keratoconus; epithelium, cornea; tomography, optical coherence

ÖZET Amaç: Çalışmanın amacı, korneal çapraz bağlama sonrası epitelyal yeniden düzenlenmenin topografik veriler ışığında incelenmesidir. **Gereç ve Yöntemler:** Kırk üç keratokonus hastasının 63 gözü, bu retrospektif çalışmaya dâhil edilmiştir. Korneal çapraz bağlama tedavisi öncesi ve tedavi sonrası 1, 6 ve 12. aylarda keratometri (K) değerleri ve korneal topografi, Scheimpflug topografi ile değerlendirilirken, kornea epitel kalınlığı, ön segment optik koherens tomografi ile değerlendirilmiştir. **Bulgular:** Korneal çapraz bağlama tedavisi sonrası ortalama santral kornea kalınlığında (p<0,007), ortalama K değerinde (p=0,014) ve maksimum K değerinde (p=0,049) istatistiksel anlamlı azalma izlendi. Korneal çapraz bağlama tedavisinden 1 ay sonra superior korneal epitel kalınlığı, istatistiksel anlamlı olarak daha ince (p<0,001); maksimum ve minimum korneal epitel kalınlığı arasındaki fark daha az idi, takip boyunca değişim olmadı. Korneal çapraz bağlama tedavisi sonrasındaki takip süresince santral 5 mm kornea alanındaki epitel kalınlığının standart sapması, istatistiksel anlamlı olarak daha az idi (p=0,008). **Sonuç:** Korneal çapraz bağlama tedavisinden 1 yıl sonra, korneal epitel kalınlığında anlamlı bir düzgünleşme izlendi. Korneal epitelin iyileşme sürecinin daha iyi değerlendirilmesi ve korneal çapraz bağlama sonrası iyileşme sürecinin anlaşılması, daha verimli tedavi protokollerinin geliştirilmesine yardımcı olacaktır.

Anahtar Kelimeler: Çapraz bağlama, kornea; keratokonus; epitelyum, kornea; tomografi, optik koherens

Keratoconus (KC) is a progressive corneal disorder characterized by thinning, steepening, and protrusion of the cornea.[1] The mechanical strength of the cornea is known to decrease in this non-inflammatory condition, and novel treatment methods have been proposed to overcome this phenomenon.[2]

Corneal crosslinking (CXL) modifies the stromal structure of the cornea by creating covalent bonds between collagen fibrils and the surrounding protein network to increase the biomechanical rigidity of the cornea using ultraviolet A (UVA) and riboflavin (vitamin B_2).[3,4] Mechanical strength of the

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cornea were reported to increase after CXL, while anterior curvature was reduced.[4,5] The "Dresden protocol" is accepted as the standard protocol for CXL.[6] In this technique, corneal epithelium is removed to increase riboflavin penetration to cornea and riboflavin is administered to cornea to increase UVA absorption level.

The importance of corneal epithelial thickness profile evaluation is better understood today especially for the diagnosis of KC and assessment of a refractive surgery candidate.[7,8] The change in corneal epithelium has been thought to start in the sub-clinical stage of KC and these changes might be seen in keratoconic eyes without significant topographic abnormalities.[9,10] Corneal epithelium thickness changes may mask underlying irregularities of the cornea.[11] It is well demonstrated that the epithelium was thinner at the apex of a keratoconic eye, and thicker around the cone, which can make the assessment of the stromal irregularities harder.[7]

Changes in the epithelial thickness may affect post-operative topographic findings of keratoconic eyes and thus assessment of these patients. We aimed to evaluate the effect of epithelium-off CXL on regional corneal epithelial thickness over 1 year and to correlate these changes with pre-operative topographic findings of the patients.

MATERIAL AND METHODS

This retrospective study included patients diagnosed with progressive KC, graded II to III according to the Amsler-Krumeich classification. The study followed the principles of the Declaration of Helsinki and approved by the Ethical Board of İstanbul Okan University (Approval date: 18.5.2020 and document no: 56665618-204.01.07).

