Original Article

Tomographic assessment of the thinnest corneal point following customized epithelium-off cross-linking for progressive ectasia

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ABSTRACT

Background: Customized corneal cross-linking (CXL) enables spatially individualized ultraviolet-A (UVA) irradiation of ectatic corneas. However, changes in the thickness and spatial location of the thinnest corneal point remain insufficiently characterized. This study evaluated 1 year changes in these parameters following customized epithelium-off CXL for progressive corneal ectasia. Secondary aims were to assess keratometric, visual, refractive, and corneal aberrometric outcomes and correlations of age with baseline, 1 year postoperatively, and longitudinal changes in thinnest-point location and pachymetry.

Methods: This retrospective complete-case analysis included eligible eyes with available baseline and 1 year follow-up data from consecutive patients undergoing customized epithelium-off CXL. Treatment was performed using the Mosaic platform with individualized spatial irradiation patterns planned from preoperative tomographic maps. The treatment pattern was geometrically centered on the pupil, with a patient-specific offset derived from the x and y coordinates of the thinnest corneal point to target the ectatic region using spatially graded UVA irradiation. Corneal pachymetry and thinnest-point x and y coordinates were measured with the Sirius 3D Corneal Topographer at baseline and 1 year. Secondary outcomes were maximum keratometry (Kmax), mean keratometry (Kmean), corrected and uncorrected distance visual acuity (CDVA and UDVA), refractive astigmatism, and total coma.

Results: The study included 32 eyes of 23 patients, 12 men (52.2%) and 11 women (47.8%), with a mean (standard deviation [SD]) age of 24.39 (4.13) years (range 19–34); 28 eyes (87.5%) had keratoconus and four (12.5%) had post-LASIK ectasia. Mean (SD) thinnest corneal thickness decreased significantly from 442.28 (31.09) μm preoperatively to 405.75 (29.71) μm at 1 year ($P < 0.001$), with no significant changes in the x or y coordinates of the thinnest corneal point (both $P > 0.05$). Significant reductions occurred in Kmax, Kmean, CDVA, and total coma (all $P < 0.05$), whereas UDVA and refractive astigmatism did not change significantly (both $P > 0.05$). Age was not significantly correlated with preoperative or 1 year x or y coordinates, or with preoperative or postoperative thinnest corneal thickness (all $P > 0.05$). A moderate positive correlation with change in the y coordinate ($r = +0.444$; $P < 0.05$) was not retained after adjustment for within-subject inter-eye correlation using a mixed-effects model ($P > 0.05$).

Conclusions: Customized epithelium-off CXL was associated with significant 1 year reductions in thinnest corneal thickness and corneal steepness, improvements in selected visual and aberrometric outcomes, and no statistically significant systematic change in the x or y coordinates of the thinnest corneal point. Larger prospective controlled studies with longer follow-up are needed to determine the durability and clinical significance of these structural changes.

KEYWORDS

keratoconus, ectasia, LASIK, laser-assisted intrastromal keratomileusis, corneal collagen cross-linking, epithelium-off corneal cross-linking, epi off CXL, corneal topographies, visual acuities, corneal thickness measurement

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INTRODUCTION

Corneal ectasia comprises a heterogeneous group of disorders characterized by progressive corneal thinning and biomechanical weakening, leading to corneal protrusion and distortion, irregular astigmatism, and visual impairment, with stromal scarring occurring in advanced disease [1–3]. Ectatic changes may involve the central or paracentral cornea and occur most commonly in keratoconus, but may also develop following corneal refractive surgery [3, 4]. Keratoconus is the most prevalent form of corneal ectasia and typically manifests as a bilateral disorder, whereas post-refractive surgery ectasia, including post-laser-assisted in situ keratomileusis (post-LASIK) ectasia, is considerably less common [2, 4].

Biomechanical evidence supports the concept that corneal ectasia involves focal biomechanical weakening, which promotes localized deformation and redistribution of corneal stress [1]. Computational finite-element modeling further suggests that corneal collagen crosslinking (CXL) may be optimized by preferentially stiffening biomechanically weakened corneal regions, thereby enhancing cone flattening and biomechanical restoration [5, 6]. Compared with conventional uniform irradiation, regional increases in corneal elastic modulus are predicted to produce greater flattening and corneal regularization. Given the spatial heterogeneity of keratoconus and other ectatic disorders, customized CXL uses eye-tracking technology and spatially selective ultraviolet-A (UVA) irradiation to induce regional changes in corneal stiffness rather than applying a uniform treatment pattern across the cornea. By preferentially targeting biomechanically compromised regions, customized CXL aims to enhance maximum keratometry (Kmax) flattening and corneal regularization, with potential improvements in visual function [7, 8]. Emerging long-term clinical evidence has further demonstrated sustained Kmax flattening and improved corneal regularization following customized treatment [9]. By stabilizing disease progression, CXL may also reduce the need for more invasive interventions, particularly corneal transplantation, while preserving future options for refractive and visual rehabilitation [10–12].

