



Epithelial-Island Corneal Crosslinking in the Treatment of Progressive Keratoconus Patients with Thin Corneas: 2-Year Visual, Refractive, Keratometric, Tomographic, and Aberrometric Outcomes

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Abstract

Objectives: To evaluate the visual, refractive, tomographic, and aberrometric outcomes of epithelial-island corneal collagen crosslinking (CXL) treatment in halting progression in keratoconic eyes with thin corneas.

Materials and Methods: We retrospectively reviewed the charts of consecutive patients with advanced keratoconus who had a thinnest corneal thickness (TCT) of <380 µm as measured by anterior segment optic coherence tomography and underwent epithelial-island CXL. The procedure involved tomography-guided customized epithelial debridement, followed by corneal saturation with iso-osmolar and hypo-osmolar riboflavin solutions and ultraviolet-A irradiation (30 min, 3.0 mW/cm²). Best spectacle-corrected distance visual acuity (CDVA), manifest refraction (MR), slit lamp biomicroscopy, corneal tomography, corneal aberrometry, and endothelial cell count (ECC) were evaluated before CXL and at postoperative months 12 and 24.

Results: The study included 10 eyes of 9 patients with a median age of 29.5 (range, 17-51) years. The median postoperative follow-up time was 24.0 (12.0-108.0) months. The median preoperative TCT was 324.0 (232.0-380.0) µm. Preoperatively, the median CDVA was 1.00 (0.70-1.80) logarithm of the minimum angle of resolution, MR spherical equivalent was -18.00 (-25.00 to -6.00) diopters (D), maximum keratometry value was 84.75 (59.80-99.00) D, vertical coma was -1.068 (-6.428 to 0.613) D, and ECC was 2568 (2021-2750) cells/mm². At postoperative year 1 and year 2, there were no statistically significant changes in any of these parameters (all p>0.05). No significant haze, endothelial cell loss, or any other clinically significant adverse event was encountered in any of the eyes.

Conclusion: Epithelial-island CXL seems to be an effective alternative treatment modality in halting progression in keratoconic eyes with thin corneas. Further studies with a longer follow-up and a larger sample size would help to establish the long-term safety and efficacy of this treatment modality.

Keywords: Corneal crosslinking, epithelial-island corneal crosslinking, customized epithelial debridement, keratoconus, thin cornea

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Introduction

Corneal collagen crosslinking (CXL) is the only proven effective treatment for halting the progression of ectasia in keratoconus.¹ Corneal CXL was introduced by Wollensak et al.¹ and involves application of iso-osmolar 0.1% riboflavin solution to de-epithelized corneal stroma for 30 minutes, followed by ultraviolet-A (UVA) irradiation (365 nm, 3 mW/cm²) for another 30 minutes while iso-osmolar riboflavin application is continued. Known as the “Standard protocol” or “Dresden protocol”, this is the most commonly used CXL protocol, and the safety and efficacy of this procedure have been demonstrated in *in vivo* and *in vitro* studies, as well as randomized clinical trials.^{2,3} The



main limitation of the technique is the requirement of a corneal stromal thickness of at least 400 μm to protect the endothelial and deeper ocular structures from UVA exposure.⁴ However, in many cases of advanced progressive keratectasia, minimal stromal thickness is below 400 μm . To overcome this limitation, several alternative approaches have been described, including the use of hypo-osmolar riboflavin,⁵ reduced UVA exposure time (Sub400 protocol),⁶ transepithelial CXL,⁷ contact lens-assisted CXL,⁸ lenticule-assisted CXL,⁹ peripheral CXL,¹⁰ and epithelial-island CXL.¹¹ However, the short- and long-term outcomes of these alternative protocols have not been fully elucidated.¹²

The aim of this study was to evaluate the visual, refractive, keratometric, tomographic, and aberrometric outcomes of epithelial-island CXL in patients with progressive keratoconus and thin corneas.

