Original Article

Six-month longitudinal analysis of visual, tomographic, and densitometric changes after corneal collagen cross-linking in keratoconus

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ABSTRACT

Background: Keratoconus is a progressive corneal ectasia commonly treated with corneal collagen cross-linking (CXL) to halt further progression. Although transient anterior stromal haze frequently develops after CXL, its impact on visual recovery remains unclear. This study aimed to examine the correlation between postoperative changes in corneal densitometry, visual acuity, topography, and pachymetry in eyes with keratoconus undergoing CXL.

Methods: This retrospective study included eyes with progressive keratoconus undergoing epithelium-off accelerated CXL. Pre- and postoperative assessments included measuring corrected distance visual acuity (CDVA), manifest refraction, and slit-lamp biomicroscopy examination, along with Pentacam HR imaging. Densitometry was quantified across three stromal depths and four annular zones. Follow-up evaluations were performed at day 1, week 1, and months 1, 3, and 6 post-CXL.

Results: Twenty-four eyes from 24 patients with progressive keratoconus (median age, 21.9 years; 79.2% male) were evaluated over a six-month period following CXL. At six months significant improvements were observed in CDVA, accompanied by reductions in flat keratometry, central corneal thickness, and thinnest pachymetry (all $P < 0.05$). Corneal densitometry increased significantly at one month and partially regressed by six months across all stromal depths and within all concentric annular zones from 0.0–2.0 mm to 6.0–10.0 mm and their corresponding total values (all $P < 0.05$). Baseline anterior 0.0–2.0 mm densitometry demonstrated a significant inverse correlation with CDVA (r = -0.50, $P < 0.05$). At one month, CDVA correlated inversely with anterior (r = -0.47, $P = 0.003$) and mid-stromal (r = -0.58, $P = 0.006$) 0.0–2.0 mm densitometry, and with anterior 2.0–6.0 mm densitometry (r = -0.45, $P = 0.045$). By six months, no significant correlations were found between CDVA or absolute keratometric parameters and densitometry at any depth, zone, or total value (all $P > 0.05$), indicating stabilization of both visual and structural recovery.

Conclusions: Accelerated epithelium-off CXL yielded significant visual and structural improvements in progressive keratoconus over six months. Corneal densitometry followed a characteristic postoperative pattern, with an early peak at one month followed by partial regression. Early stromal backscatter increases were significantly correlated with visual acuity, but these relationships diminished by six months, consistent with recovery of corneal clarity and vision. Longer-term studies are warranted to clarify the prognostic utility of densitometry for visual and tomographic outcomes after CXL.

KEYWORDS

keratoconus, pellucid marginal degeneration, densitometries, light scattering, corneas, corneal stromas, corneal topographies, vitamin B2, riboflavin, epithelium-off CXL

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INTRODUCTION

Corneal collagen cross-linking (CXL) is a well-established therapeutic procedure aimed at halting the progression of keratoconus by enhancing the biomechanical rigidity and resistance of corneal collagen to keratectasia [1]. This biomechanical reinforcement is achieved through a photochemical reaction between a photosensitizing agent, typically riboflavin, and ultraviolet-A (UV-A) irradiation, which induces photopolymerization of stromal collagen fibers [1].

Thermomechanical testing has revealed distinct structural and biomechanical differences between the anterior and posterior stromal layers following riboflavin/UV-A treatment [2]. These variations are believed to underlie the development of postoperative stromal haze and the characteristic demarcation line observed on slit-lamp examination and confirmed by confocal microscopy and anterior segment optical coherence tomography (AS-OCT) [3].

Corneal densitometry provides a quantitative means of assessing stromal transparency [4], while rotating Scheimpflug imaging enables objective evaluation of corneal haze [5, 6]. In this study, we aimed to characterize postoperative changes in corneal haze following CXL by quantifying densitometry values across specific stromal regions and to explore their potential correlations with intermediate-term visual acuity, topography, and pachymetry outcomes.

METHODS

This retrospective study included eyes with progressive keratoconus that underwent CXL at the Cornea Division, Department of Ophthalmology, Dokuz Eylul University Hospital, Izmir, Turkiye, between February 2016 and February 2020. Approval for the study was obtained from the institutional ethics committee (approval number: 2021/20–20). Written informed consent was obtained from all participants before surgery in accordance with institutional and regulatory guidelines. The study adhered to the tenets of the Declaration of Helsinki.

Eyes of patients with progressive keratoconus who were scheduled for CXL were included. Disease progression was defined [7, 8] as the presence of one or both of the following within the preceding 24 months: (1) a documented decrease in visual acuity associated with increased irregular astigmatism, or (2) an increase in the steepest keratometry (K_s) value or astigmatism exceeding 1.0 diopter (D) on manifest refraction. No upper or lower keratometry limit was applied as an inclusion criterion. Exclusion criteria were comorbid ocular disease, clinically significant corneal scarring, a minimum corneal thickness < 375 μm [8, 9], a history of chemical ocular injury, or a systemic condition potentially impairing epithelial healing.

All patients underwent a complete ocular examination, including manifest refraction, measurement of corrected distance visual acuity (CDVA) using a Snellen chart at 6 m under standardized illumination (Nidek Co., Ltd., Gamagori, Aichi, Japan), detailed slit-lamp biomicroscopy (Topcon SL-D2; Topcon Corporation, Tokyo, Japan) examination, and dilated fundus examination under slit-lamp with a non-contact +90 D lens (Volk Optical, Inc., Mentor, OH, USA). Corneal tomography, topography, and pachymetry were performed using a rotating Scheimpflug camera (Pentacam, Oculus Optikgerate GmbH, Wetzlar, Germany). Contact lens wearers were instructed to discontinue lens wear before imaging for at least 3 days for soft contact lenses, ≥ 1 week for soft extended-wear lenses, and ≥ 2 weeks for soft toric or rigid gas-permeable lenses.

All procedures were performed by the same corneal surgeon (C.A.U.) using an accelerated CXL protocol with a treatment duration of 10 min [10]. After topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine, Alcon Pharmaceuticals, USA), a central 8.5-mm epithelial debridement was performed using a blunt hockey knife. A 0.1% riboflavin solution (Medio Cross D; Peschke Meditrade GmbH, Huenenberg, Switzerland) was instilled every 2 min for 20 min. UV-A irradiation at 365 nm was then applied for 10 min at an irradiance of 9 mW/cm², delivering a total energy dose of 5.4 J/cm². Riboflavin instillation was continued every 2 min during irradiation. A therapeutic soft contact lens was applied at the conclusion of the procedure.

Postoperative examinations were performed at 1 day, 1 week, 1 month, 3 months, and then at 6 months intervals. The postoperative regimen included topical ofloxacin 0.3% (Exocin®, Allergan Inc., Irvine, CA, USA) and 0.1% fluorometholone (FML®, Allergan Inc., Irvine, CA, USA) four times daily, along with preservative-free artificial tears containing 0.15% sodium hyaluronate (EyeStil, SIFI S.P.A., Turkiye). The contact lens was removed on postoperative day 3 once epithelial healing was confirmed, and topical antibiotics were discontinued thereafter. Topical corticosteroids were tapered over 3 weeks, and artificial tears were continued as needed.