The Sirius 3D Corneal Topographer combines a rotating Scheimpflug camera with Placido-disc topography to provide comprehensive assessment of the anterior segment and quantitative evaluation of corneal pachymetry and anterior and posterior corneal surface geometry. During noncontact acquisition, the system captures a series of radial Scheimpflug images while rotating around the optical axis of the eye and acquires dense point-by-point data from the anterior and posterior corneal surfaces for three-dimensional reconstruction of corneal and anterior segment structures [13, 14]. This integrated imaging approach enables detailed characterization of corneal thickness and anterior and posterior surface geometry, plus facilitates spatial localization of corneal landmarks, including the thinnest corneal point [13–15]. In the present study, these tomographic and pachymetric data were used to inform individualized planning of the customized CXL treatment pattern.

This study aimed to evaluate 1 year changes in the thickness and spatial location of the thinnest corneal point following customized epithelium-off CXL in eyes with progressive corneal ectasia. Secondary aims were to assess changes in keratometric, visual, refractive, and corneal aberrometric outcomes and to examine the correlations of age with baseline, postoperative, and longitudinal changes in thinnest-point location and pachymetry.

METHODS

This retrospective interventional case series screened consecutive patients who underwent customized epithelium-off CXL between 1 January and 29 June 2019 at Dar El-Oyoun Eye Laser Center, Muscat, Oman. The analysis included eligible eyes with complete preoperative and 12-month follow-up data. The study protocol was reviewed and approved by the Institutional Review Board of Dar El-Oyoun Eye Laser Center, and the study was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after a detailed explanation of the study objectives, examination procedures, potential risks and benefits, and voluntary nature of participation. Participants were informed of their right to withdraw at any time without prejudice to their ongoing care or treatment. All patient data were anonymized and handled confidentially in accordance with institutional data protection policies.

Eligible eyes had progressive keratoconus or post-LASIK ectasia, a central corneal thickness (CCT) > 400 μm, corrected distance visual acuity (CDVA) worse than 0.1 logarithm of the minimum angle of resolution (logMAR), complete clinical records, and completion of all scheduled follow-up visits through the 1 year assessment. Eyes with a CCT ≤ 400 μm, Vogt striae, corneal scarring, previous corneal hydrops, prior intracorneal ring implantation, or previous CXL were excluded.

Eyes were considered to have progressive corneal ectasia based on serial clinical and tomographic evidence of progression, interpreted in accordance with the principles outlined in the Global Consensus on Keratoconus and Ectatic Diseases [16]. Progression was confirmed on at least two consecutive examinations performed over a minimum interval of six months (typically within the 12 months preceding treatment). For clinical decision-making, eyes were considered eligible for customized CXL if they exhibited one or more of the following objective changes: (1) an increase in Kmax ≥ 1.0 D; (2) an increase in manifest refractive cylinder ≥ 1.0 DC; (3) an increase in manifest refraction spherical equivalent ≥ 0.50 D toward greater myopia; or (4) a decrease in thinnest corneal pachymetry ≥ 20 μm (or ≥ 5% from baseline). These objective findings were interpreted together with serial tomographic assessment and overall clinical judgment, including deterioration in CDVA not attributable to other ocular disease.

To minimize the confounding effects of contact lens-induced corneal warpage and epithelial molding on corneal topographic and pachymetric measurements, patients who regularly wore contact lenses were instructed to discontinue lens

wear before both the baseline preoperative evaluation and the 1 year postoperative assessment. Patients wearing rigid gas-permeable lenses were instructed to discontinue lens wear for a minimum of 3 weeks, whereas soft contact lens wearers were instructed to discontinue lens wear for at least 2 weeks. Compliance with the cessation protocol was confirmed by patient history and slit-lamp examination at each study visit. This protocol was intended to minimize contact lens-induced alterations in corneal shape and improve the reliability of Sirius topographic and pachymetric measurements, thereby reducing the likelihood of postoperative changes in thinnest-point location and corneal thickness reflecting transient contact lens-related effects rather than customized corneal cross-linking [17–19].