Sixty-three eyes of 43 patients with KC, who were treated with CXL between March 2016 and January 2018, were analysed. Inclusion criteria were clinically and topographically documented progressive corneal ectasia, and corneal thickness greater than 350 μm at its thinnest point. Exclusion criteria were active ophthalmic inflammation or infection, severe dry eye, patiens with collagen crosslinking, corneal ring implantation, and any type of keratoplasty; herpetic keratitis, presence of any corneal scar, pregnancy or lactation, or any systemic disease that may affect healing. The criteria for progression were increase in the steepest keratometry ≥1.00 diopter (D); cylinder increase ≥1.00 D; myopia increase ≥0.50 D; and visual acuity decrease due to irregular astigmatism and corneal ectasia.[12]

A complete ophthalmic examination was performed in all patients, including visual acuity testing, slit-lamp and fundoscopic examinations, and topography with a rotating Scheimpflug camera (Pentacam HR, Oculus Optikgerate GmbH) and Fourier-domain optical coherence tomography (OCT) (RTVue, Optovue, Inc.) pre-operatively and 1, 6, and 12 months after the CXL. Mean (K_{mean}) and maximum (K_{max}) keratometric values and elevation data were recorded. Epithelial thickness was evaluated by Fourier domain OCT. The wide-angle adaptor lens was used to obtain a transverse resolution of 15 mm (focused spot size). Pachymetry+Corneal Power scan pattern was used for corneal mapping. The corneal adaptor module software generated the OCT scan to provide the corneal and epithelial-thickness maps. Epithelial mapping was obtained by the commercial software included.[13] For this study, measurements were taken from the central 5 mm of the cornea. Central corneal thickness (CCT), epithelial thickness, and the standard deviation (SD) of the epithelial thickness were evaluated. The thinnest corneal and epithelial points were recorded.

Prior to the CXL procedure, corneal epithelium of 9 mm in diameter was mechanically removed. The corneas were pre-treated with riboflavin 0.12% topical ophthalmic solution every 2 minutes for 30 minutes. The CXL treatment was performed using the UV-X System. The UVA irradiation was applied using 3 mW/cm^2 irradiance for 30 minutes and one riboflavin was instilled every 2 minutes during the irradiance. Following treatment, a contact lens was applied and kept for 3 days until the epithelium was healed. Topical antibiotic and corticosteroids were prescribed.

Statistical Package for Social Sciences software (version 17.0, SPSS, Inc.) was used for statistical analysis. Shapiro-Wilk test was used to assess data

normality. To evaluate differences between two means, the paired samples t-test was used for parametric data, and Wilcoxon test was used for the non-parametric data. Correlation analysis was performed using Pearson's correlation in parametric data and using Spearmen's Rank correlation in non-parametric data. Comparison of difference between SD of epithelial thickness data at baseline and follow-up visits was tested with Levene's test for equality of variances. A level of $p<0.05$ was assumed statistically significant for all tests. In multiple comparisons, Bonferroni correction was used.

RESULTS

Sixty-three eyes of 43 patients were enrolled in this study. Twenty-nine (67.9%) patients were male and 14 (32.6%) were female. The mean age of the patients was 24.19±5.67 years (range: 15-37).

Table 1 shows the pre- and post-operative keratometric values and CCT measurements. Mean K_{mean}, and K_{max} were significantly decreased after the CXL and did not change during post-operative period (p=0.890, p=0.785 respectively). The pre-operative mean CCT was significantly higher than the CCT throughout the post-operative follow-up and mean CCT did not significantly change between the 1st, 6th, and 12th months (p=0.461).

Table 2 shows mean regional epithelial thickness measurements at different time points and their comparison. The mean pre-operative superior epithelial thickness was significantly higher than the mean superior epithelial thickness at the 1st, 6th, and 12th months. There was a slight increase in the mean epithelial thickness in the inferior region, but the difference was statistically insignificant. The difference between the minimum and maximum epithelial thickness decreased significantly in the post-operative period and did not significantly change between the 1st, 6th, and 12th months. Standard deviation of the mean epithelial thickness of the central 5 mm cornea was significantly less at the 1st month then baseline and did not significantly change during follow-up.