Corneal densitometry was measured using Pentacam HR imaging (Oculus Inc., Wetzlar, Germany) [11]. The device quantifies stromal light backscatter in grayscale units (GSUs) ranging from 0 (maximum transparency) to 100 (maximum opacity) [12]. Measurements were obtained at three stromal depths (anterior, mid-stromal, posterior) across four concentric annular zones (0.0–2.0, 2.0–6.0, 6.0–10.0, and 10.0–12.0 mm), along with the total value for each zone and the overall total corneal densitometry value [11–13]. All scans were reviewed to ensure optimal image quality according to manufacturer-defined quality control parameters.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Normality of data distribution was evaluated with the Shapiro–Wilk test and Q–Q plot inspection. As CDVA and densitometry data were not normally distributed, continuous variables were summarized as median (interquartile range [IQR]). Pre- to postoperative comparisons were conducted using the Wilcoxon signed-rank test. When three or more timepoints were being analyzed, the Friedman test with Dunn-Bonferroni post hoc comparisons was used. Correlations between changes in densitometry and visual, pachymetry, or keratometry outcomes were examined using Spearman's rank correlation coefficient.

For analyses involving multiple annular zones or stromal layers, *P*-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method. All statistical tests were two-sided, and a *P*-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 24 eyes from 24 patients with progressive keratoconus were included in the analysis. Median (IQR) age of participants was 21.9 (8.5) years (range 12–35), and the majority were male (n = 19; 79.2%) (Table 1). All eyes showed complete epithelial closure by postoperative day 3, and there were no intraoperative or postoperative complications. All patients attended each scheduled follow-up visit during the six-month period.

Table 1 summarizes the baseline demographic characteristics of the study population and compares the baseline and six-month postoperative functional, topography, and pachymetry parameters. At six months following CXL a significant reduction was observed in the flat keratometry (K_f) reading, central corneal thickness, (CCT) and thinnest point pachymetry (TPP), accompanied by a significant improvement in CDVA (all $P < 0.05$). Changes in other parameters were not statistically significant (all $P > 0.05$; Table 1). Similarly, compared with baseline a significant improvement in median (IQR, range) CDVA [0.46 (0.18, 0.18–0.9) decimal] was observed at one month postoperatively ($P = 0.01$). Maximum corneal astigmatism decreased from 7.7 D at baseline to 5.7 D at six months post-CXL, although this change did not reach statistical significance ($P = 0.30$).

Table 1. Baseline demographic characteristics and comparison of baseline and six-month postoperative functional, topography, and pachymetry parameters

Variables	Baseline Value	At 6-month	*P*-value
Age (y), Median ± IQR (Range)	**21.9 ± 8.5 (12 to 35)**	**-**	**-**
Sex (Male / Female), n (%)	**19 (79.2) / 5 (20.8)**	**-**	**-**
SEQ (D), Median ± IQR (Range)	**- 5.33 ± 3.62 (- 18.3 to 1.0)**	**- 5.79 ± 4.95 (- 20.1 to 0)**	**0.2**
K_f (D), Median ± IQR (Range)	**46.59 ± 3.74 (38.7 to 55.0)**	**45.76 ± 4.15 (36.9 to 54.4)**	**0.02**
K_s (D), Median ± IQR (Range)	**49.56 ± 3.86 (41.2 to 57.1)**	**50.32 ± 4.45 (39.2 to 58.7)**	**0.54**
K_{avg} (D), Median ± IQR (Range)	**47.75 ± 3.80 (39.9 to 56.0)**	**47.97 ± 4.19 (38 to 56.5)**	**0.81**
CCT (µm), Median ± IQR (Range)	**467.29 ± 37.74 (416 to 543)**	**439.58 ± 47.45 (341 to 515)**	**0.003**
TPP (µm), Median ± IQR (Range)	**454.54 ± 37.8 (383 to 527)**	**423.47 ± 57.2 (256 to 503)**	**0.01**
CDVA (decimal), Median ± IQR (Range)	**0.29 ± 0.24 (0.01 to 0.9)**	**0.49 ± 0.16 (0.28 to 0.9)**	**< 0.001**

Abbreviations: IQR, interquartile range; D, diopter; SEQ, spherical equivalent; K_f, flattest simulated keratometric reading; K_s, steepest simulated keratometric reading; K_{avg}, average simulated keratometric reading; CCT, central cornea thickness; TPP, thinnest point pachymetry; CDVA, corrected distance visual acuity. Note: *P*-values < 0.05 are shown in bold.

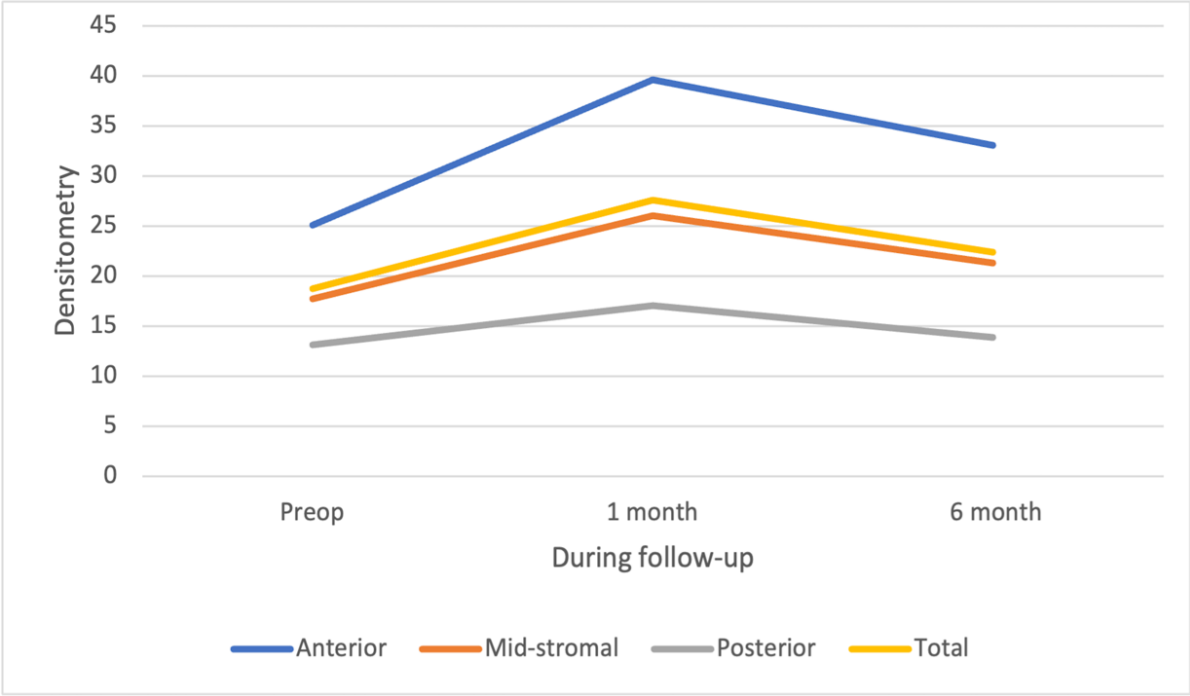

Figure 1. Longitudinal changes in corneal densitometry (grayscale units) within the anterior, mid-stromal, and posterior layers of the 0.0–2.0 mm zone, along with the corresponding total value, measured preoperatively and at one and six months after corneal collagen cross-linking (CXL).

