Corneal Haze and Densitometry in Keratoconus after Collagen Cross-Linking by Three Different Protocols

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Abstract

Purpose: To evaluate postoperative corneal haze and corneal densitometry following three different corneal cross-linking (CXL) protocols; standard, accelerated, and trans-epithelial (TE).

Methods: The study recruited 104 eyes (53 patients) with progressive keratoconus divided into three groups: Group I were subjected to standard CXL, Group II to TE-CXL, and Group III to accelerated CXL (A-CXL) (10 mW/cm^2 for 9 min). Subjective and objective corneal haze measures were evaluated before and 3, 6, and 12 months post-CXL using slit-lamp biomicroscopy and Pentacam Sheimpflug camera.

Results: There was a significant difference in corneal densitometry between the three groups at 3 and 6 months post-CXL ($P < 0.0001$). By the 12th month, a significant statistical difference was observed only in zones (0–2 mm) and (2–6 mm) in both the anterior and the central layers. In Group I, the densitometry value of the preoperative anterior stromal layer (anterior 120 μm) was 19.42 ± 1.81. Then, it peaked at 23.12 ± 1.21 at 3 months ($P < 0.0001$), reached 19.82 ± 1.19 at 6 months ($P = 0.007$), and decreased to 19.33 ± 3.23 ($P > 0.05$) at 12 months. In Group II, the preoperative densitometry value of the anterior layer was 19.41 ± 1.21, peaked at 19.72 ± 1.12 at 3 months ($P = 0.02$), reached 19.04 ± 1.18 at 6 months ($P = 0.052$), and increased to 19.13 ± 1.37 at 12 months ($P = 0.84$). In Group III, the preoperative densitometry value of the anterior stromal layer was 19.53 ± 2.23. Then, it peaked at 24.80 ± 1.08 at 3 months ($P < 0.0001$), decreased to 21.75 ± 1.11 at 6 months ($P < 0.0001$), and reached 19.77 ± 2.26 at 12 months ($P = 0.047$). There was no significant correlation between the visual acuity changes and the total corneal densitometry.

Conclusion: The TE-CXL group showed a better and earlier recovery from the haze, while the A-CXL group showed a delay in recovering and persistent increased corneal densitometry, mainly in the anterior 120 μ.

Keywords: Accelerated, Corneal Haze, Cross-linking, Densitometry, Keratoconus

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INTRODUCTION

Since corneal collagen cross-linking (CXL) was firstly introduced at the Technical University of Dresden in Germany in the 1990s,[1] the keratoconus (KC) treatment option was radically evolved, aiming to slow disease progression and reinforce the corneal stromal tissue, thus reducing the need for keratoplasty.

Notwithstanding the favorable clinical and refractive results,[2-4] CXL–like other surgical interventions–has some early and late complications that should be taken into consideration.[5]

Following the conventional protocol, post-CXL corneal haze is a common clinical consequence with an incidence of up to 90%.[6] The exact causes of corneal haze after CXL are not obviously understood. Keratocytes apoptosis activated keratocytes, corneal lamellae remodeling,[7,8] extracellular

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matrix, associated honeycomb-lacunar edema, new CXL bonds,[9] and epithelial debridement[10,11] may robustly contribute to the post-CXL haze. The standard Dresden protocol[12] was evolved and modified in favor of shortening the overall time of the procedure or decreasing the related complications.[13,14] The current research has been designed to evaluate the post-CXL corneal haze subjectively and objectively and compare the effects of the three different CXL protocols (standard, accelerated, and trans-epithelial [TE]) on postoperative corneal transparency.

METHODS

The study was designed as a retrospective cohort study. The local Ethics Committee of Faculty of Medicine, Mansoura University approved this study (IRB: 17.02.17) which was performed in accordance with the principles of the Declaration of Helsinki. The surgical procedures in all groups were conducted by the author after the patients signed a preoperative, written consent form.

Collected data were selected from the medical records of adult patients with previously documented progressive KC who underwent CXL as a primary sole surgical intervention. The inclusion criteria included 18- to 30-year-old patients with progressive KC Grade I to III, according to the Amsler–Krumeich grading system, and a preoperative corneal thickness of 400 μm or more at the thinnest location and completed an 1-year follow-up. Patients with any previous ocular surgeries, current ocular diseases, such as vitreoretinal disorders, glaucoma, or cataract, or additional surgical intervention, such as intrastromal corneal rings, photorefractive keratectomy, or refractive procedures, were excluded from the study. KC progression was documented using two or more of the following criteria: an increase of 1.0 diopter (D) in K max readings, an increase of 1.0 D in the posterior K readings, an increase of 0.50 D or more in spherical equivalent, and a decrease in more than 2% in the pachymetry in the previous 6 months. The patients were retrospectively enrolled and listed according to three different corneal CXL strategies. Group I were subjected to standard CXL (S-CXL), Group II were subjected to TE-CXL, and Group III were subjected to accelerated CXL (A-CXL).

In Group I, the S-CXL group, the central 8 mm corneal epithelium was scraped with a surgical blade. One drop of the Riboflavin solution 0.1% (Ricrolin, Sooft, Italy) was applied to the corneal surface every 3 min for half an hour. This is followed by 30-min exposure to ultraviolet A (UVA) irradiation (370 nm/3 mW/cm²) using a UVA system (CBM X-linker, Italy). Throughout the irradiation time, the riboflavin solution was administered to the corneal surface at 2-min intervals. Finally, the ocular surface was washed well by a balanced salt solution. Then, a therapeutic contact lens was placed on the cornea until total re-epithelization.

In Group II, the TE-CXL protocol was applied. Two drops of Riboflavin (Ricrolin TE 0.1%, Sooft, Italy) were applied to the intact corneal epithelium every 5 min for 30 min without any disruption. The rest of the procedure and irradiation technique was carried out as described in Group I.