Table 3 presents the correlation analysis between the epithelial thickness and corneal topo-

TABLE 1: Pre-operative and post-operative mean corneal and epithelial thickness measurements.

	n	Mean	SD	Minimum	Maximum	t value	p value
Pre CCT (μm)	63	468.16	35.74	380	528	2.818	0.007*
Post CCT (μm)	63	463.60	38.25	378	532		
Pre K_{mean}(D)	63	46.80	2.53	40.7	53.6	2.56	0.014*
Post K_{mean} (D)	63	46.57	2.47	40	52		
Pre K_{max} (D)	63	53.44	3.99	45.7	67.3	2.017	0.049*
Post Kmax (D)	63	53.12	3.90	45.6	64.3		
Pre SNIT (μm)	63	61.00	22.82	13	106	-1.228	0.226
Post SNIT (μm)	63	64.60	20.80	28	129		
Pre SI (μm)	63	55.79	26.07	-3	105	0.382	0.705
Post SI (μm)	63	54.60	23.72	-3	105		
Pre SEp (μm)	63	55.74	4.77	45	65	4.754	0.001*
Post SEp(μm)	63	53.07	4.07	46	65		
Pre IEp (μm)	63	51.91	5.93	43	74	-1.422	0.162
Post IEp (μm)	63	52.95	4.00	42	61		
Pre MaxEp (μm)	63	61.40	7.58	43	84	0.904	0.371
Post MaxEp (μm)	63	60.40	5.11	51	71		
Pre MinEp (μm)	63	43.23	5.60	28	56	-0.080	0.936
Post MinEp (μm)	63	43.48	4.97	27	53		

SD: Standard deviation; Min: Minimum; Max: Maximum; Pre: Pre-operative; Post: 1 year post-operative; CCT: Central corneal thickness; K_{mean}: Mean keratometry; K_{max}: Maximum keratometry; SNIT: Difference between superonasal and inferotemporal corneal thickness; SI: Difference between superior and inferior corneal thickness; SEp: Epithelial thickness in the superior zone at 5 mm; IEp: Epithelial thickness in the inferior zone at 5 mm; MaxEp: Maximum epithelial thickness at 5 mm zone; MinEp: Minimum epithelial thickness at 5 mm zone; t: Critical value for dependent means.

TABLE 2: Mean regional epithelial thickness of cornea and comparison of the measurements.

		Pre CXL	1st month	6th month	12th month
Superior corneal epithelial thickness (µm)		55.74	52.13	53.02	53.07
	Pre CXL		<0.001*	<0.001*	<0.001*
	1st month			0.008*	0.009*
	6th month				0.844
Inferior corneal epithelial thickness (µm)		51.91	50.82	52.96	52.95
	Pre CXL		0.057	0.110	0.112
	1st month				
	6th month				0.800
SD of mean corneal epithelial thickness		5.7	3.6	3.7	3.5
	Pre CXL		0.033*	0.025*	0.008*
	1st month			0.895	0.690
	6th month				0.862
Min-max corneal epithelial thickness of the cornea (µm)		-18.17	-16.99	-16.97	-16.92
	Pre CXL		0.011*	0.010*	0.006*
	1st month			0.921	0.874
	6th month				0.895

*Statistically significant; CXL: Corneal crosslinking; SD: Standard deviation; Min: Minimum; Max: Maximum.

TABLE 3: Correlation between epithelial thickness changes and pre-operative keratometric, pachymetric and elevation data of the patients.

		Pre- and post-operative corneal epithelial thickness change			
		Superior	Inferior	Minimum	Maximum
Pre K1 (D)	Correlation coefficient	-0.091	0.265	0.012	0.117
	p value*	0.564	0.086	0.938	0.456
Pre K2 (D)	Correlation coefficient	-0.215	0.126	-0.282	-0.208
	p value*	0.166	0.421	0.067	0.182
Pre K_{mean} (D)	Correlation coefficient	-0.162	0.209	-0.138	-0.045
	p value*	0.298	0.178	0.376	0.777
Pre K_{max} (D)	Correlation coefficient	-0.238	0.098	-0.255	-0.231
	p value*	0.124	0.531	0.099	0.135
Pre CCT (µm)	Correlation coefficient	0.260	-0.160	-0.008	-0.068
	p value*	0.092	0.304	0.959	0.667
Pre Thinnest (µm)	Correlation coefficient	0.281	-0.154	-0.041	-0.065
	p value*	0.068	0.325	0.796	0.679
Pre Fele (µm)	Correlation coefficient	-0.277	0.049	-0.055	-0.030
	p value*	0.072	0.756	0.728	0.849
Pre Bele (µm)	Correlation coefficient	-0.262	0.145	0.013	-0.020
	p value*	0.090	0.353	0.934	0.899
Pre D index	Correlation coefficient	-0.244	0.229	-0.016	0.020
	p value**	0.116	0.139	0.918	0.900