Table 2. Changes in corneal densitometry over the six-month follow-up period after corneal collagen cross-linking across stromal depths and annular zones

Variable	Preoperative, Median (IQR)	1-month post-op, Median (IQR)	6-month post-op, Median (IQR)	Pairwise comparisons			
				P_1	P_2	P_3	P_4
CD anterior 0.0–2.0 mm (GSU)	25.11 (2.38)	39.61 (10.72)	33.09 (8.10)	**< 0.001**	**< 0.001**	**0.002**	**0.007**
CD mid-stromal 0.0–2.0 mm (GSU)	17.72 (1.22)	26.06 (6.33)	21.30 (4.53)	**< 0.001**	**< 0.001**	**0.005**	**< 0.001**
CD posterior 0.0–2.0 mm (GSU)	13.12 (1.11)	17.06 (4.01)	13.87 (2.07)	**< 0.001**	**< 0.001**	0.19	**< 0.001**
CD total 0.0–2.0 mm (GSU)	18.65 (1.33)	27.57 (6.47)	22.76 (4.71)	**< 0.001**	**< 0.001**	**0.003**	**< 0.001**
CD anterior 2.0–6.0 mm (GSU)	21.57 (1.85)	31.00 (6.09)	25.13 (4.94)	**< 0.001**	**< 0.001**	**0.003**	**< 0.001**
CD mid-stromal 2.0–6.0 mm (GSU)	15.46 (1.01)	20.78 (4.12)	16.78 (2.74)	**< 0.001**	**< 0.001**	0.059	**< 0.001**
CD posterior 2.0–6.0 mm (GSU)	12.21 (0.83)	14.73 (3.55)	12.45 (1.49)	**< 0.001**	**< 0.001**	0.46	**0.001**
CD total 2.0–6.0 mm (GSU)	16.42 (1.08)	22.16 (4.13)	17.92 (3.20)	**< 0.001**	**< 0.001**	0.067	**< 0.001**
CD anterior 6.0–10.0 mm (GSU)	20.65 (5.37)	24.06 (5.90)	20.99 (5.58)	**< 0.001**	**< 0.001**	0.74	**< 0.001**
CD mid-stromal 6.0–10.0 mm (GSU)	15.77 (4.17)	17.42 (4.52)	15.77 (4.37)	**0.04**	**0.002**	0.83	**0.005**
CD posterior 6.0–10.0 mm (GSU)	12.31 (1.90)	13.36 (2.96)	12.37 (2.38)	0.60	-	-	-
CD total 6.0–10.0 mm (GSU)	16.25 (3.71)	18.28 (4.32)	16.38 (3.99)	**< 0.001**	**< 0.001**	0.88	**0.003**
CD anterior 10.0–12.0 mm (GSU)	30.83 (13.03)	31.92 (13.54)	31.44 (13.31)	0.84	-	-	-
CD mid-stromal 10.0–12.0 mm (GSU)	23.77 (8.83)	25.60 (11.29)	23.49 (8.92)	0.70	-	-	-
CD posterior 10.0–12.0 mm (GSU)	17.63 (4.68)	19.43 (6.86)	17.41 (5.23)	0.85	-	-	-
CD total 10.0–12.0 mm (GSU)	24.06 (8.53)	25.65 (10.23)	24.11 (8.81)	0.98	-	-	-

Abbreviations: Post-op, postoperative; CD, corneal densitometry; mm, millimeters; GSU, grayscale units. Note: *P*-values < 0.05 are shown in bold; P_1 compares the three time points (preoperative, one-month postoperative, and six-month postoperative) using the Friedman test; P_2, P_3, and P_4 denote *P*-values derived from pairwise comparisons using the Dunn–Bonferroni post hoc test, where P_2 compares preoperative values with one-month postoperative values, P_3 compares preoperative values with six-month postoperative values, and P_4 compares one-month with six-month postoperative values.

Table 2 summarizes the changes in corneal densitometry over the six-month follow-up period across three stromal depths and four concentric annular zones, along with the total value for each zone. Figure 1 illustrates the longitudinal variation in corneal densitometry within the 0.0–2.0 mm zone across the same time-points.

A significant overall trend was observed in corneal densitometry changes across all three stromal depths within the 0.0–2.0 mm to 6.0–10.0 mm concentric annular zones and their corresponding total values, and across anterior and mid-stromal depths within the 6.0–10.0 mm zone and their corresponding total values (all $P < 0.05$). Densitometry values showed an initial increase at one month postoperatively, followed by a gradual decline up to six months after CXL. Pairwise comparisons evidenced a significant increase in densitometry at one month compared with baseline across all stromal depths and zones, showing a significant trend (all $P < 0.05$). This increase was followed by a significant decrease at six months compared with one month (all $P < 0.05$), although mean values remained higher than baseline. When comparing six-month values to baseline, a significant reduction in densitometry persisted at the anterior and mid-stromal depths, as well as in the total densitometry value of the 0.0–2.0 mm zone and the anterior depth of the 2.0–6.0 mm zone (all $P < 0.05$). No significant trend was identified at the posterior stromal depth within the 6.0–10.0 mm zone, nor at any stromal depth or total value within the 10.0–12.0 mm zone (all $P > 0.05$) (Table 2).

Comprehensive correlation data are presented in Table 3. Flat keratometry (Kf) decreased significantly at six months compared with baseline ($P < 0.05$) (Table 1). The magnitude of this reduction (ΔKf = preoperative Kf − 6-month Kf) was positively moderately correlated with densitometry in the mid-stromal 0.0–2.0 mm zone and the total cornea (r = + 0.427, P = 0.038; r = + 0.442, P = 0.031, respectively). In contrast, the absolute 6-month keratometry values (Kf, Ks, or Kavg) showed no significant correlations with densitometry at any stromal depth, annular zone, or for the total value (all $P > 0.05$) (Table 3).

CCT and TPP were both significantly reduced at six months compared with baseline (both $P < 0.05$) (Table 1). Lower CCT at six months was significantly moderately or strongly inversely correlated with higher densitometry values in the anterior and mid-stromal depths of the 0.0–2.0 mm annulus, as well as with total densitometry value of the 0.0–2.0 mm zone (all $P < 0.05$) (Table 3). Similarly, lower TPP at six months showed a significant moderate or strong inverse correlation with higher densitometry values across all three stromal depths and with total densitometry value of the 0.0–2.0 mm zone (all $P < 0.05$) (Table 3). Baseline CDVA showed a significant inverse moderate correlation with preoperative anterior 0.0–2.0 mm densitometry (r = - 0.50, P = 0.02). CDVA improved significantly from baseline to one month (P = 0.01) and from baseline to six months ($P < 0.001$), while no significant difference was found between the one- and six-month visits ($P > 0.05$). At one month, CDVA demonstrated a significant inverse moderate correlation with densitometry in the anterior (r = - 0.47, P = 0.003) and mid-stromal (r = - 0.58, P = 0.006) depths of the 0.0–2.0 mm zone, and in the anterior depth of the 2.0–6.0 mm zone (r = - 0.45, P = 0.045). No significant correlations were detected at other depths or zones (all $P > 0.05$) at this time point. At six months post-CXL, no significant correlation was observed between CDVA and densitometry at any stromal depth, annular zone, or total value (all $P > 0.05$) (Table 3).