Eligible participants underwent a standardized comprehensive ophthalmic examination preoperatively and at the 1 year follow-up. The examination included objective refraction using an autorefractometer (KR-8800; Topcon Corporation, Tokyo, Japan); assessment of CDVA using a Snellen chart projected with an Auto Chart Projector (CP-670; Nidek Co., Ltd., Gamagori, Japan), with values converted to logarithm of the minimum angle of resolution (logMAR) notation for statistical analysis; slit-lamp biomicroscopy of the anterior segment (Photo-Slit Lamp BX 900; Haag-Streit, Koeniz, Switzerland); intraocular pressure measurement by Goldmann applanation tonometry (Applanation Tonometer 900; Haag-Streit, Koeniz, Switzerland); and dilated fundus examination by indirect ophthalmoscopy (BETA 200; HEINE Optotechnik GmbH, Herrsching, Germany) using a 20 D lens (Volk Optical Inc., Mentor, OH, USA). Corneal topography and pachymetry were assessed using the Sirius 3D Corneal Topographer (CSO, Costruzione Strumenti Oftalmici, Florence, Italy), which integrates Scheimpflug imaging with Placido-disc topography to characterize the anterior and posterior corneal surfaces and generate corneal pachymetric maps [20, 21]. Corneal ectasia was diagnosed based on distortion of the retinoscopic red reflex, characterized by a scissoring reflex, in conjunction with ectatic patterns identified on corneal topography using the Sirius 3D Corneal Topographer.

Preoperative corneal thickness was measured using the Sirius 3D Corneal Topographer in accordance with the manufacturer's acquisition protocol [21]. The geometric corneal center served as the reference origin for the instrument's software-generated Cartesian coordinate system, and the spatial location of the thinnest corneal point was recorded as the corresponding x and y coordinates provided by the Sirius software [15]. Before each acquisition, participants were instructed to blink to restore a smooth precorneal tear film. The chin and forehead were placed on the supports, and participants fixated on the central target with eyes fully open, avoiding blinking during image acquisition. Tomographic and pachymetric maps were subsequently reviewed and analyzed using the device software.

The customized UVA irradiation pattern was planned individually from preoperative tomographic maps and implemented using three nested treatment zones on the Mosaic system. The treatment pattern was geometrically centered on the pupil to enable eye-tracking during UVA delivery, while a patient-specific offset was calculated by subtracting the x and y coordinates of the pupil center from those of the thinnest corneal point, thereby positioning the highest-fluence treatment zone over the ectatic region. The posterior elevation map was used exclusively to determine treatment-zone dimensions rather than treatment centration. The shortest diameter of the region of abnormal posterior elevation defined the smallest (inner) treatment zone, the maximal diameter defined the outer treatment zone, and the intermediate treatment zone was defined as the arithmetic mean of the two. The treatment profile was spatially graded, with greater cumulative UVA exposure in the innermost treatment zone and progressively lower exposure toward the periphery, consistent with previously described customized CXL strategies [9, 22].

Customized epithelium-off CXL was performed using the Mosaic customized treatment-planning platform integrated with the Avedro KXL II System (Model KXL II-370; Avedro, Inc., Waltham, MA, USA). Following topical anesthesia with tetracaine hydrochloride 0.5% ophthalmic solution (Bausch & Lomb Incorporated, Rochester, NY, USA), the central 9-mm corneal epithelium was removed. A dextran-free 0.1% riboflavin solution (VibeX™; Avedro, Inc., Waltham, MA, USA) was instilled every 2 minutes for 10 minutes. UVA irradiation (370 nm) was subsequently delivered according to the individualized three-zone treatment plan at an on-phase irradiance of 30 mW/cm² using a 1-second-on and 1-second-off pulsed protocol. The outer, intermediate, and inner treatment zones received cumulative fluences of 5.4–7.2, 7.4–10.0, and 10.0–15.0 J/cm², respectively. The full treatment area initially received the programmed outer-zone base fluence over approximately 6–8 minutes of elapsed UVA irradiation. Irradiation was subsequently continued within the intermediate and inner zones until their programmed cumulative fluences were reached. Accordingly, the total elapsed UVA irradiation time varied according to the individualized treatment plan and the maximum fluence delivered to the innermost zone, ranging from approximately 11 minutes 7 seconds to 16 minutes 40 seconds. Treatment-zone diameters, offsets, and spatial fluence distributions were individualized according to the preoperative tomographic findings, with the highest cumulative fluence delivered to the innermost zone and progressively lower fluences delivered to the intermediate and outer zones, consistent with previously described spatially graded customized CXL protocols [9, 22].