*Pearson's correlation; ** Spearmen's Rank correlation; Pre: Pre-operative; K1: Keratometry at the flattest meridian; K2: Keratometry at the steepest meridian; K_{mean}: Mean keratometri; K_{max}: Keratometry at the steepest point; Thinnest: Total corneal thickness at thinnest point; Fele: Front elevation; Bele: Back elevation; CCT: Central corneal thickness; Maximum: Maximum corneal epithelial thickness at central 5.0 mm; Minimum: Minimum corneal epithelial thickness at central 5.0 mm; D: D index for Belin Ambrossio Enhanced Ectasia display.

graphic values. No statistically significant correlations were found between corneal epithelial thickness changes and pre-operative keratometric, pachymetric and elevation data of the patients as well as the D index for Belin Ambrossio Enhanced Ectasia display.

DISCUSSION

In the present study, SD-OCT was used to investigate regional epithelial thickness changes over one year after CXL, and the relation between such changes and severity of KC was investigated. We found a statistically significant decrease in the superior epithelial thickness and improved regularity across the central cornea post-operatively, indicating significant epithelial remodeling after the procedure, but no significant correlation between epithelial thickness changes and pre-operative KC parameters.

Anterior segment module of the SD-OCT is a valuable diagnostic tool for corneal visualization. The epithelial mapping software is useful not only for detection of KC and forme fruste KC cases but also for the short- and long-term assessment of the healing process after interventions, such as CXL.[14,15]

Epithelial thickness is reported to be more evenly distributed in normal eyes compared to keratoconic eyes.[16] The mean epithelial thickness was found as 53.4±4.6 μm in the normal population, being slightly thinner in the center and superiorly with minimal variations between the regions.[16-18] In the keratoconic eyes, Reinstein et al. reported that the corneal epithelium tends to be thinner over the apex and thicker over the adjacent areas also known as the "doughnut pattern" which can be demonstrated with SD-OCT.[7] Temstet et al. investigated the use of epithelial mapping in the diagnosis of forme fruste KC and reported that the epithelial thickness and location of the thinnest zone identified by SD-OCT might be used for the early diagnosis of this disorder.[19] Epithelial thickness variation was also reported to be higher in keratoconic eyes compared to normal population with a difference up to 20 μm.[20,21]

In the current study, we investigated long-term changes in the epithelial thickness profile after CXL. In the first month after CXL, moderate epithelial thinning was observed in both superior and inferior corneal regions. The thinning in the superior region was statistically significant; whereas it was insignificant in the inferior region. Thinning of the epithelium in the first month was reported in previous studies, and explained by the effects of riboflavin and UVA on trophic modulator secretion, rather than the effects of mechanical debridement and regeneration of the epithelium.[13,22,23] In Zhang et al's study where epithelial thickness change in transepithelial CXL was investigated, a reduction in thickness was also observed post-operatively, which helped us understand that this effect was not solely secondary to corneal mechanical debridement, but the CXL operation itself.[22]

In the current study, we investigated long-term changes in the epithelial thickness after CXL. In the first month after CXL, moderate epithelial thinning was observed in both superior and inferior corneal regions. The thinning in the superior region was statistically significant; whereas it was insignificant in the inferior region. After the first month, the thickness in the superior and inferior regions tended to increase towards 6 months. Less significant changes were observed between the 6th month and 1 year post-operative measurements. Modest thinning in the superior region by the 6th month was the only statistically significant change in the epithelial thickness profile. In Haberman et al's study significant thinning was observed in multiple inferior and nasal areas, whereas there was no significant change in the thickness of the superior epithelium which is in contrast with our study.[21] Thinning of the superior region in the present study was consistent with findings of Rocha et al. which demonstrated that epithelial thickness was significantly thinner at specific points above and below the center after CXL.[13] Although the slight increase in the inferior corneal epithelium was statistically insignificant, the hypertopic response over the flattening cone might have been the reason for this slight trend of thickening.