In Group III, the A-CXL group, Riboflavin (Vibex Rapid 0.1%, Avedro, USA) was applied to the corneal surface every 2 min for 10 min after the mechanical removal of the 8 mm epithelium from the central region. Then, UVA irradiation was performed for 9 min using an irradiation UVA device (CBM Vega 10 mW X-Linker, Firenze, Italy). The sequential steps that followed were the same as in Group I. Table 1 displays the parameters of UVA irradiation systems and the riboflavin solution used in the three groups.

Antibiotic eye drops (Vigamox; Alcon, Inc., USA) were given to the patients for 7 days until full epithelial healing had occurred. Then, they were replaced by combined topical steroid and antibiotic eye drops (Tobradex; Alcon, Inc., USA) for a further 3 weeks with gradual tapering. Eye lubricant drops (Refresh Tears; Allergan, Inc., USA) were prescribed for 1 month and continued for 3 months in indicated cases.

The corneal haze assessment was carried out by the author using slit-lamp biomicroscopy. Different stages and severity were classified from Grade 0 to Grade 4 as follows:[15]
- Grade 0: No haze "clear cornea"
- Grade 0.5: Minimal haze detected only by a meticulous examination with oblique illumination
- Grade 1: Haze with clear visibility of the full iris details
- Grade 2: Haze mildly obscuring the iris details
- Grade 3: Haze moderately hiding the iris and lens details
- Grade 4: Severe haze with total obstruction of the anterior chamber details.

According to the Scheimpflug principle, corneal optical densitometry was assessed (*backward light scatter*) by an add-on corneal densitometry program to the customary software of the Pentacam Scheimpflug camera (Oculus Pentacam®; Oculus Optikgerate GmbH, Wetzlar, Germany). All measurements were conducted in a dim room preoperatively and at 3 6, and 12 months after the operation. They were repeated three times in all the patients. The program automatically located the corneal apex and the densitometry map. Then, a 12-mm-diameter area around the apex was displayed. For a more elaborate analysis, the corneal densitometry values were recorded in different corneal layers and for each concentric zone. According to the device software, the values of the corneal densitometry of the whole cornea were displayed for three layers based on the depth, the anterior layer (anterior 120 μm), the posterior layer (posterior 60 μm), and the central layer without a particular thickness (between the anterior and the posterior layers). In addition, the total densitometry values of a 12-mm diameter area were exhibited in four concentric zones: 0-2 mm, 2-6 mm, 6-10 mm, and 10-12 mm. The first three zones were included in the comparison between the groups [Figure 1].

Statistical analysis
Statistical analysis was performed using IBM Statistical Package for Social Science (SPSS) software (version 20.00, SPSS,

Chicago, IL, USA). The normality of variables' distribution was tested using the Shapiro–Wilks test. A repeated-measures analysis of variance (ANOVA) test was used to analyze and compare the postoperative changes in each group at each time point. In addition, a one-way ANOVA test was used to compare the three groups. Furthermore, a linear regression test was used for correlation analyses between the best corrected visual acuity at each time point and the changes in the corneal haze after each protocol. A $P < 0.05$ was statistically significant.

RESULTS

Among 216 eyes subjected to CXL (94 in the S-CXL group, 50 in the TE-CXL group, and 72 in the A-CXL group), only 104 eyes fulfilled the inclusion criteria and were included in this study. The total included eyes were 104 of 53 patients with progressive KC. Group I included 41 eyes (21 patients), Group II included 29 eyes (15 patients), and Group III included 34 eyes (17 patients).

At the end of 1 year, the accelerated epithelial-off CXL (10 mW/cm^2 for 9 min) appeared to have similar effects to the S-CXL on slowing the progression of KC in adults while

the TE-CXL showed visual and topographic regression at 12 months to reach the preoperative values after an initial improvement. Apart from the corneal haze and densitometry, Table 2 summarizes the statistical analysis of all estimated pre and postoperative parameters in the three groups.

The analysis of the mean values of subjective corneal haze demonstrated significant differences between the three groups ($P < 0.0001$) with better results in favor of Group II. Figure 2 shows the changes in subjective corneal haze in the three groups at the follow-up time points.

During the early postoperative period (1–3 months) in Group I, the majority of the eyes (65.7%) had Grade 2 corneal haze, 20% of the eyes had Grade 3, and 14.3% had Grade 1. The corneal haze severity continued to improve until it reached somewhere near the preoperative value at 6 months with the majority having grade (0–0.5).

Three months postoperative in Group II, the majority of the eyes (74.1%) had Grade 1, (18.5%) of the eyes had Grade 2, and (7.4%) had Grade 3. By the 6th month, nearly all eyes showed clear corneas subjectively.

Table 1: The parameters of ultraviolet A irradiation systems and riboflavin solutions used in the three groups

	Group I	Group II	Group III
Surgical device	The CBM vega X linker (mono-led)	The CBM vega X linker (mono-led)	The CBM-10 mw X linker (high-emitter diode UVA light)
Irradiation power (mW/cm^2)	3	3	10
Irradiation wavelength (nm)	370	370	370
Energy dose (J/cm^2)	5.4	5.4	5.4
Irradiation time (min)	30	30	9
De-epithelialization	Epithelial-off (epithelial removal)	Epithelial-on (no epithelial removal)	Epithelial-off (epithelial removal)
Beam profile	Homogeneous flat	Homogeneous flat	Homogeneous flat
Light emission	Continuous wave	Continuous wave	Continuous wave
Irradiated area diameter (mm)	8	8	8
Riboflavin solution	Ricrolin: 0.1% riboflavin isoosmolar solution with 20% dextran - impregnation time is 15 min	Ricrolin TE: 0.1% riboflavin, slightly hypo-osmolar, with 15% dextran - with trometamol and sodium EDTA 0.01% - impregnation time is 30 min	Vibex rapid: 0.1% riboflavin, Saline with HPMC, no dextran. It has a diffusion rate of twice that of standard riboflavin
Riboflavin application	Was applied to the cornea every 3 min for 30 min. During irradiation, riboflavin solution was applied every 2 min	Was applied as two drops every 5 min for 30 min. During irradiation, riboflavin solution was applied every 2 min	Was applied every 2 min for 10 min. During irradiation, riboflavin solution was applied as one drop every 2 min to ensure saturation