Materials and Methods

The study was approved by the Ankara University Faculty of Medicine, Human Research Ethics Committee (decision no: İ11-790-23, date: 21.12.2023) and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient or their legal guardian.

The charts of consecutive progressive keratoconus patients who underwent CXL were reviewed retrospectively. Those with thin corneas who underwent epithelial-island CXL using iso-osmolar riboflavin 0.1%/dextran 20% and hypo-osmolar riboflavin 0.1% solutions were included in the study. "Thin cornea" was defined as a thinnest corneal thickness (TCT) of <380 μm measured by preoperative anterior segment optical coherence tomography (AS-OCT). Exclusion criteria included the use of hydroxypropyl methylcellulose during the CXL procedure, a history of herpetic keratitis or other corneal disease, a history of autoimmune disease, and pregnancy or breastfeeding.

All patients were examined at baseline, at postoperative month 1, 3, and 6, and yearly thereafter. The following were recorded during each visit: uncorrected distance visual acuity, best spectacle-corrected distance visual acuity (CDVA), manifest refraction (MR), corneal tomography with pachymetry and aberrometry (Pentacam, Oculus GmbH, Wetzlar, Germany), AS-OCT (Visante, Carl Zeiss Meditec, Dublin, CA, USA), and endothelial cell count (ECC) on *in vivo* confocal microscopy (HRT II, Rostock Cornea Module, Heidelberg, Germany). Prior to CXL, patients discontinued rigid gas permeable contact lens wear for 4 weeks and soft contact lens wear for at least 2 weeks. Keratoconus progression was defined as an increase of at least 1 diopter (D) in maximum keratometry (Kmax) on

consecutive corneal tomography measurements obtained during the postoperative follow-up period.

Surgical Technique

Corneal tomography measurements were reviewed immediately before surgery. On the pachymetric maps, displacement of the cone apex from the geometric center of the cornea was calculated in the x and y coordinates. Before the procedure, with the patient seated at the biomicroscope, the vertical and horizontal meridians of the cornea were marked with a Mendez marker, and the geometric center of the cornea was marked with a Sinsky hook.

The CXL procedure was performed under sterile conditions in an operating room, using the same protocol for all cases. After positioning the patient in the supine position, the surgical field was draped and topical anesthesia was applied (0.5% proparacaine hydrochloride; Alcaine, Alcon Laboratories, Texas, USA). Then, 10-12 consecutive ultrasound pachymetry measurements were obtained as close as possible to the marked geometric center of the cornea. The mean of the three thinnest readings was calculated. The cone apex location was identified by measuring the vertical and horizontal offsets previously determined from the corneal tomography pachymetric maps using a caliper. An 8- to 9-mm epithelial debridement was performed, preserving an epithelial island of approximately 3×3-mm over the cone apex. The cornea was then saturated with iso-osmolar riboflavin 0.1% in dextran 20% solution (MedioCross D, Peschke Meditrade GmbH, Germany) for 30 minutes. Corneal thickness was subsequently measured at the central cornea by ultrasound pachymetry, and the mean of the three thinnest readings was recorded. Hypo-osmolar riboflavin 0.1% solution (MedioCross H, Peschke Meditrade GmbH, Germany) was then instilled for an additional 30 minutes, after which the measurement was repeated. Once a stromal thickness of >400 μm was achieved, UVA irradiation was initiated (365 nm, 3.0 mW/cm²; UV-X system, IROC AG, Switzerland). During the UVA phase, instillation of iso-osmolar riboflavin 0.1% in dextran 20% solution was continued. At the end of the procedure, a silicone hydrogel soft contact lens was placed (Air Optix Night & Day Aqua, Alcon Laboratories, Texas, USA).

Postoperatively, topical antibiotic drops (0.5% moxifloxacin, 4x1; Vigamox, Alcon Laboratories, Texas, USA) and artificial tears (1.4% polyvinyl alcohol + 0.6% povidone, 4x1; Novaqua single-dose eye drops, Deva Holding, İstanbul, Türkiye) were prescribed. Once complete re-epithelialization was confirmed at postoperative follow-up, the contact lens was removed and topical corticosteroid therapy was initiated (1% prednisolone acetate 4 times

daily; Pred Forte, Allergan, Dublin, Ireland), then tapered to discontinuation while monitoring for the development of corneal haze. All patients were warned not to rub their eyes and were advised to wear sunglasses.