All patients underwent the same postoperative treatment protocol. Immediately after the procedure, a bandage contact lens (ACUVUE OASYS®; Johnson & Johnson Vision, Jacksonville, FL, USA) was placed to promote re-epithelialization and retained until complete epithelial closure was confirmed by slit-lamp biomicroscopy. Postoperative treatment consisted of topical levofloxacin 5 mg/mL (Oftaquix®; Santen Pharmaceutical Co., Ltd., Osaka, Japan), administered four times daily for 7 days; dexamethasone 0.1% eye drops (Santeson® ophthalmic solution 0.1%; Santen Pharmaceutical Co., Ltd., Osaka, Japan), administered four times daily for 2 weeks and subsequently tapered according to clinical response; preservative-free artificial

tears (Hyalein® Mini; Santen Pharmaceutical Co., Ltd., Osaka, Japan), used as needed up to six times daily; and carbomer 0.2% ophthalmic gel (Viscotears®; Bausch & Lomb, Rochester, NY, USA), applied once nightly. Patients were instructed to avoid eye rubbing and refrain from swimming and using eye makeup for at least 2 weeks postoperatively. Follow-up examinations were scheduled at 1 week and at 1, 3, 6, and 12 months postoperatively. At the 12-month visit, corneal tomographic and pachymetric imaging was repeated using the same Sirius 3D Corneal Topographer and acquisition protocol as at baseline.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were summarized as mean (standard deviation [SD]), non-normally distributed variables as median and interquartile range (IQR), categorical variables as frequencies and percentages. Preoperative and 1 year postoperative measurements were compared according to data distribution. Paired *t*-tests were used for normally distributed paired continuous variables, the Wilcoxon signed-rank test was used for non-normally distributed paired variables. Changes in secondary keratometric, visual, refractive, and corneal aberrometric outcomes were assessed using paired comparisons, with mean changes and corresponding 95% confidence intervals (CIs) reported. Because some participants contributed both eyes, linear mixed-effects models with patient-specific random intercepts were performed as sensitivity analyses to account for within-subject inter-eye correlation; the primary analyses remained based on paired comparisons. Spearman rank correlation analysis was used to assess correlations between age and preoperative values, 1 year postoperative values, and changes in the x and y coordinates of the thinnest corneal location and thinnest corneal thickness. Variables showing statistically significant correlations in univariate analyses were subsequently evaluated using mixed-effects regression models to account for within-subject inter-eye correlation. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant.

RESULTS

The study included 32 eyes of 23 patients, comprising 12 men (52.2%) and 11 women (47.8%). Mean (SD) age was 24.39 (4.13) years (range, 19–34). Fourteen patients (60.9%) had unilateral involvement and 9 (39.1%) had bilateral involvement. Of the 32 eyes, 19 (59.4%) were right eyes and 13 (40.6%) were left eyes. Twenty-eight eyes (87.5%) had keratoconus, 5 of them advanced keratoconus; 4 eyes (12.5%) had post-LASIK ectasia (Table 1).

Changes in secondary keratometric, visual, refractive, and corneal aberrometric outcomes from baseline to 1 year after customized CXL are summarized in Table 2. At 1 year postoperatively, significant reductions were observed in Kmax (mean change, −2.70 D; 95% CI, −4.20 to −1.30; P < 0.05) and Kmean (mean change, −1.20 D; 95% CI, −2.00 to −0.40; P < 0.05). CDVA improved significantly (mean change, −0.06 logMAR; 95% CI, −0.09 to −0.02; P < 0.05), whereas the improvement in UDVA did not reach statistical significance (P > 0.05). Refractive astigmatism showed no significant change either (P > 0.05). Total coma decreased significantly at 1 year (mean change, −0.09 μm; 95% CI, −0.17 to −0.02; P < 0.05) (Table 2).

At 1 year after customized CXL, no significant change was observed in the spatial location of the thinnest corneal point. The median x coordinate changed from −0.25 (IQR, −0.55 to 0.43) preoperatively to −0.33 (IQR, −0.54 to 0.35) at 1 year (P > 0.05). Similarly, the median y coordinate changed from −0.55 (IQR, −0.84 to −0.41) preoperatively to −0.63 (IQR, −0.80 to −0.48) at 1 year (P > 0.05). In contrast, mean (SD) thinnest corneal thickness decreased significantly from 442.28 (31.09) μm preoperatively to 405.75 (29.71) μm at 1 year (P < 0.001) (Table 3), corresponding to a mean change of −36.53 μm (95% CI, −43.21 to −29.85 μm) and a median reduction of 35.00 μm (IQR, 25.00–47.50 μm; range, 9.00–85.00 μm). All 32 eyes (100%) demonstrated a reduction in thinnest corneal thickness at 1 year. The observed reduction remained statistically significant in the mixed-effects model (β = −36.53; 95% CI, −43.21 to −29.85; P < 0.001), confirming the robustness of the findings after accounting for within-subject inter-eye correlation. Descriptive subgroup analysis showed numerically comparable mean (SD) reductions in thinnest corneal thickness in eyes with keratoconus (36.2 [17.8] μm; n = 28) and post-LASIK ectasia (38.0 [19.1] μm; n = 4), although the small post-LASIK subgroup precluded meaningful statistical comparison.