Group I: Standard cross-linking, Group II: Trans-epithelial cross-linking, Group III: Accelerated cross-linking. UVA: Ultraviolet A, HPMC: Hydroxy propyl methyl cellulose, EDTA: Ethylenediaminetetraacetic acid, TE: Trans-epithelial
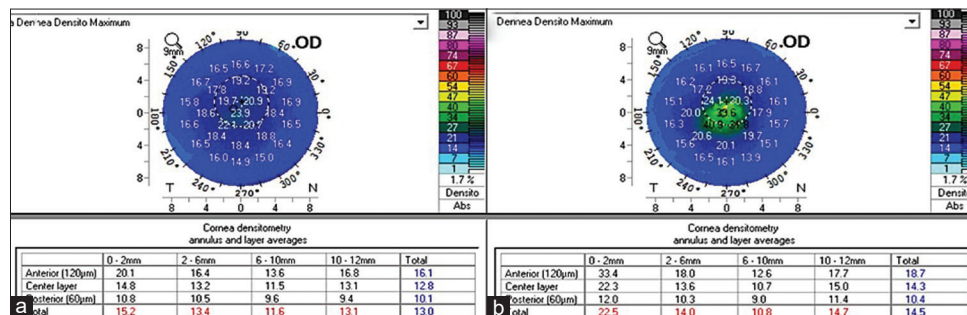

Figure 1: A demonstration of corneal densitometry measurement in a keratoconus patient before the accelerated cross-linking (a) and after 6 months (b)

At the end of 6 months in Group III, about 67.5% of the eyes had Grade 2, 20% had Grade 1, and only 12.5% had Grade 3. At the end of 1 year, 82.5% of the eyes had Grade 0.5, 10% had Grade 1, and only 7.5% had Grade 3. Figure 3 shows the slit-lamp biomicroscopic image of corneal haze in different two cases treated by the S-CXL and the A-CXL protocols.

In Group I, the mean densitometry values of all layers and zones were statistically significantly elevated at the end of 3 months compared with its baseline values ($P < 0.05$). Then,

they decreased at 6 months with statistically significant changes between the values at 6 months and baseline in the anterior layer and zones 0–2 mm and 2–6 mm of the central layer with ($P = 0.006$ and $P = 0.001$, respectively). The preoperative mean densitometry in the anterior stroma was 19.42 ± 1.81, peaked at 23.12 ± 1.21 at 3 months ($P < 0.0001$), and reached 19.82 ± 1.19 at 6 months ($P = 0.007$). At the end of 1 year, the values of corneal densitometry in all layers approached the baseline values with insignificant differences ($P > 0.05$).

In Group II, there was a significant peak in all the values of all layers at 3 months that were decreased at 6 months
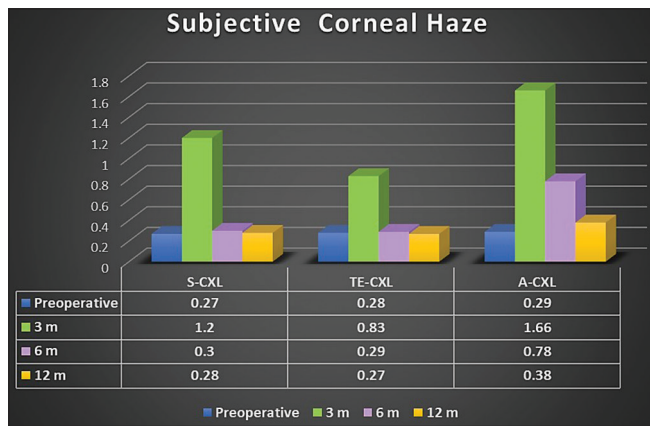

Figure 2: Means of subjective corneal haze in the three groups at the follow-up time points
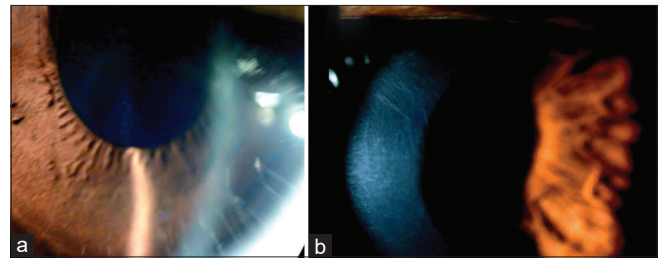

Figure 3: Slit-lamp biomicroscopic photographs of corneal haze after collagen cross-linking (CXL). Corneal haze Grade 1 in a patient treated with the standard corneal collagen CXL (Group I) 3 months after surgery (a). Corneal haze Grade 2 in a patient treated with the accelerated corneal collagen CXL (Group III) 3 months after surgery (b)

Table 2: The mean pre and post cross-linking parameters in all studied groups and its *P* values

	Group I (*n*=41 eyes)	Group II (*n*=29 eyes)	Group III (*n*=34 eyes)	*P*	*P*1	*P*2	*P*3
Age	23.44±1.98	22.22±1.44	22.55±2.15	0.141	0.056	0.162	0.597
Gender							
Males	10	12	13	0.566	0.494	0.298	0.717
Females	8	6	5				
UCVA logMAR (months)							
Preoperative	0.80±0.04	0.82±0.04	0.79±0.22	0.841	1.00	1.00	0.854
6	0.46±0.20	0.48±0.20	0.45±0.22	0.886	1.00	1.00	0.875
12	0.45±0.03	0.68±0.03	0.43±0.32	0.030*	0.042*	0.344	0.032*
BCVA logMAR (months)							
Preoperative	0.46±0.20	0.48±0.03	0.47±0.03	0.756	1.00	1.00	1.00
6	0.31±0.11	0.38±0.02	0.32±0.02	0.612	0.0728	1.00	0.681
12	0.29±0.20	0.48±0.02	0.35±0.02	0.001*	0.003*	9.32	0.003*
K max (months)							
Preoperative	48.14±0.45	48.34±0.45	47.87±0.33	0.624	1.00	0.460	0.755
6	45.60±0.45	46.18±0.45	45.47±0.25	0.771	0.847	1.00	0.899
12	45.40±0.32	47.98±0.32	45.72±0.25	<0.0001*	<0.0001*	0.842	<0.0001*
CCT (months)							
Preoperative	463.44±6.19	449.91±6.66	473±20.50	0.156	0.378	0.214	0.062
6	447.68±5.38	435.1±5.02	462±21.31	0.172	0.118	0.110	0.066
12	444.25±5.19	431.24±5.31	460±16.74	0.177	0.654	0.105	0.028*
Thinnest CT (months)							
Preoperative	439.91±6.66	435.91±6.66	448.17±32.30	0.166	0.066	0.077	0.067
6	425.11±5.02	404.1±5.02	435.50±31.20	0.212	0.847	0.085	0.051
12	420.24±5.31	400.24±5.31	434.20±31.20	0.214	1.00	0.077	0.049*