Statistical Analysis

The data were described using frequency and percentage for categorical variables and as mean ± standard deviation (median; range) for numerical variables. Changes over time were assessed using the Wilcoxon signed-rank test or the Friedman test. Statistical analysis was performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, ABD). A p value of <0.05 was considered statistically significant.

Results

Between March 2014 and March 2022, epithelial-island CXL was performed in 17 eyes of 16 patients. Ten eyes of 9 patients with at least 1 year of follow-up were included in the study.

The mean age was 34.2±14.2 (median, 29.5; range, 17-51) years. All cases were classified as stage 4 keratoconus according to the Amsler-Krumeich grading system.¹³ Four patients had a history of atopy. Complete epithelial closure was achieved at a mean of 3.3±0.8 (median, 3; range, 2-4) days postoperatively. The mean follow-up time was 37.2±30.2 (median, 24.0; range, 12.0-108.0) months. Prolonged corneal edema or severe corneal haze were not observed in any case during the follow-up period.

In all cases, the cornea was sequentially treated with iso-osmolar riboflavin followed by hypo-osmolar riboflavin during the CXL procedure.

The mean preoperative TCT was 314.7±48.0 (median, 324.0; range, 232.0-380.0) µm and the Kmax was 82.8±10.8 (median, 84.8; range, 59.8-99.0) D. At postoperative year 1, TCT was 298.1±56.1 (median, 290.0; range, 218.0-386.0) µm and Kmax was 80.3±10.2 (median, 81.3; range, 58.8-99.2) D, demonstrating clinical stability (p=0.944 and p=0.196, respectively). No clinically significant progression was observed in CDVA, MR, tomographic indices, aberrometry values, or ECC values at postoperative year 1 (p>0.05) (Table 1).

Six patients (7 eyes) completed the 2-year postoperative follow-up. Clinical stability was maintained across all visual, refractive, keratometric, tomographic, and aberrometric parameters at the 2-year follow-up visit (all p>0.05) (Table 1).

In the postoperative period, 6 patients were fitted with scleral lenses, while 4 eyes of 3 patients were followed without lenses. None of the eyes required keratoplasty.

The 7 eyes of 7 patients followed for less than 1 year after epithelial-island CXL were lost to follow-up due to non-attendance of scheduled visits. In this group, the mean (median; range) follow-up time was 1.7±1.0 (1; 1-3) months and preoperative Kmax, TCT, and CDVA values were 86.2±11.5 (90.2; 68.8-97.8) D, 305.3±64.7 (269.0; 267.0-380.0) µm, and 1.40±1.40 (1.69; 1.70-1.00) logarithm of the minimum angle of resolution, respectively.

Table 1. Comparison of preoperative and postoperative visual, refractive, keratometric, tomographic, and aberrometric values in patients who underwent epithelial-island corneal crosslinking