Table 3. Correlations between corneal densitometry values and functional, tomography, and pachymetry parameters at the six-month visit after corneal collagen cross-linking across stromal depths and annular zones

Variable	CDVA	Kf	Ks	Kavg	CCT	TPP
CD anterior 0.0–2.0 mm (GSU)	*P*-value= 0.89 r-value= - 0.33	*P*-value= 0.33 r-value= - 0.24	*P*-value= 0.27 r-value= - 0.29	*P*-value= 0.2 r-value= - 0.33	***P*-value= 0.029** **r-value= - 0.56**	***P*-value= 0.02** **r-value= - 0.58**
CD mid-stromal 0.0–2.0 mm (GSU)	*P*-value= 0.69 r-value= + 0.1	*P*-value= 0.18 r-value= - 0.34	*P*-value= 0.24 r-value= - 0.30	*P*-value= 0.13 r-value= - 0.39	***P*-value= 0.006** **r-value= - 0.66**	***P*-value= 0.003** **r-value= - 0.71**
CD posterior 0.0–2.0 mm (GSU)	*P*-value= 0.7 r-value= + 0.09	*P*-value= 0.74 r-value= - 0.08	*P*-value= 0.91 r-value= - 0.02	*P*-value= 0.68 r-value= - 0.11	*P*-value= 0.07 r-value= - 0.46	***P*-value= 0.04** **r-value= - 0.52**
CD total 0.0–2.0 mm (GSU)	*P*-value= 0.98 r-value= - 0.005	*P*-value= 0.35 r-value= - 0.24	*P*-value= 0.4 r-value= - 0.22	*P*-value= 0.26 r-value= - 0.29	***P*-value= 0.009** **r-value= - 0.64**	***P*-value= 0.004** **r-value= - 0.69**
CD anterior 2.0–6.0 mm (GSU)	*P*-value= 0.62 r-value= + 0.12	*P*-value= 0.64 r-value= - 0.12	*P*-value= 0.45 r-value= - 0.2	*P*-value= 0.36 r-value= - 0.24	*P*-value= 0.27 r-value= - 0.3	*P*-value= 0.27 r-value= - 0.3
CD mid-stromal 2.0–6.0 mm (GSU)	*P*-value= 0.27 r-value= + 0.27	*P*-value= 0.54 r-value= - 0.16	*P*-value= 0.53 r-value= - 0.16	*P*-value= 0.38 r-value= - 0.23	*P*-value= 0.17 r-value= - 0.36	*P*-value= 0.16 r-value= - 0.37
CD posterior 2.0–6.0 mm (GSU)	*P*-value= 0.27 r-value= + 0.27	*P*-value= 0.92 r-value= - 0.02	*P*-value= 0.93 r-value= - 0.02	*P*-value= 0.77 r-value= - 0.07	*P*-value= 0.11 r-value= - 0.42	*P*-value= 0.16 r-value= - 0.37
CD total 2.0–6.0 mm (GSU)	*P*-value= 0.41 r-value= + 0.2	*P*-value= 0.38 r-value= - 0.23	*P*-value= 0.36 r-value= + 0.02	*P*-value= 0.24 r-value= - 0.31	*P*-value= 0.26 r-value= - 0.3	*P*-value= 0.26 r-value= - 0.3
CD anterior 6.0–10.0 mm (GSU)	*P*-value= 0.67 r-value= + 0.1	*P*-value= 0.98 r-value= - 0.004	*P*-value= 0.81 r-value= - 0.06	*P*-value= 0.64 r-value= - 0.12	*P*-value= 0.99 r-value= 0.0	*P*-value= 0.77 r-value= + 0.08
CD mid-stromal 6.0–10.0 mm (GSU)	*P*-value= 0.58 r-value= + 0.13	*P*-value= 0.9 r-value= + 0.03	*P*-value= 0.86 r-value= + 0.04	*P*-value= 0.91 r-value= - 0.03	*P*-value= 0.67 r-value= + 0.11	*P*-value= 0.51 r-value= + 0.18
CD posterior 6.0–10.0 mm (GSU)	*P*-value= 0.25 r-value= + 0.28	*P*-value= 0.9 r-value= + 0.02	*P*-value= 0.88 r-value= + 0.04	*P*-value= 0.88 r-value= - 0.03	*P*-value= 0.9 r-value= + 0.03	*P*-value= 0.82 r-value= + 0.06
CD total 6.0–10.0 mm (GSU)	*P*-value= 0.58 r-value= + 0.13	*P*-value= 0.8 r-value= + 0.06	*P*-value= 0.85 r-value= + 0.05	*P*-value= 0.94 r-value= - 0.01	*P*-value= 0.76 r-value= + 0.08	*P*-value= 0.61 r-value= + 0.14
CD anterior 10.0–12.0 mm (GSU)	*P*-value= 0.69 r-value= - 0.1	*P*-value= 0.9 r-value= + 0.02	*P*-value= 0.81 r-value= - 0.06	*P*-value= 0.88 r-value= - 0.04	*P*-value= 0.73 r-value= + 0.09	*P*-value= 0.49 r-value= + 0.18
CD mid-stromal 10.0–12.0 mm (GSU)	*P*-value= 0.9 r-value= - 0.03	*P*-value= 0.55 r-value= + 0.16	*P*-value= 0.82 r-value= + 0.05	*P*-value= 0.75 r-value= + 0.08	*P*-value= 0.61 r-value= + 0.14	*P*-value= 0.45 r-value= + 0.2
CD posterior 10.0–12.0 mm (GSU)	*P*-value= 0.68 r-value= + 0.1	*P*-value= 0.35 r-value= + 0.24	*P*-value= 0.54 r-value= + 0.16	*P*-value= 0.52 r-value= + 0.17	*P*-value= 0.7 r-value= - 0.1	*P*-value= 0.86 r-value= - 0.04
CD total 10.0–12.0 mm (GSU)	*P*-value= 0.95 r-value= + 0.01	*P*-value= 0.65 r-value= + 0.12	*P*-value= 0.94 r-value= + 0.01	*P*-value= 0.87 r-value= + 0.04	*P*-value= 0.5 r-value= + 0.15	*P*-value= 0.42 r-value= + 0.22
CD total anterior (GSU)	*P*-value= 0.76 r-value= + 0.07	*P*-value= 0.48 r-value= - 0.18	*P*-value= 0.29 r-value= - 0.28	*P*-value= 0.24 r-value= - 0.3	*P*-value= 0.53 r-value= - 0.1	*P*-value= 0.59 r-value= - 0.15
CD total mid-stromal (GSU)	*P*-value= 0.64 r-value= + 0.1	*P*-value= 0.54 r-value= - 0.16	*P*-value= 0.43 r-value= - 0.2	*P*-value= 0.29 r-value= - 0.27	*P*-value= 0.6 r-value= - 0.1	*P*-value= 0.68 r-value= - 0.11
CD total posterior (GSU)	*P*-value= 0.14 r-value= + 0.35	*P*-value= 0.8 r-value= - 0.06	*P*-value= 0.68 r-value= - 0.11	*P*-value= 0.53 r-value= - 0.16	*P*-value= 0.64 r-value= - 0.1	*P*-value= 0.72 r-value= - 0.09
CD total (GSU)	*P*-value= 0.73 r-value= + 0.08	*P*-value= 0.55 r-value= - 0.16	*P*-value= 0.39 r-value= - 0.23	*P*-value= 0.27 r-value= - 0.29	*P*-value= 0.57 r-value= - 0.15	*P*-value= 0.67 r-value= - 0.11

Abbreviations: CDVA, corrected distance visual acuity; K, keratometry reading; CCT, central corneal thickness; TPP, thinnest point pachymetry; CD, corneal densitometry. *P*-values < 0.05 are shown in bold; "r" values represent correlation coefficients derived from the Spearman rank correlation test.