Age was not significantly associated with preoperative or 1 year postoperative thinnest corneal thickness or with the preoperative or postoperative x or y coordinates of the thinnest corneal location (all P > 0.05) (Table 4). Although univariate analysis showed a moderate positive correlation between age and the change in the y coordinate of the thinnest corneal location (r = + 0.444, P < 0.05) (Table 4), this association was no longer significant after adjustment for within-subject inter-eye correlation using a mixed-effects model (P = 0.092).

Table 1. Demographic and clinical characteristics of the study participants

Characteristic	Value
Age (y), Mean ± SD (Range)	24.39 ± 4.13 (19.0 to 34.0)
Sex (Male/ Female), n (%)	12 (52.2) / 11 (47.8)
Patient-level involvement (Unilateral / Bilateral), n (%)	14 (60.9) / 9 (39.1)
Eye laterality (OD / OS), n (%)	19 (59.4) / 13 (40.6)
Diagnosis (KCN / Post-LASIK ectasia), n (%)	28 (87.5) / 4 (12.5)

Abbreviations: y, years; SD, standard deviation; n, numbers; %, percentage; OD, right eye; OS, left eye; KCN, keratoconus; LASIK, laser-assisted in situ keratomileusis.

Table 2. Changes in secondary clinical outcomes from baseline to 1 year after customized corneal cross-linking

Outcome	Preop	1 year postop	Mean change	95% CI for change	*P* -value
Kmax (D), Mean ± SD	54.80 ± 6.20	52.10 ± 5.90	−2.70	−4.20 to −1.30	**0.008**
Kmean (D), Mean ± SD	47.30 ± 4.50	46.10 ± 4.20	−1.20	−2.00 to −0.40	**0.042**
CDVA (logMAR), Mean ± SD	0.34 ± 0.21	0.28 ± 0.19	−0.06	−0.09 to −0.02	**0.031**
UDVA (logMAR), Mean ± SD	0.78 ± 0.35	0.72 ± 0.32	−0.06	−0.15 to 0.03	0.064
Astigmatism (DC), Mean ± SD	3.40 ± 2.10	3.00 ± 2.00	−0.40	−1.00 to 0.20	0.124
Total coma (μm), Mean ± SD	0.48 ± 0.22	0.39 ± 0.19	−0.09	−0.17 to −0.02	**0.019**

Abbreviations: Preop, preoperative; Postop, postoperative; CI, confidence interval; Kmax, maximum keratometry; D, dioptres; SD, standard deviation; Kmean, mean keratometry; CDVA, corrected distance visual acuity; logMAR, logarithm of the minimum angle of resolution; UDVA, uncorrected distance visual acuity; DC, diopter cylinder; μm, micrometer. Note: *P*-values < 0.05 are shown in bold; Astigmatism indicates refractive astigmatism; Refractive astigmatism was analyzed as the absolute magnitude of the cylindrical refractive error; Mean change was calculated as the 1-year postoperative value minus the preoperative value.

Table 3. Changes in the coordinates and pachymetry of the thinnest corneal location from baseline to 1 year after customized corneal cross-linking

Outcome	Time point	Mean ± SD	Median (IQR)	*P*-value
Thinnest-location x coordinate	**Preoperative**	−0.13 ± 0.67	−0.25 (−0.55, 0.43)	0.197
	1 year	−0.18 ± 0.56	−0.33 (−0.54, 0.35)	
Thinnest-location y coordinate	**Preoperative**	−0.59 ± 0.27	−0.55 (−0.84, −0.41)	0.495
	1 year	−0.61 ± 0.29	−0.63 (−0.80, −0.48)	
Thinnest corneal thickness, μm	**Preoperative**	442.28 ± 31.09	445.00 (426.00, 464.50)	**<0.001**
	1 year	405.75 ± 29.71	402.50 (382.50, 422.50)	

Abbreviations: SD, standard deviation; IQR, interquartile range; μm, micrometer. Note: *P*-value < 0.05 is shown in bold.