	Preoperative (n=10)	1 year (n=10)	2 years (n=7)	p
CDVA (logMAR)	0.99±0.37 (1.00; 0.70-1.80)	0.95±0.33 (1.00; 0.70-1.60)	0.79±0.29 (1.00; 0.40-1.00)	0.051
MRcyl (D)	-5.14±2.04 (-6.00; -8.00 to -2.00)	-4.69±2.25 (-5.50; -8.00 to -2.00)	-4.90±2.56 (-6.00; -8.00 to -2.00)	1.000
MRSE (D)	-15.86±7.72 (-18.00; -25.00 to -6.00)	-16.86±6.79 (-21.00; -25.50 to -6.00)	-14.21±6.93 (-15.00; -21.25 to -6.00)	0.392
K1 (D)	66.37±7.63 (66.25; 49.40-75.60)	67.21±7.81 (67.95; 49.00-77.50)	64.36±7.88 (65.60; 49.40-73.40)	0.957
K2 (D)	69.28±7.83 (70.25; 50.80-77.90)	70.59±7.54 (70.70; 50.70-79.60)	67.07±8.64 (68.70; 49.60-75.80)	0.075
TCT (µm)	314.67±47.99 (324.00; 232-380)	298.08±56.07 (290.00; 218-386)	330.33±66.16 (317.50; 244-434)	0.960
CCT (µm)	404.56±52.65 (395.00; 346-503)	379.38±67.59 (360.00; 289-492)	419.50±84.16 (372.00; 358-544)	0.440
Kmax (D)	82.84±10.84 (84.75; 59.80-99.00)	80.32±10.20 (81.25; 58.80-99.20)	74.48±8.66 (77.45; 58.30-81.70)	0.443

Table 1. Continued				
	Preoperative (n=10)	1 year (n=10)	2 years (n=7)	P
ISV	163.00±39.68 (160.00; 120-230)	170.71±39.91 (170.50; 111-226)	159.71±35.66 (162.00; 114-220)	0.108
IVA	0.91±0.35 (0.93; -0.25 to 1.55)	0.83±0.32 (0.86; 0.33-1.39)	0.91±0.22 (0.98; 0.55-1.17)	0.270
KI	1.37±0.18 (1.37; 1.17-1.72)	1.38±0.15 (1.34; 1.14-1.65)	1.37±0.09 (1.36; 1.21-1.46)	0.673
CKI	1.19±0.08 (1.18; 1.07-1.34)	1.18±0.11 (1.16; 1.00-1.40)	1.15±0.08 (1.12; 1.06-1.27)	0.172
Rmin	4.12±0.62 (3.98; 3.41-5.64)	4.29±0.59 (4.16; 3.40-5.74)	4.45±0.68 (4.26; 3.58-5.79)	0.065
IHA	45.70±0.62 (3.98; 3.41-5.64)	35.69±20.40 (34.60; 6.10-69.60)	33.69±21.11 (26.40; 0.40-82.30)	0.682
IHD	0.199±0.132 (0.158; 0.048-0.483)	0.186±0.117 (0.179; 0.043-0.438)	0.194±0.065 (0.189; 0.136-0.315)	0.308
Vertical coma	-1.723±2.106 (-1.068; -6.428 to 0.613)	-1.122±1.946 (-0.199; -5.210 to 1.796)	-1.255±0.981 (-1.216; -2.457 to -0.073)	0.552
Horizontal coma	-0.537±2.307 (-0.887; -3.625 to 2.568)	-0.251±2.098 (-0.376; -4.021 to 2.950)	-0.309±2.589 (-1.269; -3.833 to 2.481)	0.825
ECC (cells/mm ²)	2453.0±407.6 (2568; 2021-2750)	2405.0±219.42 (2510; 2261-2621)	2418.25±249.15 (2498; 2209-2523)	0.957

Values are presented as mean ± standard deviation (median; range). P values were calculated using Friedman two-way analysis of variance by ranks for dependent samples. CDVA: Corrected distance visual acuity, logMAR: Logarithm of the minimum angle of resolution, MRcyl: Manifest refraction cylinder, MRSE: Manifest refraction spherical equivalent, K1: Flat keratometry, K2: Steep keratometry, TCT: Thinnest corneal thickness, CCT: Central corneal thickness, Kmax: Maximum keratometry, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Central keratoconus index, Rmin: Minimum sagittal curvature, IHA: Index of height asymmetry, IHD: Index of height decentration, ECC: Endothelial cell count

Discussion

In our study, epithelial-island CXL provided clinical stabilization of visual, refractive, keratometric, tomographic, and aberrometric parameters over a 2-year follow-up period in patients with progressive keratoconus and thin corneas. No significant endothelial cell loss, endothelial dysfunction, prolonged corneal edema or any other clinically significant adverse event was encountered in any eye.