DISSCUSSION

A total of 24 eyes with progressive keratoconus were followed for six months after epithelium-off CXL. All patients completed follow-up, achieving full epithelial healing by day 3, and none experienced complications. Significant postoperative improvements included higher CDVA and reductions in K_f, CCT, and TPP. Corneal densitometry increased at one month and declined by six months, remaining above baseline with significant trends across all three stromal depths in the central zones. Densitometry demonstrated a moderate inverse correlation with CDVA at one month but no association at six months. The magnitude of K_f reduction showed a moderate positive correlation with densitometry in the central 0.0–2.0 mm zone, whereas absolute six-month keratometric values were not correlated with densitometry at any depth or zone. At six months, both CCT and TPP exhibited significant moderate-to-strong correlations with densitometry in the central 0.0–2.0 mm zone.

Although CXL is considered a safe and effective method to halt keratoconus progression [14], transient anterior stromal haze is common and typically resolves without requiring treatment [15]. Preoperative densitometry has also been identified as a predictor of postoperative increases in corneal backscatter and scar formation [16]. These factors contextualize our early postoperative densitometry findings and their clinical relevance.

Our densitometry results align closely with the temporal pattern described by Ziaei et al. [17]. In both their study and ours, an early, transient increase in corneal backscatter was observed at one month after CXL, followed by a decline at month 6. Ziaei et al. [17] report that continuous epithelium-off accelerated CXL (c-ACXL) produced a significant rise in total

densitometry at 1 and 3 months with return to baseline by month 6 [17]; similarly, we observed a significant increase in densitometry at one month and a significant decrease from one to six months. Thus, the broad temporal course—early haze peaking within the first month and substantial resolution by six months—is concordant between the two studies. The pattern and spatial distribution of long-term densitometric change differed as Ziaei et al. [17] reported stable densitometry values until final follow-up beyond six months for c-ACXL, whereas in our cohort six-month values were significantly reduced compared with baseline at the anterior and mid-stromal depths, as well as in the total densitometry value of the 0.0–2.0 mm zone and the anterior depth of the 2.0–6.0 mm zone. They summarized total layer densitometry values over the entire 0.0–12.0 mm annular diameter, while we report depth-resolved and zone-specific values (0.0–2.0, 2.0–6.0, 6.0–10.0, and 10.0–12.0 mm), which can uncover localized central changes that may be masked by whole-cornea averaging. Differences in patient demographics (age range of Ziaei et al.'s participants 14–42 years [17] and ours 12–35 years), riboflavin formulation, and epithelial removal diameter (Ziaei et al. used an 8.0-mm debridement [17] and we used an 8.5-mm debridement) may also modulate both magnitude and spatial pattern of densitometry change.

The two studies likewise provide complementary insights regarding structure-function relationships. Ziaei et al. [17] found that greater early corneal haze at one month after epithelium-off continuous CXL was associated with steeper preoperative keratometry and with eyes that experienced greater flattening at 24 months [17]. In our series, baseline CDVA showed a significant, moderately inverse correlation with preoperative anterior 0.0–2.0 mm densitometry. At one month, CDVA demonstrated significant moderate inverse correlations with densitometry in the anterior and mid-stromal depths of the 0.0–2.0 mm zone, as well as the anterior depth of the 2.0–6.0 mm zone. By six months post-CXL no significant correlations were observed between CDVA and densitometry at any stromal depth, annular zone, or for the total value. Although the magnitude of K_f reduction showed a moderate positive correlation with mid-stromal 0.0–2.0 mm and total corneal densitometry, absolute six-month keratometry values did not correlate with densitometry values. In contrast, six-month pachymetric measures demonstrated significant moderate-to-strong inverse correlations with higher densitometry values in the 0.0–2.0 mm zone. These findings suggest that biomechanical and anatomic factors could influence the degree of early stromal backscatter, and early densitometry increases do not necessarily predict persistent visual impairment, as significant CDVA improvement was observed by six months after CXL.

Clinically, the concordance between studies that epithelium-off accelerated CXL commonly induces early postoperative haze—most marked within the first month—and that this largely resolves by six months [17] is reassuring and supports current counseling points for patients undergoing epithelium-off protocols. The depth- and zone-specific reductions in central densitometry observed in our cohort at six months merit further investigation; they could reflect long-term stromal remodeling or compaction after successful cross-linking, differences in tear-film or epithelial status at the measurement timepoints, or device-related measurement variability when comparing total [17] versus layer-resolved analyses.

Factors that temper direct comparisons include the differing study designs, as Ziaei et al. [17] performed a prospective, randomized comparison of different CXL modalities with follow-up to 24 months [17], whereas our study is a retrospective single-arm evaluation; differences in densitometry reporting, as they reported total 0.0–12.0 mm densitometry values [17] versus layer- and zone-specific metrics in the current study; and variability in sample size and baseline disease characteristics. Future studies that standardize imaging protocols, stratify by baseline keratometry and pachymetry values, and extend follow-up beyond six months are required to test effects of these apparent differences and to determine whether the reduction in central densitometry values we observed represents a durable structural change.

Our results and those of Hafezi et al. [18] converge in demonstrating that CXL produces measurable tomography and densitometry changes while generally stabilizing keratoconus. Both studies observed postoperative reductions in corneal thickness and changes in densitometry following epithelium-off CXL. Hafezi et al. [18] reported a mean (SD) decrease in thinnest stromal thickness of 14.5 (21.7) μm and a small mean (SD) increase in densitometry (+2.00 [2.07] GSU) at 12 months; our cohort showed a statistically significant reduction in pachymetry measurements at six months (median CCT and TPP decreased by approximately 27.7 μm and 31.1 μm, respectively) with an early, transient increase in densitometry at one month followed by a decline to levels that in some central layers were close to baseline at six months. Thus, although both studies demonstrate early wound healing-related increases in corneal densitometry, the temporal profiles and final outcomes differ, likely reflecting variations in patient characteristics, treatment protocols, and, importantly, the methodologies used for densitometry reporting. Hafezi et al. [18] reported total anterior, central, posterior, and average densitometry values, whereas our analysis incorporated a more granular approach. In addition to reporting total anterior, mid-stromal, posterior, and overall densitometry values, we quantified layer-specific densitometry values at three stromal depths, as well as total values across four concentric annular zones. This higher-resolution characterization may account for differences in the observed patterns of postoperative densitometric change.