The SD of epithelial thickness at the superior and inferior region was significantly less at the 1st month then baseline and did not significantly change during follow-up in our study. In addition, the difference between the minimum and maximum epithelial thicknesses decreased after CXL which was consistent with other studies.[12,13] Rocha et al. reported that a decrease was observed in surface variability 3 months after standard CXL.[13] However, the measurements were performed manually with the SD-OCT in their study. Later, Haberman et al. used

automated epithelial mapping software to assess regional epithelial thickness changes over time after accelerated CXL, and reported that the corneal epithelium became more regular across the central 6.0 mm 6 months after accelerated CXL.[23] Similarly, in Lautert et al.'s study, the mean minimum epithelial thickness increased, whereas the mean maximum epithelial thickness decreased after CXL, reducing the difference between the minimum and maximum epithelial thickness.[12] The decrease in epithelial thickness range and the SD across different points by 6 months after CXL procedure, may indicate a more uniform distribution in epithelial thickness as reported in those studies.

Changes in the epithelium may affect the refractive power and higher-order aberrations (HOAs) of the cornea.[24,25] Epithelial thickness changes may affect the anterior curvature and the regularity of the surface of the cornea and may play a role in the improvement of topographic regularity after CXL but it is speculative whether one might expect direct clinical impacts on the visual acuity of the patients solely from the small changes of epithelial thickness in our study.

Another objective of this study was to assess the impact of epithelial thickness change on pre-operative keratometric and pachymetric findings and elevation data. In Lautert et al's study, the epithelial thickness range, which decreased modestly after CXL, was found to be strongly correlated with maximum keratometric value in keratoconic eyes.[12] However, in the present study, no statistically significant correlation was found between the pre-operative keratometric or pachymetric outcomes of the patients and the change in epithelial thickness profile. In addition, no significant correlation was found between the back and front elevation, and the D score reported by the Belin/Ambrosio display and post-operative epithelial thickness change. This may be due to the limited sample size in our study as well as the baseline variability in our cohort. A larger study sample might provide more data on this aspect; however; we believe it is hard to predict the amount of epithelial thickness change based on the pre-operative findings.

The present study has several limitations. The principal study limitations are the sample size and lower accuracy and repeatability of imaging techniques in keratoconic eyes compared to normal eyes.[26] This study was limited to analysing post-operative epithelial thickness change and correlation with the pre-operative keratometry and elevation profiles. In order to understand the impact of epithelial remodelling on visual quality, measurement of the HOAs or contrast sensitivity on a case-by-case basis might provide further information to demonstrate the clinical relevance of these findings.

CONCLUSION

In summary, the results of our study imply that the corneal epithelium becomes thinner in the superior region, and more regular across the central 5.0 mm during one year follow-up after CXL. No significant correlation was found between these changes and pre-operative keratometric, pachymetric, or elevation data. Spectral domain SD-OCT is a valuable tool to monitor epithelial thickness changes over time after corneal surgical interventions such as CXL. Further studies are required to understand the contribution of epithelial remodeling and normalization to the post-operative healing process and visual quality.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Başak Bostancı Ceran, Şennur Kalender;* ***Design:*** *Başak Bostancı Ceran, Şennur Kalender;* ***Control/Supervision:*** *Akif Özdamar;* ***Data Collection and/or Processing:*** *Başak Bostancı Ceran, Şennur Kalender;* ***Analysis and/or Interpretation:*** *Başak Bostancı Ceran, Şennur Kalender;* ***Literature Review:*** *Şennur Kalender, Akif Özdamar;* ***Writing the Article:*** *Başak Bostancı Ceran, Şennur Kalender;* ***Critical Review:*** *Serdar Özateş, Akif Özdamar;* ***References and Fundings:*** *Başak Bostancı Ceran;* ***Materials:*** *Başak Bostancı Ceran.*

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