*Significant differences at ($P<0.05$). Repeated measure ANOVA and Chi-square test. *P*: Difference between 3 groups, *P*1: Difference between Group I and Group II, *P*2: Difference between Group I and Group III, *P*3: Difference between Group II and Group III. Group I: Standard CXL, Group II: Trans-epithelial CXL, Group III: Accelerated CXL. UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, K max: Maximum K reading; CCT: Central corneal thickness, CXL: Cross-linking, ANOVA: Analysis of variance

with statistically insignificant differences from the baseline values ($P > 0.05$). Throughout 12 months, the values remained insignificantly changed from the baseline values ($P > 0.05$). The preoperative mean densitometry in the anterior stroma was 19.41 ± 1.21, peaked at 19.72 ± 1.12 at 3 months ($P = 0.02$), decreased to 19.04 ± 1.18 at 6 months ($P = 0.052$), and reached 19.13 ± 1.37 at 12 months ($P = 0.84$).

In Group III, the mean corneal densitometry values remained significantly higher than the baseline values of the anterior and central layers mainly zones (0–2 mm) and (2–6 mm) with ($P < 0.05$) although they were significantly decreased at six and 12 months compared with their measurements at 3 months. The preoperative mean densitometry in the anterior stroma was 19.53 ± 2.23, peaked at 24.80 ± 1.08 at 3 months ($P < 0.0001$), decreased to 21.75 ± 1.11 at 6 months ($P < 0.0001$), and reached 19.77 ± 2.26 at 12 months ($P = 0.047$).

Figures 4 and 5 show the changes in the corneal densitometry values of the different corneal layers and zones in the three groups at the follow-up time points.

Despite an insignificant difference in corneal densitometry preoperatively, the densitometry in all stromal layers reached a peak by the end of 3 months with a significant difference between the three groups ($P < 0.0001$). By the end of 6 months, the densitometry values were decreased with a statistically significant difference between the S-CXL and the TE-CXL groups in the anterior layer; the mean densitometry values of the total anterior layer were 19.82 ± 1.19 in the S-CXL group and 19.04 ± 1.18 in the TE-CXL group ($P = 0.049$) while the total densitometry values in the central and the posterior layers showed an insignificant difference ($P = 0.051$ and 0.055, respectively). However, the densitometry readings at 6 months in the A-CXL group revealed significantly higher values than the other two groups in all layers mainly zones (0–2 and 2–6 mm) with $P < 0.0001$ [Figures 4 and 5].

By the end of 1-year, corneal densitometry readings decreased to roughly reach the preoperative values in Groups I and II with insignificant differences between them. However, the significant difference between Groups III and the other two groups was still present, predominantly in the anterior and the middle layers (0–2 and 2–6 zones). Table 3 demonstrates in detail the mean corneal densitometry values postoperatively at 12 months in all studied groups, their differences from the preoperative readings, and the P values.

For more details, Supplementary Table 1 shows the mean preoperative corneal densitometry in all studied groups, Supplementary Tables 2 and 3 show the mean postoperative corneal densitometry at 3 months and 6 months, respectively.

Corneal densitometry showed an insignificant correlation of the BCVA postoperatively at each time point in the three groups ($P > 0.05$). After 1 year, the correlation coefficients (r) were 0.021 in the S-CXL group, 0.059 in the TE-CXL group, and 0.072 in the A-CXL group. There were no serious intra or postoperative complications in any group.

DISCUSSION

In the current study, the mean values of corneal densitometry were peaked at the end of 3 months postoperatively with significant differences among the three groups. This is in agreement with a previously reported study by Alzahrani et al.[16]

Besides, there was a significant variance in the improvement of corneal haze post-CXL treatment among the three groups. The A-CXL group started to improve between 6 and 12 months, the corneal densitometry values decreased with time, drawing near, but not reaching, the baseline values. The corneal densitometry in the S-CXL group started to improve at 6 months and draw near the baseline values at 12 months while the TE-CXL group
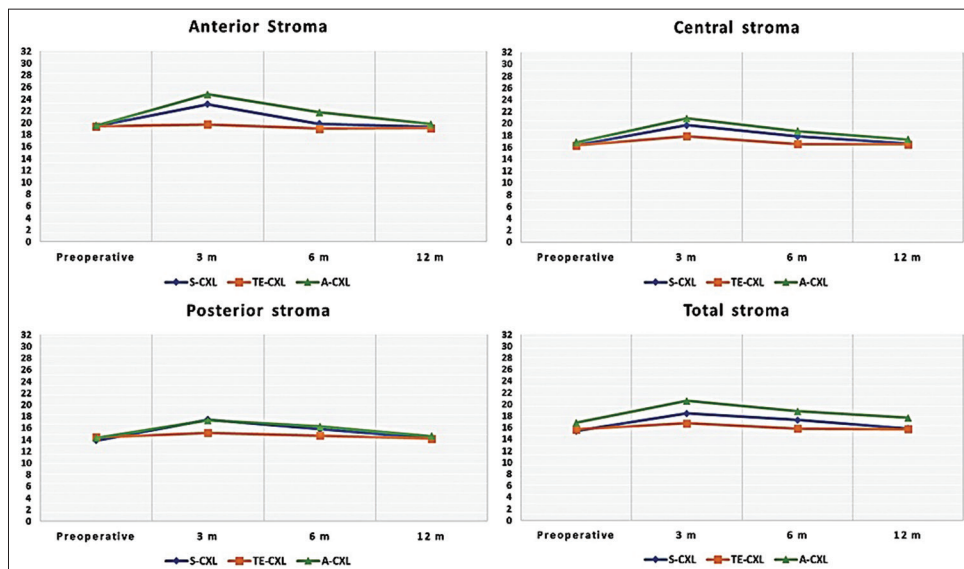