Hafezi et al. [18] studied an ultrathin cornea population (mean age 29.1 years) with stromal thickness 214–398 μm treated with low-fluence ("sub400") protocol (3 mW/cm² with irradiation time adapted to stromal thickness), reporting outcomes to 12 months [18]. We excluded corneas < 375 μm and treated eyes using an accelerated protocol (9 mW/cm² for 10 minutes; total energy 5.4 J/cm²) in an unselected progressive-KC population (median age 21.9 years). These protocol differences may have influenced the depth and extent of cross-linking and the wound-healing response: Hafezi et al. [18] found that demarcation-

line depth had a moderate positive correlation with irradiation time. We did not measure demarcation-line depth in this series, which limits direct mechanistic comparison, but our depth-resolved densitometry analysis revealed localized central reductions of densitometry values at six months that would be obscured by global 0.0–12.0 mm averaging. Thus, Hafezi et al.'s population [18] and individualized low-fluence regimen [18], and our thicker-cornea cohort treated with a higher irradiance accelerated protocol, are not directly comparable but are complementary in defining the spectrum of CXL responses.

Hafezi et al. [18] reported flattening of keratometry value and no significant change in CDVA at 12 months, whereas we observed a significant improvement in CDVA by one and six months alongside a significant decrease in K_f reading but no consistent change in K_s or K_{avg} readings. The apparent discrepancy in visual outcomes of the two studies may reflect differences in baseline disease severity, patient age, or follow-up duration, and emphasizes that densitometry or tomography changes do not translate uniformly into short-term functional benefit across cohorts and protocols.

Hafezi et al. [18] demonstrate that individualized low-fluence CXL can safely extend treatment to ultrathin corneas with a high (90%) rate of tomographical stability at 12 months, expanding the treatable population [18]. Our findings complement this by showing that accelerated epithelium-off CXL in thicker corneas produces an initial, transient increase in corneal densitometry values without sustained detrimental effect on CDVA and, in selected central layers, may be followed by reduced densitometry at six months—a pattern that could reflect long-term stromal remodeling. However, different inclusion criteria, treatment parameters, follow-up duration, and densitometry reporting [18] limit direct comparison of outcomes. Prospective studies aiming at head-to-head comparisons with standardized imaging protocols and longer follow-up would be valuable to determine how protocol and baseline characteristics affect observed densitometry, tomography, and functional outcomes observed.

Studying 22 eyes of 22 patients with a mean (SD) age of 29.5 (10.1) years (range 15–59) diagnosed as progressive keratoconus treated with accelerated CXL of 18-mW/cm^2 irradiance for 5 minutes, Chan et al. [19] reported a markedly prolonged mean (SD) duration of detectable densitometric haze (18.2 [3.8] months in the central 0–2 mm zone and 10.9 [2.5] months in the 2–6 mm zone) and observed corneal thinning while haze was present but not after haze resolution. They further documented progressive flattening of maximum keratometry one year after haze resolution, supporting the concept of ongoing biomechanical remodeling beyond the period of clinically detectable haze [19]. In contrast, our six-month longitudinal series documented an early, pronounced increase in densitometry at one month after accelerated epithelium-off CXL followed by a significant decline by six months. At six months we observed localized reductions in anterior and mid-stromal densitometry depths and in total densitometry of the central 0.0–2.0 mm annulus relative to baseline, whereas Chan et al. [19] characterized haze as persisting substantially longer in many eyes. Several explanations account for these apparent discrepancies. First, Chan et al. [19] defined haze duration as time until densitometry returns to the preoperative value, which implies that return to baseline may occur well beyond six months in many patients; accordingly, our 6-month endpoint may be too early to capture the full temporal course in eyes whose densitometry normalizes. Second, differences in patient age and treatment parameters can materially alter the wound-healing response and the timing of densitometry normalization. Third, they reported anterior, central, posterior, and total densitometry values across only two concentric annular zones (0.0–2.0 and 2.0–6.0 mm), using these parameters to derive survival estimates of haze duration [19]. In contrast, our analysis employed depth-resolved and zone-specific densitometry across four concentric annular zones. This expanded zonal assessment may capture more comprehensive stromal changes than analyses limited to the two central zones.

Chan et al. [19] observed that maximum keratometry continued to decrease after haze resolution shows that longer-term tomography remodeling can continue after densitometry measures have normalized, suggesting that demarcation of haze is not a simple surrogate for the biomechanical endpoint [19]. Likewise, our finding that CDVA improved by one and six months despite the early densitometry increase concurs with the notion that transient haze does not necessarily predict persistent functional deficit. Additionally, we observed significant inverse correlations at six months between pachymetry parameters and central densitometry, indicating that stromal compaction or remodeling may be reflected in both pachymetry and densitometry metrics—an observation compatible with Chan et al.'s report of corneal thinning while haze was present [19]. Clinical outcomes of both studies [19] indicate that clinicians should anticipate heterogeneous temporal responses after CXL, whereby some patients may exhibit prolonged detectable haze extending beyond six months and others may evidence densitometry recovery by six months. These differences have practical implications for patient counseling and timing of outcome assessment. Finally, prospective studies that have standardized imaging protocols, quantify baseline severity, record exact CXL parameters, and follow patients beyond 12–24 months are required to determine which factors predict prolonged haze, persistent densitometry elevation, or durable tomography flattening.

The biophysical insights presented by Kamaev et al. [20] offer an important mechanistic framework for interpreting the temporal densitometry and tomography changes observed in our clinical series. Their *ex vivo* modeling of riboflavin-mediated CXL [20] established that the photochemical kinetics of the reaction are strongly governed by oxygen diffusion and consumption within the corneal stroma. Specifically, they showed a rapid depletion of intrastromal oxygen immediately after UV-A exposure, with the rate and extent of depletion modulated by UV-A irradiance and temperature [20]. Theoretical and experimental findings from their study suggested that Type I (radical-mediated) mechanisms dominate under oxygen-limited conditions, whereas Type II (oxygen-dependent) reactions prevail during the initial phases when oxygen availability is higher [20]. Our longitudinal *in vivo* observations align indirectly with these mechanistic principles, as reflected in the temporal pattern

of corneal densitometry and tomography remodeling following standard epithelium-off accelerated CXL. The early postoperative increase in densitometry at one month in our cohort likely reflects stromal compaction and collagen photoproduct formation during the phase dominated by radical-mediated cross-links in the oxygen-depleted microenvironment described by Kamaev et al. [20], while the subsequent reduction in densitometry and partial restoration of optical clarity by six months is consistent with gradual normalization of stromal architecture as oxygen homeostasis and keratocyte repopulation occur. Moreover, our finding of a significant inverse correlation between central pachymetry parameters and densitometry values supports the notion that CXL-induced structural reorganization, and not merely transient edema, underlies the observed optical backscatter changes. While Kamaev et al. [20] conducted their investigation in an *ex vivo* porcine model focused on photochemical kinetics rather than clinical outcomes, their work provides the fundamental explanation [20] for the temporal and spatial variations observed in our human cohort. Our results thus represent the clinical manifestation of the biochemical dynamics they described: rapid oxygen consumption initiating radical-driven collagen cross-linking, followed by stromal remodeling that manifests as transient densitometry elevation and subsequent optical recovery. Integrating these mechanistic insights [20] with our clinical findings reinforces the importance of oxygen kinetics in determining both the safety and efficacy of accelerated CXL protocols, highlighting that optimization of irradiance, exposure duration, and corneal oxygenation may further refine visual and structural recovery trajectories.