In the standard Dresden protocol, UVA surface irradiation at 3 mW/cm² induces crosslinking within the anterior 300 µm of the corneal stroma.¹⁴ *In vitro* studies have established a UVA cytotoxicity threshold of 0.36 mW/cm² for corneal endothelial cells,¹⁵ and a minimum stromal thickness of 400 µm prior to UVA irradiation has been emphasized as a prerequisite for the safe application of the standard protocol. Although corneal thickness in early and moderate keratoconus typically ranges from 410 to 470 µm,¹⁶ this safety threshold cannot be met in advanced keratoconus, where standard UVA doses carry a risk of endothelial injury. Kymionis et al.¹⁷ reported

endothelial cell loss in thin corneas (<400 µm) treated with the standard CXL protocol. Alternative CXL protocols have been described for keratoconus cases with thin corneas.¹² The use of hypo-osmolar riboflavin was found to be safe in corneas with a stromal thickness greater than 330-345 µm,^{5,18} with long-term effectiveness comparable to that of the standard Dresden protocol.¹⁸ In contrast, transepithelial CXL has been shown to be less effective than the standard Dresden protocol. Reduced UVA exposure time as in the Sub400 protocol,⁶ contact lens-assisted CXL,⁸ lenticule-assisted CXL,⁹ peripheral CXL,¹⁰ and epithelial-island CXL¹¹ have emerged as promising alternatives for thin corneas. However, their long-term efficacy and safety profiles have not yet been fully established.

Epithelial-island CXL is an alternative CXL protocol specifically designed for thin and ultra-thin corneas. It can be used alone or in combination with hypo-osmolar riboflavin. In this technique, individualized epithelial debridement is performed prior to riboflavin application to preserve the epithelium overlying the cone apex. The aim is to provide approximately 50 µm of additional barrier over

the corneal endothelium in this region before UVA exposure in order to prevent endothelial cytotoxicity. One study employing this technique reported reduced postoperative pain and faster epithelial healing.¹⁹ It is thought that the preserved epithelial border acts as a refractive surface, directing UVA irradiation toward the mid-stromal layers,²⁰ while the debrided peripheral epithelial zones facilitate riboflavin penetration beneath the island.²¹

The epithelial-island CXL technique was first described by Kymionis et al.¹¹ They performed epithelial-island CXL using iso-osmolar riboflavin solution in 2 eyes of 2 patients, one with keratoconus and one with iatrogenic ectasia, with TCT values of 380 and 375 μm .¹¹ At postoperative month 9, topographic measurements were reported to be stable, with no deterioration in endothelial cell density or morphology.¹¹ Subsequently, Mazzotta and Ramovecchi²⁰ performed epithelial-island CXL in 10 eyes with keratoconus (mean TCT: 384 μm ; range 368-391 μm), preserving a 3.25-mm diameter epithelial island over the cone apex during keratectomy. However, they used both iso-osmolar and hypo-osmolar riboflavin solutions. Clinical stabilization of visual acuity, keratometry, pachymetry, coma aberrations, and ECC was reported at postoperative year 1.²⁰ The authors suggested that epithelial-island CXL may offer a safer and more effective treatment option for thin corneas compared to transepithelial CXL.²⁰ Using a similar protocol, Omar et al.²¹ reported clinical stability in visual acuity, mean keratometry, and Kmax in 30 eyes with keratoconus (preoperative mean TCT: 377 μm) over a 1-year follow-up period. AS-OCT assessment of the demarcation line revealed a more superficial but clearly identifiable line (at 216 μm and 300 μm) in the region overlying the preserved epithelial island. Although greater visual and keratometric improvement was reported compared to previous studies, a 2.6% ECC loss was observed and attributed to the exclusive use of iso-osmolar riboflavin. The authors proposed that the addition of hypo-osmolar riboflavin and preservation of a larger epithelial island over the cone apex may provide additional protection against endothelial cytotoxicity.²¹ In contrast, Seyyar et al.¹⁹ treated 40 keratoconus eyes with epithelial-island CXL using only iso-osmolar riboflavin and preserving a mean 2-mm diameter epithelial island, and reported refractive and keratometric improvement and stable ECC at postoperative year 1. However, a key distinction in that study was that the mean preoperative TCT was 413 μm (range, 341-528 μm), which may explain why iso-osmolar riboflavin alone was sufficient to ensure endothelial safety.