Figure 4: Corneal densitometry in the different corneal layers in the three groups at the follow-up time points
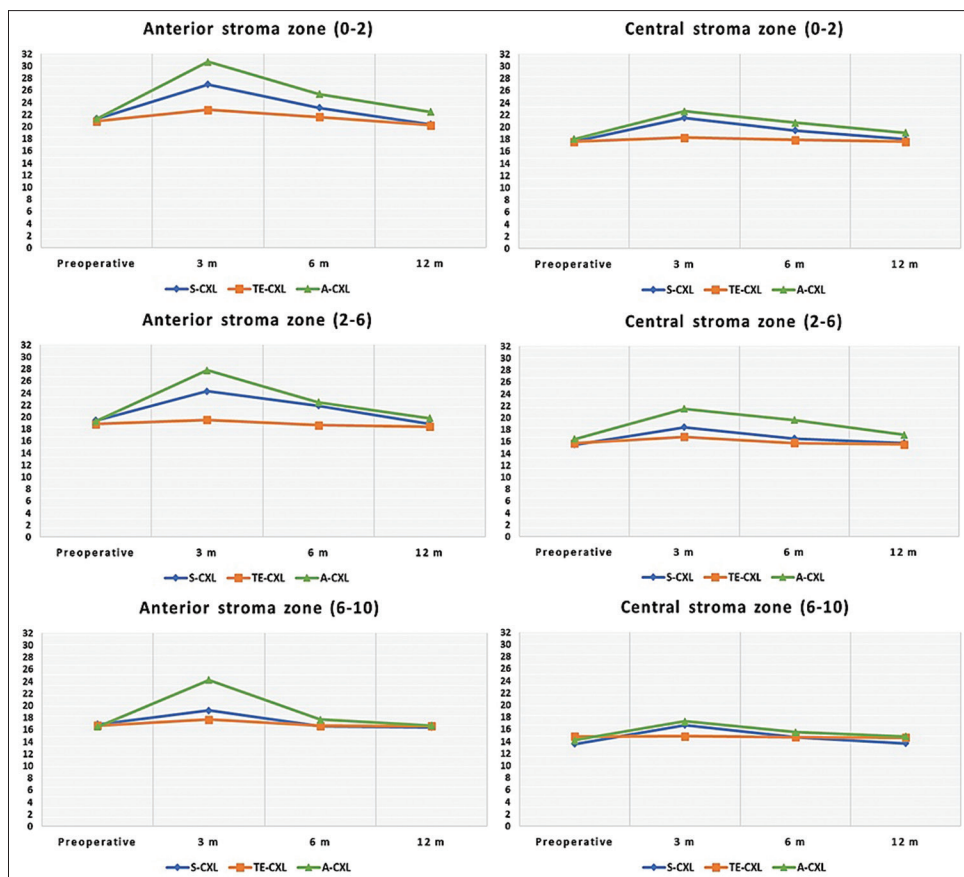
Figure 5: Corneal densitometry of the three concentric zones (anterior and central layers) at different time points

recorded a better and earlier recovery from the haze than the other two groups, it started to improve between three and 6 months and reached the preoperative values nearly by the end of 6 months. These results were consistent with the previous studies of corneal densitometry.[17-19] However, Greenstein *et al*.[6] stated that a significant decrease in densitometry and slit-lamp haze was noted between the values at 6 and 12 months after the S-CXL protocol, but they did not reach the baseline values at 1 year. Shen *et al*.[20] found that the densitometry values were significantly decreased in KC eyes at 1 year after the A-CXL protocol, but they were still higher than the values in myopic individuals. Moreover, Lai *et al*.[21] reported that, after TE-CXL, corneal haze peaked at 1 month, plateaued between 1 and 3 months, and reached baseline values between 3 and 12 months.

Since the same parameters of the UV rays were used in Groups I and II, in the author's estimation, this might be owing to two factors. The first factor is the role of the epithelium in the corneal haze path.[22] It is known that corneal epithelial injury is one of the main factors in the complex corneal wound healing process.[23] The prominent initial alteration after the epithelial injury is the keratocyte apoptosis, along with associated inflammatory reactions in the anterior corneal stroma. This triggers the production of mature myofibroblasts and promotes an unorganized extracellular matrix secretion.[24] When these

changes become settled in the anterior stroma, corneal haze becomes evident. Once myofibroblasts apoptosis is established and keratocytes occupy the anterior corneal stroma, the corneal haze recedes with time.[25] This may explain that the lesser effect the TE-CXL has, the lesser keratocyte damage there is. The second factor is riboflavin absorption behavior. Hypo-osmolar riboflavin appears to be highly unsteady with a short break-up time (90 s) compared with isotonic riboflavin (22 min). Therefore, it has limited absorption and less efficiency of penetration.[25] On the other hand, Razmjoo *et al*. stated that intact corneal epithelium had an insignificant role in decreasing corneal haze after the CXL protocol.[10]

In the present study, a considerable number of eyes in Group III required a longer time than the other two groups to get back to the baseline level of corneal haze. Some investigators had theorized that the equal efficiency of A-CXL compared to the conventional CXL[26,27] while others theorized that the conventional CXL protocol was more effective with a deeper demarcation mark.[28,29] The inverse correlation between UV ray intensity and CXL reaction depth might be in favor of the standard protocol.[30] This controversy could require further evaluation.