Table 4. Correlations between age and baseline, 1 year, and changes in thinnest-location coordinates and pachymetry

Outcome	Statistic	Baseline	1 year	Change
Thinnest-location x coordinate	**Correlation Coefficient**	r = + 0.046	r = + 0.096	r = −0.086
	***P*-value**	0.802	0.602	0.640
Thinnest-location y coordinate	**Correlation Coefficient**	r = −0.011	r = + 0.213	**r = + 0.444**
	***P*-value**	0.953	0.242	**0.011**
Thinnest corneal thickness	**Correlation Coefficient**	r = + 0.067	r = + 0.221	r = −0.307
	***P*-value**	0.715	0.224	0.088

Note: *P*-value < 0.05 is shown in bold; *r*, Spearman rank correlation coefficient.

DISCUSSION

The present study evaluated 1 year structural and clinical changes following customized epithelium-off CXL in eyes with progressive corneal ectasia. The principal finding was a significant reduction in thinnest corneal thickness, from a mean (SD) of 442.28 (31.09) μm preoperatively to 405.75 (29.71) μm at 1 year, corresponding to a mean reduction of 36.5 μm. This pachymetric reduction occurred without a significant change in the spatial location of the thinnest corneal point, as neither the x nor the y coordinate differed significantly between baseline and 1 year. These findings suggest that the observed postoperative thinning was not accompanied by a significant displacement of the thinnest corneal location during the study.

The significant reduction in thinnest corneal thickness observed in the present study differs from findings reported with oxygen-supplemented transepithelial customized CXL [23, 24]. Mazzotta et al. [23] reported no significant change in minimum corneal thickness at 6 months, despite improvements in Kmax, visual acuity, and higher-order aberrations following an epithelium-on customized protocol with supplemental oxygen. Their mean (SD) minimum corneal thickness decreased from 472.66 (21) μm at baseline to 464.71 (24.38) μm at 6 months, but this difference was not statistically significant [23]. Similarly, Kamiya et al. [24] reported no significant 1 year change in thinnest pachymetry after epithelium-on, accelerated, oxygen-supplemented customized CXL, with mean (SD) values changing from 449 (42) μm preoperatively to 445 (40) μm at 1 year [24]. Several methodological and clinical differences may contribute to these contrasting findings, including epithelial status during CXL, supplemental oxygen use, UVA irradiation parameters and spatial treatment profiles, baseline disease severity, study populations, and follow-up duration [23, 24]. The present study used an epithelium-off customized protocol and included eyes with both keratoconus and post-LASIK ectasia, whereas Mazzotta et al. [23] and Kamiya et al. [24] evaluated oxygen-supplemented epithelium-on customized CXL in progressive keratoconus. Moreover, Kamiya et al. [24] included patients across a broader age range (12–40 years) and a wider spectrum of keratoconus severity. These differences limit direct comparisons across studies and preclude attribution of the greater pachymetric reduction observed in the present cohort to any single treatment component.

The present findings are broadly consistent with previous evidence indicating that spatially customized CXL can induce corneal flattening and functional improvement in progressive corneal ectasia [9, 22, 25, 26]. At 1 year, Kmax decreased by a mean of 2.70 D and Kmean by 1.20 D, accompanied by significant improvements in CDVA and total coma. These changes are consistent with the biomechanical rationale that spatially individualized UVA delivery may induce regionally

differentiated stiffening and corneal shape remodeling [27, 28]. Nevertheless, direct comparisons across studies require caution because customized CXL protocols differ substantially in treatment centration, irradiation geometry, fluence distribution, epithelial management, and baseline disease severity [9, 22, 25, 26].

The 1 year findings of Gil et al. [25] provide a particularly relevant comparison because their customized treatment also used the Mosaic System and three concentric treatment areas centered on the thinnest corneal point. In their prospective trial of 37 eyes with progressive keratoconus, mean (SD) Kmax decreased significantly from 58.50 (7.84) D at baseline to 57.05 (7.27) D at 1 year, corresponding to a mean flattening of approximately 1.45 D, while mean (SD) CDVA improved significantly from 0.38 (0.19) to 0.20 (0.16) logMAR [25]. In the present study the mean reduction in Kmax was larger (2.70 D) but the improvement in CDVA was smaller (0.06 logMAR). Gil et al. [25] observed a modest but statistically significant reduction in minimum pachymetry, from a mean (SD) of 449.26 (41.62) μm at baseline to 443.26 (41.06) μm at 1 year, compared with the substantially greater reduction in thinnest corneal thickness observed in the present cohort, from 442.28 (31.09) to 405.75 (29.71) μm. This contrast is noteworthy, given that both studies used a three-zone customized treatment strategy delivered with the Mosaic platform. However, the protocols differed in several respects. Gil et al. [25] used excimer laser-assisted epithelial removal and zone-specific fluences of 5.4, 7.2, and 10 J/cm², whereas the present study used mechanical epithelial removal and a broader spatially graded fluence range extending to 15 J/cm². Other factors that may have contributed to the divergent pachymetric responses include differences in baseline disease characteristics, treatment-zone geometry, spatial dose distribution [25], and cohort composition, as the present study included eyes with post-LASIK ectasia in addition to progressive keratoconus.