Pircher et al. [12] evaluated 31 eyes with progressive keratoconus from 31 patients (71.0% [n = 22] male, mean [SD] age 30 [11] years; range 18–58). Our densitometry time course broadly corroborates their observation that corneal densitometry increases early after epithelium-off CXL and peaks within the first 3 months [12]. Both series documented a marked rise in anterior-stroma densitometry at early follow-up, consistent with a short-term wound-healing response to photochemical stromal modification and highest densitometry values in the 0.0–2.0 mm zone for the entire corneal depth at all post-CXL visits. Pircher et al. [12] additionally measured forward-directed retinal light-scattering, which peaked at one month and remained modestly above the preoperative level at 12 months; this complements their densitometry data and highlights that corneal optical quality at post-CXL visits may follow a related but not identical temporal course to posterior-segment metrics. Pircher et al. [12] reported that mean densitometry in the central 0.0–2.0 mm zone remained significantly elevated at 12 months, and retinal straylight likewise remained above baseline at one year [12], whereas in our cohort densitometry increased at one month but declined by six months. Functionally, Pircher et al. [12] found no correlation between densitometry and CDVA, whereas we observed significant inverse moderate correlations between preoperative anterior 0.0–2.0 mm densitometry and baseline CDVA and between anterior and mid-stromal 0.0–2.0 mm densitometry and CDVA at one month, as well as anterior 2.0–6.0 densitometry at one month, with no such significant correlation at six months. Whereas Pircher's data suggest persisting statistically significantly elevated densitometry values in the 0.0–2.0 mm zone one year after standard Dresden protocol for CXL, our accelerated-treatment protocol demonstrated early densitometric change that significantly resolved at central annular zones by six months with concomitant CDVA recovery. Several factors likely account for these observed discrepancies. First, treatment protocols differed: Pircher et al. [12] used the Dresden protocol, whereas our series employed an accelerated epithelium-off protocol. Differences in irradiance [20, 21] and exposure dynamics affect oxygen kinetics and the balance of photochemical pathways, which in turn influence stromal microstructural changes and wound healing [21]. Second, Pircher et al. [12] extended follow-up to 12 months and quantified retinal straylight by capturing forward scatter that may remain elevated despite recovery of high-contrast CDVA [12]; our study did not measure retinal straylight and ended at six months, so persistent subtle light scatter beyond our observation window could have been missed. Third, although both studies employed Pentacam HR Scheimpflug densitometry, the analytic granularity differed substantially. Our analysis incorporated depth-resolved and zone-specific measurements across four concentric annular zones, reporting total values for each zone and demonstrating significant reductions in central anterior and mid-stromal densitometry at six months. In contrast, Pircher et al. [12] evaluated anterior, middle, and posterior stromal layers across three annular zones (0.0–2.0, 2.0–6.0, and 6.0–10.0 mm) over a longer postoperative interval. Finally, differences in age, epithelial removal diameter, treatment protocol, and sample size may further modulate both the magnitude and persistence of densitometry and straylight changes. These comparisons have practical implications. Both studies indicate that clinicians should counsel patients about early postoperative increases in corneal scatter and potential transient effects on optical quality.

Pircher et al.'s persistent straylight elevation at 12 months [12] underscores that measures of quality of vision beyond high-contrast acuity can remain affected even when CDVA recovers, which may be relevant to patient symptoms such as glare. Our finding of CDVA improvement by one and six months despite early densitometry increase suggests that transient anterior stroma backscatter does not necessarily translate into sustained visual acuity loss and may reflect reversible wound-healing processes or later stromal remodeling that can restore or even improve central transparency. The two studies are complementary, as Pircher et al. [12] emphasize the potential for prolonged forward scatter after Dresden-protocol CXL [12], while our accelerated-protocol cohort demonstrates earlier densitometry recovery and functional gain by six months. Harmonized, prospective studies that combine depth-resolved densitometry, standardized CXL parameters, formal straylight testing, and longer follow-up are needed to reconcile these differences and to determine how protocol selection, baseline morphology, and patient characteristics influence both objective scatter metrics and patient-reported quality of vision.

The temporal profile of densitometric change observed in our study is broadly consistent with the pattern described by Gupta et al. [22], who measured anterior, central, posterior, and total densitometry corneal densitometry values across four concentric annular zones (0.0–2.0, 2.0–6.0, 6.0–10.0, and 10.0–12.0 mm) and reported an early postoperative rise in anterior stromal backscatter following all three CXL modalities, with peak haze occurring within the first to three months and subsequent gradual decline toward baseline by 6–12 months. In their cohort [22], the conventional epithelium-off (standard Dresden protocol) CXL demonstrated the greatest transient increase in anterior stromal haze, whereas both contact lens-assisted and transepithelial CXL techniques produced substantially milder and shorter-lived densitometry elevations [22]. Similarly, in our series employing an accelerated epithelium-off protocol (9 mW/cm² for 10 minutes, total fluence 5.4 J/cm²), densitometry increased significantly at one month but decreased thereafter. This early peaking and recovery trajectory parallels that observed in less invasive or lower-fluence protocols reported in Gupta et al.'s comparative analysis [22].

Despite protocol differences, both investigations highlight that CXL-induced haze is a transient, self-limiting phenomenon that typically resolves within the first postoperative year. However, key distinctions emerge regarding the magnitude and clinical correlates of densitometry change. Gupta et al. [22] found no significant correlation between densitometry and CDVA across all protocols, whereas our study revealed a significant inverse moderate correlation between early postoperative (one-month) anterior and mid-stromal densitometry of the 0.0–2.0 mm zone and CDVA, suggesting a transient visual impact of early backscatter that normalizes as corneal clarity improves. Furthermore, by six months, our cohort exhibited a statistically significant improvement in CDVA despite persistent subclinical densitometry alterations in select zones, underscoring that functional recovery can precede complete stromal optical normalization.

Methodologically, the differences in irradiance profiles or treatment protocols likely underpin these variations [22]. The accelerated epithelium-off CXL treatment protocol used in our study maintains the biomechanical efficacy of standard CXL while reducing total exposure time, potentially limiting the depth and duration of photochemical reactions responsible for stromal haze formation [23-25]. In contrast, Gupta et al.'s findings [22] suggest that the traditional epithelium-off Dresden protocol induces more pronounced and sustained backscatter [22], whereas transepithelial and contact lens–assisted modifications attenuate this effect by reducing UV-A transmission. Our results align with those of Gupta et al. [22] in confirming that corneal densitometry rises transiently after CXL but largely recovers within six months. The additional finding in our cohort of a transient inverse correlation between densitometry and CDVA provides further evidence that early postoperative haze may have short-term functional consequences, but these effects are reversible as stromal remodeling progresses.

Our results are broadly concordant with several core observations reported by Csorba et al. [26], notably that CXL produces early increases in central anterior stromal backscatter and that densitometry change is most pronounced in the central 0.0–2.0 mm zone. They identified the anterior layer of the 0.0–2.0 mm ring as the single most characteristic parameter of post-CXL densitometry change (area under curve = 0.936) [26], a finding that complements our depth- and zone-resolved observation of marked anterior and mid-stromal densitometry central shifts. Both studies therefore emphasize the clinical relevance of depth-resolved, central-zone analysis rather than relying solely on total-cornea averages.