Since the same photon numbers interact with the collagen fibrils in different CXL protocols, it is conceivable that the current results (higher and persistent corneal density in

Table 3: The mean postoperative corneal densitometry at 12 months in all studied groups and *P* values

Corneal densitometry layer/zone (µm/mm)	Mean±SD (difference: Post-pre)			*P*	*P1*	*P2*	*P3*
	Group I (*n*=41 eyes)	Group II (*n*=29 eyes)	Group III (*n*=34 eyes)				
Anterior							
0-2	20.41±3.21 (−0.95±2)	20.28±1.93 (−0.64±0.41)	22.47±2.48 (1.14±0.23)	<0.0001*	1.000	<0.0001*	<0.0001*
2-6	18.82±2.23 (−0.62±0.28)	18.41±1.85 (−0.44±0.33)	19.82±1.66 (0.51±0.16)	0.009	1.000	0.060	0.010*
6-10	16.43±2.46 (−0.48±1.03)	16.63±2.42 (−0.07±0.69)	16.73±1.75 (0.21±0.86)	0.052	1.000	0.047	0.465
Total	19.33±3.23 (−0.09±1.42)	19.13±1.37 (−0.28±0.16)	19.77±2.26 (0.24±0.03)	0.269	1.000	0.726	0.360
Central							
0-2	17.98±1.07 (0.35±1.67)	17.61±0.96 (−0.01±0.58)	19.07±1.14 (1.04±0.038)	0.002*	1.000	0.005*	0.006*
2-6	15.76±1.20 (0.25±1.12)	15.52±1.02 (−0.21±0.87)	17.12±1.37 (0.68±0.9)	<0.0001*	1.000	0.001*	0.001*
6-10	13.71±1.14 (0.09±0.8)	14.66±1.89 (−0.17±0.41)	14.83±1.24 (0.59±0.26)	0.935	1.000	1.000	0.1000
Total	16.63±1.13 (0.3±1.09)	16.53±1.17 (0.22±0.19)	17.32±1.24 (0.47±0.17)	0.87	1.000	0.220	0.127
Posterior							
0-2	14.32±1.23 (−0.15±0.03)	14.30±1.06 (−0.04±0.34)	14.52±1.22 (−0.03±0.99)	0.739	1.000	1.000	1.000
2-6	13.28±1.13 (−0.05±0.28)	13.25±1.14 (−0.07±0.99)	14.08±1.25 (−0.04±0.97)	0.062	1.000	0.111	0.132
6-10	12.44±1.41 (0.18±0.31)	13.35±1.21 (−0.12±0.82)	12.84±1.23 (0.02±0.33)	0.435	1.000	0.870	0.730
Total	14.26±1.22 (0.39±0.93)	14.24±1.01 (−0.21±0.41)	14.66±1.42 (0.34±0.21)	0.592	1.000	1.000	0.924
Total							
0-2	17.31±1.24 (−0.09±0.49)	17.27±1.22 (−0.05±0.65)	18.29±1.34 (−0.58±0.59)	0.032	1.000	0.040	0.091
2-6	16.48±1.60 (0.25±0.74)	16.33±3.14 (0.82±0.92)	17.55±1.05 (1.19±1.15)	0.012*	1.000	0.046	0.059
6-10	14.86±1.08 (0.94±1.34)	14.58±1.95 (−0.46±0.12)	15.28±1.32 (0.76±0.99)	0.243	1.000	0.8000	0.300
Total	15.84±1.06 (0.39±1.17)	15.76±1.14 (0.04±0.17)	17.69±1.35 (0.86±1.18)	0.001*	1.000	0.004*	0.007*

*Significant differences at *P*<0.05. One-way ANOVA and post hoc tests. *P*: Difference between 3 groups, *P1*: Difference between Group I and Group II, *P2*: Difference between Group I and Group III, *P3*: Difference between Group II and Group III. Group I: Standard CXL, Group II: Trans-epithelial CXL, Group III: Accelerated CXL. ANOVA: Analysis of variance, SD: Standard deviation, CXL: Cross-linking

the A-CXL group) may be an outcome of the difference in soaking duration and the concentrations of different riboflavin solutions.[31,32] Corneal stromal saturation and absorption traits of different riboflavin solutions were evaluated by several studies.[33,34] It was reported that the riboflavin concentration during the epithelial-off CXL is about seven-fold higher in the anterior stroma compared with its concentration in the epithelial-on CXL, which is well correlated with the density of keratocytes apoptosis and the depth of the demarcation line.[35] Despite the constant homogeneous consumption of riboflavin in both the standard and the accelerated protocols, the consumption of the riboflavin solution during the S-CXL irradiation of the corneal stroma was stated to be 20% more than that achieved during the A-CXL one (consumption of riboflavin was 87% ± 2% in the S-CXL instead of 67% ±3% in the A-CXL).[36] This might explain that there is a higher concentration of the riboflavin solution (VibeX Rapid 0.1%, Avedro, USA) in the anterior corneal stroma of the A-CXL group than the riboflavin solution (Ricrolin 0.1%, Sooft, Italy) in the conventional CXL. Further investigations should be conducted on this topic to clarify the relation between the different riboflavin concentrations and the CXL efficiency as well as the corneal healing process.

Another explanation of the current results is that the substantial role of oxygen in the CXL photochemical reaction improved the polymerization outcomes. The S-CXL protocol was theorized to permit stable oxygen consumption and further re-diffusion out of the corneal tissue.[37] Theoretically, the A-CXL protocol might lead to inadequate time for oxygen diffusion. High-irradiance CXL was suggested to be the cause of reducing the oxygen diffusion capacity and increasing its consumption.[38] Currently, continuous A-CXL was used rather than pulsed CXL. Continuous epithelium-off A-CXL appears to cause more corneal haze than pulsed epithelium-off A-CXL and pulsed TE-CXL, especially in the early postoperative period.[39]

It was hypothesized that the pulsed CXL light was better in achieving sufficient oxygen diffusion required for the CXL reaction.[40,41] The reduction of the oxygen level below the certain perilous threshold will cause the tissue to return to aerobic metabolism[42] and lose the corneal tissue transparency as one of the clinical consequences that ensued from the aerobic metabolic process.[43] Hypoxia also was reported as a factor that affects cell migration and corneal wound healing.[44] This might explain the delay in recovering from the haze in Group III. This is another interesting topic for further research to reveal whether or not hypoxia associated with high-irradiance CXL affects the healing process.