Our keratometric findings are consistent with those of the earlier comparative study by Seiler et al. [26], who reported more frequent Kmax flattening of at least 2 D after customized CXL than after standard uniform CXL (7/19 eyes [37%] vs. 2/19 eyes [11%]), and a significantly greater mean (SD) corneal regularization index (5.2 [2.7] D vs. 4.1 [3.1] D) at 1 year. Their customized irradiation patterns were centered on the maximum posterior float, with total energy levels ranging from 5.4 to 10 J/cm² [26]. The mean 2.70 D reduction in Kmax observed in the present study therefore lies within a pattern of evidence, suggesting that spatially customized irradiation can produce clinically meaningful corneal flattening. However, the present study differs methodologically because treatment planning incorporated thinnest-point coordinates to calculate a patient-specific offset from the pupil for treatment targeting, while posterior elevation geometry was used for treatment-zone sizing. Moreover, unlike Seiler et al. [26], the present study specifically evaluated longitudinal changes in the x and y coordinates of the thinnest corneal point.

Similar agreement is evident with the randomized trial by Nordstrom et al. [9], in which individualized topography-guided CXL used an asymmetric treatment zone centered on the area of maximum corneal steepness, with energies ranging from 7.2 to 15.0 J/cm². Kmax decreased significantly after customized treatment but not after uniform 9-mm CXL, and visual acuity improved following the customized procedure [9]. The significant reductions in Kmax and Kmean and the improvement in CDVA observed in the present study are consistent with those findings. Nevertheless, treatment targeting differed, as Nordstrom et al. centered irradiation on the area of maximum corneal steepness [9], whereas the present workflow used thinnest-point coordinates to calculate a patient-specific offset from the pupil for treatment targeting, with posterior elevation geometry used to determine treatment-zone dimensions. This distinction is potentially important because anterior curvature, minimum pachymetry, and posterior elevation represent distinct geometric manifestations of ectatic disease and should not be assumed to identify the same spatial location within an ectatic cornea [1, 29].

Our findings are consistent with those of Cassagne et al. [22], who reported greater Kmax flattening and CDVA improvement after topography-guided CXL than after conventional CXL at 1 year. Their customized protocol combined cone-focused de-epithelialization with pulsed UVA irradiation at 30 mW/cm² and revealed a spatially differentiated biological response, with a shallower demarcation line and faster cellular recovery outside the cone region [22]. The reductions in Kmax and total coma, together with improved CDVA in the current study, are compatible with the broader concept that spatially selective treatment may enhance corneal regularization index [26] while concentrating the treatment effect within the ectatic region. The significant reduction in total coma in the present cohort is particularly relevant because coma is a major higher-order optical manifestation of keratoconic corneal distortion and may provide complementary evidence of treatment-related corneal regularization beyond changes in Kmax alone [30, 31].

Further support for the importance of treatment geometry comes from Shetty et al. [32], who compared four CXL irradiation profiles in eyes with keratoconus: a uniform-intensity UVA beam at 9 mW/cm² for 10 minutes; sector-based UVA irradiation; concentric rings of varying UVA intensity centered on the steepest curvature of the anterior axial map; and a ring tangential-map profile analogous to the ring axial-map profile but centered on the steepest curvature of the anterior tangential map. Although the absolute reductions in corneal curvature were similar across several protocols, the ring tangential-map approach produced the greatest reduction in curvature per unit of energy delivered to the cornea, highlighting the potential importance of the spatial relationship between irradiation geometry and corneal curvature in determining treatment efficiency [32]. These findings suggest that treatment response cannot be interpreted solely in terms of total UVA dose; beam geometry, centration, treated area, and the spatial correspondence between the irradiation pattern and the ectatic region may also influence biomechanical and topographic responses [7, 32]. In this context, the significant

Kmax flattening and reduction in total coma observed in the present study may reflect, at least in part, the spatially graded treatment strategy. However, because the present study did not include a uniform-CXL control group or compare alternative customized beam profiles, the relative contribution of treatment geometry cannot be isolated.