As evidenced by the available data, epithelial-island CXL has been applied to halt progression in a limited number of eyes with progressive keratoconus and thin corneas and has consistently been reported as a promising and reliable method. However, variability in surgical protocols and the small number of cases remain the most important limiting factors in the existing literature, including the present study. In our study, the epithelial-island CXL using a sequential iso-osmolar and hypo-osmolar riboflavin protocol halted progression and stabilized visual, refractive, and keratometric values over 2 years of follow-up in eyes with thin corneas. No procedure-related decrease in ECC was observed. Significant visual improvement was achieved with scleral lens fitting in 6 of 10 eyes. These findings demonstrate that in advanced keratoconus, progression can be halted with epithelial-island CXL and visual acuity can subsequently be improved through a less invasive approach such as scleral lens fitting, thereby avoiding the need for keratoplasty. Indeed, the anatomical and visual outcomes of lamellar or penetrating keratoplasty may be suboptimal in eyes with advanced keratoconus and no central corneal scarring. Given that keratoconus predominantly affects young individuals, it is important to recognize that eyes undergoing keratoplasty at an early age are at risk of developing long-term complications that can adversely affect visual prognosis, such as endothelial cell loss, stromal opacification, and graft failure. Moreover, post-keratoplasty irregular astigmatism may hinder adequate visual recovery, and achieving satisfactory lens tolerance and visual acuity with contact or scleral lenses in these eyes may prove challenging. Therefore, in advanced keratoconus without central scarring, the therapeutic goal should be to arrest progression while maximally preserving the native corneal tissue, thereby enabling effective visual rehabilitation with contact or scleral lenses.

Study Limitations

The main limitations of our study are its retrospective design and small sample size. Given the multiple parameters analyzed, the absence of statistically significant differences does not preclude the possibility of type II error. Furthermore, the limited sample size reduces the generalizability of our findings. However, the frequent corneal scarring and need for keratoplasty in advanced keratoconus limit the available sample size, as reported in other studies. In addition, there is currently no standardized method for determining the epithelial island to be preserved during debridement. Although we used methods employed in earlier studies, there remains the possibility of measurement errors or inaccuracies in cone

apex identification. Nevertheless, preserving a 3x3-mm epithelial island can mitigate the risk of error. Patient attrition during the follow-up period also introduces a potential risk of selection bias. In clinical practice, it is known that patients with a more stable disease course are just as likely to skip follow-ups as those who develop complications. Therefore, it is not possible to determine with certainty whether the cases with truncated or longer follow-up were clinically more stable, and the results should be interpreted with this limitation in mind. Nevertheless, our study has the longest follow-up after epithelial-island CXL treatment in the published literature. In the cohort followed for 2 years, no significant decline in ECC was observed, and *in vivo* confocal microscopy revealed no evidence of endothelial cytotoxicity.

Conclusion

In conclusion, epithelial-island CXL appears to be a safe and effective treatment option for progressive keratoconus in eyes with thin corneas. Controlled studies with larger sample sizes and extended follow-up periods are needed to confirm the safety and efficacy of this technique.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine, Human Research Ethics Committee (decision no: İ11-790-23, date: 21.12.2023) and the study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from each patient or their legal guardian.

Declarations

Authorship Contributions

Surgical and Medical Practices: Ö.Ö.U., Concept: Ö.Ö.U., Design: Ö.Ö.U., T.Ç.B., Data Collection or Processing: T.Ç.B., B.K., Analysis or Interpretation: T.Ç.B., Literature Search: T.Ç.B., Writing: T.Ç.B., Ö.Ö.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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