It is worth mentioning here that despite the difference in the corneal haze and density between the groups, it did not affect the postoperative BCVA. There were insignificant correlations between the corneal haze or density changes and the BCVA changes at each time point. Our results supported earlier reports of a poor correlation between haze and visual acuity (VA).[6,45]

However, the study was looking at the changes in corneal haze and density as a reflection of the wound healing process after different CXL protocols rather than its effect on VA. Similarly, Bouheraoua et al.[45] found no remarkable correlations between the CXL demarcation line depth after CXL and the BCVA changes at 6 months. On the other hand, Mathews et al. stated a significant correlation between the change in corneal densitometry and the decrease in higher-order aberrations at 6 months post-CXL.[46] Larger, prospective, randomized studies may be required to study this topic.

The study included some limitations such as small sample size, retrospective design, lack of histopathological study, and absence of demarcation-line depth measures.

In conclusion, there were significant variations in corneal densitometry in response to the different CXL protocols. The A-CXL group showed a delay in recovering from the haze with persistent increased corneal densitometry, mainly in the anterior 120 μ after 1 year from the surgery. There were no significant correlations between the changes in the BCVA and the changes in the corneal densitometry over time. At the end of 1 year, the accelerated epithelial-off CXL appeared to have similar effects, such as the S-CXL protocol, in slowing the progression of KC in adults. However, the TE-CXL showed visual and topographic regression that warrants more future studies with longer follow-up.

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Conflicts of interest

There are no conflicts of interest.

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Corneal densitometry layer/zone (μm/mm)	Mean±SD			P	P1	P2	P3
	Group I (n=35 eyes)	Group II (n=34 eyes)	Group III (n=35 eyes)				
Anterior							
0-2	21.36±1.21	20.92±1.52	21.33±2.25	0.228	0.342	0.232	0.275
2-6	19.44±1.95	18.85±1.52	19.31±2.82	0.109	0.121	0.084	0.113
6-10	16.91±1.43	16.70±1.73	16.52±2.61	0.423	0.623	0.582	0.322
Total	19.42±1.81	19.41±1.21	19.53±2.23	0.769	0.925	0.814	0.822
Central							
0-2	17.63±2.74	17.62±1.54	18.03±2.52	0.332	0.985	0.167	0.134
2-6	15.51±2.32	15.73±1.89	16.44±2.27	0.424	0.617	0.182	0.144
6-10	13.62±1.94	14.83±2.30	14.24±3.53	0.515	0.142	0.477	0.810
Total	16.33±2.22	16.31±2.36	16.85±2.41	0.637	0.873	0.859	0.713
Posterior							
0-2	14.47±1.26	14.34±2.45	14.55±2.21	0.627	0.755	0.517	0.321
2-6	13.33±3.41	13.32±2.13	14.12±3.22	0.512	0.367	0.520	0.304
6-10	12.26±1.72	13.47±2.03	12.82±1.56	0.324	0.862	0.423	0.097
Total	13.87±2.15	14.45±2.42	14.32±1.21	0.381	0.573	0.523	0.171
Total							
0-2	18.21±2.73	17.32±1.87	18.87±1.93	0.443	0.304	0.764	0.212
2-6	16.23±2.34	15.51±2.22	16.36±2.20	0.334	0.142	0.824	0.134
6-10	13.92±3.42	15.04±1.83	14.52±2.31	0.265	0.098	0.103	0.416
Total	15.45±3.23	15.72±2.31	16.83±2.53	0.421	0.812	0.227	0.125

*Significant differences at *P*<0.05. One-way ANOVA and *post hoc* tests. *P*: Difference between 3 groups, *P*1: Difference between Group I and Group II, *P*2: Difference between Group I and Group III, *P*3: Difference between Group II and Group III. Group I: Standard CXL, Group II: Trans-epithelial CXL, Group III: Accelerated CXL. ANOVA: Analysis of variance, SD: Standard deviation, CXL: Cross-linking

Corneal densitometry layer/zone (μm/mm)	Mean±SD (difference: Post-pre)			P	P1	P2	P3
	Group I (n=35 eyes)	Group II (n=34 eyes)	Group III (n=35 eyes)				
Anterior							
0-2	27.02±1.95 (5.66±0.74)	22.83±1.18 (1.91±.34)	30.74±1.25 (9.41±1.0)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
2-6	24.31±1.94 (4.87±.01)	19.54±1.18 (0.69±.34)	27.83±0.98 (8.52±1.84)	<0.0001*	0.001*	<0.0001*	<0.0001*
6-10	19.21±1.95 (2.3±0.52)	17.73±1.27 (1.03±.46)	24.25±1.34 (7.73±1.27)	<0.0001*	0.004*	<0.0001*	<0.0001*
Total	23.12±1.21 (3.7±.6)	19.72±1.12 (.31±.01)	24.80±1.08 (5.27±1.15)	<0.0001*	0.004*	<0.0001*	<0.0001*
Central							
0-2	21.52±1.22 (3.89±1.53)	18.27±1.32 (.65±.22)	22.62±1.14 (4.59±1.38)	<0.0001*	0.001*	<0.0001*	<0.0001*
2-6	18.42±1.33 (2.91±.99)	16.81±1.14 (1.08±.75)	21.54±1.72 (5.1±.55)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
6-10	16.70±1.23 (3.08±.71)	14.89±1.67 (.06±.63)	17.34±1.78 (3.1±1.75)	<0.0001*	0.002*	<0.0001*	<0.0001*
Total	19.72±1.42 (3.39±.8)	17.87±1.57 (1.06±.79)	20.85±1.52 (4±.89)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Posterior							
0-2	17.50±1.85 (3.03±.59)	15.72±1.59 (1.38±.86)	18.38±1.34 (3.83±.87)	<0.0001*	0.001*	0.147	<0.0001*
2-6	16.76±1.05 (3.43±2.36)	14.58±1.34 (1.26±.79)	17.02±1.50 (2.9±1.72)	<0.0001*	<0.0001*	1.000	<0.0001*
6-10	15.82±1.53 (3.56±.19)	14.83±1.31 (1.36±.72)	15.32±1.81 (2.5±.25)	0.115	0.048*	0.788	1.00
Total	17.49±1.32 (3.62±.83)	15.23±1.85 (.78±.57)	17.33±1.33 (3.01±.12)	<0.0001*	<0.0001*	1.00	<0.0001*
Total							
0-2	21.32±1.34 (3.11±1.39)	18.02±1.39 (.7±.48)	23.89±1.33 (5.02±.6)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
2-6	19.04±1.19 (2.81±1.15)	16.53±1.16 (1.02±1.06)	21.46±1.11 (5.1±1.09)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
6-10	16.27±1.20 (2.35±2.22)	15.30±1.81 (.26±.02)	18.12±1.23 (3.6±1.08)	<0.0001*	0.058	<0.0001*	<0.0001*
Total	18.45±1.19 (3±2.04)	16.76±1.81 (1.04±.5)	20.62±1.23 (3.79±1.3)	<0.0001*	<0.0001*	<0.0001*	<0.0001*