Important similarities extend to structure-function relationships. Csorba et al. [26] demonstrated that greater preoperative maximum keratometry values and larger postoperative reductions in maximum keratometry were significantly associated with greater postoperative haze formation. Moreover, generalized estimating equation analysis showed that higher postoperative densitometry adversely affected both uncorrected and best-corrected distance visual acuity, independent of preoperative maximum keratometry [26]. In our cohort we observed a moderate positive correlation between the magnitude of K_f and mid-stromal 0.0–2.0 mm and total corneal densitometry, yet absolute six-month keratometry values did not correlate with densitometry values. In contrast, six-month pachymetry measures demonstrated significant moderate-to-strong inverse correlations with higher densitometry values in the 0.0–2.0 mm zone. Csorba et al. [26] described persistent central densitometry elevation at 12 months, whereas our accelerated-protocol series demonstrated an early peak in densitometry at one month followed by a decline to six months. Correspondingly, CDVA in our cohort improved at one and six months, and—although inversely correlated with central densitometry at baseline and one month—showed no significant correlations with densitometry at six months. These discrepant outcomes likely reflect a combination of factors, including differences in follow-up duration (six months in our study versus 12 months in Csorba et al. [26]), potential differences in baseline clinical characteristics, variation in CXL protocols and energy delivery, and statistical analysis choices that diverge between the two studies. Csorba et al. [26] evaluated longitudinal changes using nonparametric Friedman tests with Bonferroni-adjusted Wilcoxon post hoc analyses, and modeled the influence of postoperative haze on visual acuity using generalized estimating equations (GEE) that adjusted for preoperative maximum keratometry [26]. In contrast, our analysis applied Benjamini-Hochberg correction for multiple comparisons and did not incorporate covariate-adjusted regression modeling. These methodological differences, particularly the inclusion of covariate adjustment in their GEE framework [26], may influence the estimated magnitude of haze effects and their apparent relationship to postoperative visual acuity outcomes.

Clinically, the two studies are complementary. Csorba et al. [26] highlight that, particularly in more advanced disease, greater tomography flattening can occur in parallel with more pronounced haze and that this haze may limit final visual acuity [26]; our data show that accelerated epithelium-off CXL can produce early, transient increases in central densitometry values without persistent deficit in CDVA by six months, and in some central layers may be associated with significant reduced

densitometry at that time point. These findings underscore the importance of depth- and zone-specific densitometry reporting, accounting for baseline keratometry and pachymetry values when interpreting post-CXL haze, and of extended follow-up, particularly in advanced cases, to fully characterize how early optical changes relate to longer-term topography and tomography remodeling and visual acuity outcome. Future prospective studies that harmonize imaging protocol and stratify by baseline severity will be required to justify these differences and to refine prognostic counseling for patients undergoing CXL.

Shetty et al. [27] and our series share important methodological commonalities that make direct comparison especially informative. Both studies evaluated outcomes after accelerated epithelium-off CXL using a 9 mW/cm² × 10-minute protocol and included densitometry and tomography assessments at six months. In both cohorts, CXL produced measurable tomographic and functional effects. Shetty et al. [27] reported reductions in keratometry indices that correlated with spherical equivalent improvement, and our study demonstrated a significant decrease in K_f at six months and an improvement in CDVA at one and six months. Thus, overall, the two reports show similar clinical efficacy for accelerated epithelium-off CXL.

Shetty et al. [27] extended the analysis to the tissue-molecular level by sampling cone epithelium and relating preoperative gene expression profiles to the magnitude of keratometry outcome. They found that a higher preoperative expression of lysyl oxidase (LOX) and a relatively lower matrix metalloproteinase 9 (MMP9) expression in cone epithelium were associated with a greater flattening response in maximum keratometry after CXL [27]. This mechanistic observation complements our imaging-based findings, as we observed an early transient increase in corneal densitometry values at one month followed by a decline to six months, and depth-resolved central densitometry at six months correlated with pachymetry parameters and the magnitude of K_f reduction. Together both studies suggest that interindividual differences in the biological substrate (e.g., baseline crosslinking enzyme activity, matrix-remodeling balance) could modulate both the extent of biomechanical stiffening and the subsequent wound-healing response that we measured as changes in densitometry, pachymetry, and keratometry parameters. Shetty et al. [27] focused on molecular predictors and used densitometry as one of several outcome measures but did not report the detailed, layer- and zone-specific densitometric time course that is central to our analysis [27]. By contrast, our study provides depth-resolved and annulus-specific densitometry trajectories (anterior, mid-stromal, posterior, and total; 0.0–2.0, 2.0–6.0, 6.0–10.0, 10.0–12.0 mm) and documents that some central anterior/mid-stromal measures decreased significantly at six months—findings that would be difficult to interpret without knowledge of the underlying tissue biology. Conversely, Shetty et al.'s epithelial gene expression data [27] offer a plausible biological explanation for why nominally similar CXL protocols produce heterogeneous tomography and optical outcomes; corneas with greater intrinsic LOX expression or lower proteolytic activity (MMP9) may be predisposed to a larger biomechanical response and potentially different wound-healing dynamics [27].

Shetty et al. [27] point to preoperative molecular markers that may predict the magnitude of keratometry response, while our depth-resolved imaging data map shows that response is expressed optically and tomographically over the first six months. These findings argue for a multimodal approach in future research: combining preoperative molecular profiling with standardized, depth-resolved Scheimpflug densitometry and extended tomography follow-up could clarify which biological factors predict greater biomechanical stiffening, more pronounced transient densitometry rise, or faster optical recovery. Such integrated studies would help advance understanding from merely identifying associations to clarifying underlying causal mechanisms, thereby informing personalized CXL protocols that optimize corneal flattening while minimizing prolonged haze.

The strengths of this study are the use of standardized imaging, and a uniform surgical technique performed by a single surgeon, allowing consistent assessment of structural and optical changes following accelerated CXL. However, its retrospective design, modest sample size, and six-month follow-up limit generalizability and the ability to characterize longer-term corneal remodeling. Additionally, the absence of a comparison group precludes direct evaluation of protocol-specific differences in densitometry dynamics. Future prospective studies with larger cohorts, extended follow-up, and comparative protocols are warranted to clarify the temporal behavior and clinical relevance of densitometric changes as a biomarker of corneal stromal response and visual acuity recovery after CXL.

CONCLUSIONS

Epithelium-off corneal accelerated CXL produced significant structural and functional improvements in progressive keratoconus over six months, including enhanced CDVA and reductions in keratometry and pachymetry parameters. Corneal densitometry exhibited a characteristic postoperative course, with an early increase followed by partial regression, while having significant correlation with visual and pachymetric changes during the early healing phase. By six months, these correlations diminished or disappeared, suggesting stabilization of both corneal clarity and visual outcomes. Overall, measuring corneal densitometry provided useful insights into stromal response and recovery following CXL treatment in progressive keratoconus. Future studies with longer follow-up and larger cohorts are warranted to refine the clinical relevance of densitometry dynamics after CXL.

ETHICAL DECLARATIONS

Ethical approval: Approval for the study was obtained from the institutional ethics committee (approval number: 2021/20–20). Written informed consent was obtained from all participants before surgery in accordance with institutional and regulatory guidelines. The study adhered to the tenets of the Declaration of Helsinki.

Conflict of interests: None.

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