An important distinction between the present study and previous customized CXL investigations lies in the spatial parameter evaluated longitudinally. Prior protocols have individualized irradiation using different anatomical or topographic targets, including the cone area [23], thinnest corneal point [25], maximum posterior float [24, 26], maximum corneal steepness [9], and axial or tangential curvature maps [32]. In contrast, the present study extended the assessment beyond treatment targeting by longitudinally evaluating the x and y coordinates of the thinnest corneal point itself. Despite a significant reduction in thinnest corneal thickness at 1 year, neither spatial coordinate showed a statistically significant systematic change at the group level. This distinction is clinically and methodologically relevant because the magnitude of minimum pachymetry and the spatial location of the thinnest point capture distinct aspects of corneal structure and may therefore provide complementary information for characterizing postoperative remodeling after customized CXL [29, 33].

Against this absence of a statistically significant systematic coordinate shift, the magnitude of the observed pachymetric reduction warrants particular consideration. Mean thinnest corneal thickness decreased by 36.53 μm at 1 year, whereas neither the x nor the y coordinate changed significantly. The magnitude of thinning was substantially greater than that reported by Gil et al. [25], who observed an approximately 6 μm reduction in minimum pachymetry at 1 year, plus contrasts with findings from previous oxygen-supplemented epithelium-on customized CXL studies, in which changes in minimum or thinnest pachymetry were not statistically significant [23, 24]. Importantly, the absence of significant changes in the x and y coordinates in the present study suggests that the observed pachymetric reduction was not accompanied by systematic migration of the thinnest corneal point. This distinction is methodologically relevant because changes in minimum corneal thickness and changes in the spatial location at which that minimum occurs represent separate dimensions of postoperative corneal remodeling.

This study has several strengths, including the 1 year longitudinal evaluation of both pachymetric changes and the spatial coordinates of the thinnest corneal point following customized epithelium-off CXL, together with assessment of complementary keratometric, visual, refractive, and aberrometric outcomes. Nevertheless, several limitations should be acknowledged. First, the relatively small sample size may limit precision and generalizability of the findings. Second, the small number of eyes with post-LASIK ectasia (n = 4) precluded meaningful comparison of treatment responses between keratoconus and post-LASIK ectasia. Third, the retrospective single-center design and absence of a conventional CXL control group preclude direct comparison with standard treatment protocols. Fourth, nine participants contributed both eyes. Linear mixed-effects models with patient-specific random intercepts were therefore used as sensitivity analyses to account for within-subject inter-eye correlation. Although these models addressed inter-eye dependence, the modest number of patients limited the precision of the adjusted estimates. Finally, although a post hoc power analysis was not performed, future prospective controlled studies should incorporate a priori sample size calculations based on a prespecified primary outcome. The 1 year follow-up period also limits assessment of the long-term stability of the observed structural and clinical changes, and follow-up was complicated by disruptions during the coronavirus pandemic. Future multicenter prospective studies with larger cohorts, adequate representation of different ectasia subtypes, and longer follow-up are warranted to confirm these findings and clarify their long-term clinical significance. Comparative studies evaluating different customized CXL parameters may further help define optimal treatment strategies.

CONCLUSIONS

Customized epithelium-off CXL was associated with significant reductions in corneal steepness and improvements in selected visual and aberrometric outcomes at 1 year in eyes with progressive corneal ectasia. Despite a significant reduction in the thinnest corneal thickness, no statistically significant changes were observed in the x or y coordinates of the thinnest corneal point. These findings support the potential of customized epithelium-off CXL as an individualized treatment approach for progressive corneal ectasia; however, the observed postoperative reduction in corneal thickness warrants consideration when interpreting intraocular pressure measurements that are influenced by corneal properties. Larger prospective controlled studies with longer follow-up are needed to confirm the durability of these outcomes, clarify the clinical significance of postoperative pachymetric changes, and identify treatment parameters associated with optimal efficacy and safety.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was reviewed and approved by the Institutional Review Board of Dar El-Oyoun Eye Laser Center, and the study was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after a detailed explanation of the study objectives, examination procedures, potential risks and benefits, and voluntary nature of participation. Participants were informed of their right to withdraw at any time without prejudice to their ongoing care or treatment. All patient data were anonymized and handled confidentially in accordance with institutional data protection policies.

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