*Significant differences at *P*<0.05. One-way ANOVA and post hoc tests. *P*: Difference between 3 groups, *P*1: Difference between Group I and Group II, *P*2: Difference between Group I and Group III, *P*3: Difference between Group II and Group III. Group I: Standard CXL, Group II: Trans-epithelial CXL, Group III: Accelerated CXL. ANOVA: Analysis of variance, SD: Standard deviation, CXL: Cross-linking

Supplementary Table 3: The mean 6 months postoperative corneal densitometry in all studied groups and its *P values*

Corneal densitometry layer/zone (*μ*m/mm)	Mean±SD (difference: Post-pre)			*P*	*P*1	*P*2	*P*3
	Group I (*n*=35 eyes)	Group II (*n*=34 eyes)	Group III (*n*=35 eyes)				
Anterior							
0–2	23.13±1.19 (1.77±0.02)	21.62±1.82 (0.7±0.3)	25.39±1.27 (4.06±0.98)	<0.0001*	0.002*	<0.0001*	<0.0001*
2–6	21.93±1.22 (2.49±0.73)	18.64±1.30 (−0.21±0.22)	22.47±0.093 (3.16±2.7)	<0.0001*	<0.0001*	0.416	<0.0001*
6–10	16.62±1.31 (−0.29±0.12)	16.66±1.15 (−0.04±0.58)	17.72±1.33 (1.2±1.28)	<0.0001*	0.045*	0.0478	<0.0001*
Total	19.82±1.19 (0.4±0.62)	19.04±1.18 (0.37±0.03)	21.75±1.11 (2.22±1.12)	<0.0001*	0.049*	<0.0001*	<0.0001*
Central							
0–2	19.44±0.69 (1.81±2.05)	17.88±1.18 (0.26±0.36)	20.72±1.23 (2.69±1.29)	<0.0001*	0.041*	<0.0001*	<0.0001*
2–6	16.51±1.19 (1±1.13)	15.77±1.18 (0.04±0.71)	19.66±1.33 (3.22±0.94)	<0.0001*	0.303	<0.0001*	<0.0001*
6–10	14.70±1.19 (1.08±0.75)	14.75±1.85 (0.08±0.45)	15.53±1.95 (1.29±1.58)	0.082	1.00	0.805	0.047*
Total	17.82±1.20 (1.49±1.02)	16.56±1.29 (0.25±1.07)	18.73±1.33 (1.88±1.08)	<0.0001*	0.051	0.048*	< 0.0001*
Posterior							
0–2	15.21±1.31 (0.74±0.05)	14.27±1.18 (0.07±1.27)	17.27±1.35 (2.72±0.86)	<0.0001*	0.058	<0.0001*	<0.0001*
2–6	15.19±1.31 (1.86±2.08)	14.31±1.31 (0.99±0.82)	16.24±1.33 (2.12±1.89)	<0.0001*	0.247	<0.0001*	<0.0001*
6–10	14.09±1.23 (1.8±0.49)	13.86±1.34 (0.39±0.69)	14.44±1.33 (1.62±0.23)	0.634	1.000	1.000	1.000
Total	15.84±1.19 (1.97±0.96)	14.75±1.31 (0.3±1.11)	16.31±1.48 (1.99±0.27)	<0.0001*	0.055	0.369	<0.0001*
Total							
0–2	19.13±1.31 (0.92±1.42)	18.36±1.14 (1.04±0.73)	20.15±1.31 (1.28±0.62)	<0.0001*	0.188	0.022*	<0.0001*
2–6	17.23±1.19 (1±1.15)	15.84±1.19 (0.33±1.03)	18.46±1.33 (2.1±0.87)	<0.0001*	0.539	0.009*	<0.0001*
6–10	14.85±1.34 (0.93±2.08)	15.45±1.27 (0.41±0.56)	16.59±1.75 (2.07±0.56)	<0.0001*	0.460	<0.0001*	0.042*
Total	17.31±1.01 (1.86±2.22)	15.83±1.41 (0.11±0.9)	18.82±1.35 (1.99±1.18)	<0.0001*	0.220	0.002*	<0.0001*

*Significant differences at *P*<0.05. One-way ANOVA and *post hoc* tests. *P*: Difference between 3 groups, *P*1: Difference between Group I and Group II, *P*2: Difference between Group I and Group III, *P*3: Difference between Group II and Group III. Group I: Standard CXL, Group II: Trans epithelial CXL, Group III: Accelerated CXL. ANOVA: Analysis of variance, SD: Standard deviation, CXL: Cross-linking