



The Study of Evaluation of Changes in Corneal Densitometry & its Effect on Visual Outcome in Patients of Keratoconus Treated with Isotonic Collagen Cross Linking Therapy in Western Part of India

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Abstract

Purpose: To evaluate the changes in preoperative and postoperative corneal densitometry and its impact on visual outcomes in keratoconus patients undergoing isotonic collagen crosslinking therapy in a Western population. This study uniquely focuses on a population in Western India, adding valuable regional data to existing research.

Methods: This prospective interventional study was conducted at Alakh Nayan Mandir Eye Institute, Udaipur, involving 50 eyes from 39 patients with progressive keratoconus treated with isotonic collagen crosslinking therapy. The study spanned from June 16, 2020, to June 16, 2021. Preoperative and postoperative assessments included uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), corneal densitometry, and slit-lamp biomicroscopy. Corneal densitometry was measured using Scheimpflug tomography (Pentacam HR, Oculus Optikgeräte GmbH) at 1, 3, and 6 months postoperatively. Statistical analysis was performed using EPI INFO Ver.7 software.

Results: The mean age of patients was 19.90 ± 4.98 years, with a nearly equal gender distribution (56% female, 44% male). Baseline mean logMAR visual acuity (UCVA) was 0.63 ± 0.32 , and mean BCVA was 0.16 ± 0.15 . At 6 months, UCVA was 0.59 ± 0.37 ($p = 0.564$) and BCVA was 0.12 ± 0.15 ($p = 0.186$). The mean Km value decreased from 49.10 ± 3.27 preoperatively to 47.81 ± 3.53 at 6 months ($p = 0.293$). Corneal pachymetry decreased significantly from 449.80 ± 43.48 to 418.96 ± 48.07 ($p < 0.001$). Corneal densitometry at 0-2 mm increased from 16.12 ± 2.08 to 21.85 ± 8.81 ($p < 0.001$), and at 2-6 mm from 13.94 ± 1.61 to 15.89 ± 5.61 ($p < 0.001$). Corneal haze peaked at 1 month postoperatively and gradually declined but remained elevated compared to baseline at 6 months.

Conclusions: Isotonic collagen crosslinking therapy in keratoconus patients resulted in significant changes in corneal densitometry and pachymetry, with a transient increase in corneal haze peaking at 1 month and gradual reduction by 6 months. Visual acuity showed stabilization postoperatively, with no significant decrease in topographic and keratometric indices. The inverse correlation between corneal pachymetry and densitometry suggests structural changes in the corneal stroma following crosslinking. This study adds unique regional data from Western India to the broader understanding of keratoconus treatment outcomes.

Keywords: Keratoconus; Densitometry; Pachymetry

Abbreviations

CXL: Corneal Collagen Crosslinking; UV: Ultraviolet; UCVA: Uncorrected Visual Acuity Examination; BCVA: Best Corrected Visual Acuity Examination; SLE: Slit-Lamp Examination; log MAR: Logarithm of the Minimum Angle of Resolution Chart.

Introduction

Keratoconus is a non-inflammatory [1], an ectatic corneal condition characterized by central or Para-central stromal thinning, apical protrusion and irregular astigmatism. The Incidence ranges between 0.3 to 2300 cases per 1,00,000 population [2]. Placido disc-based corneal topographers are commonly used for the diagnosis of Keratoconus. But, now with the advanced corneal imaging one can take 3D images of cornea with the assistance of the Scheimpflug corneal imaging camera.

Corneal collagen crosslinking was first introduced in 1990 by a research group from Dresden Technical University [3]. It has been proven that CXL is a safe and effective tool to give relative stability to the ectatic cornea [4,5]. Corneal collagen crosslinking aims at arresting the progression in a case of progressive Keratoconus [6]. Crosslinking is induced by reactive oxygen radicals formed by sensitization of riboflavin in the presence of UV rays [6]. The resulting compaction of the collagen lamellae leads to the thinning of the cornea [7]. Corneal changes after CXL occur mainly in the anterior 300 μm . These changes include an increased collagen fiber diameter, keratocyte apoptosis, changes in corneal swelling properties, and increased resistance to collagenase degradation [8-11]. The studies suggest that CXL not only strengthens the cornea, but also has beneficial effects such as, improving corrected distance visual acuity, decreasing corneal steepness, improving topography irregularity indices & uncorrected distance visual acuity [12-14].

The common side effect of corneal collagen crosslinking is corneal haze which is studied by the pathologic light scattered back to an observer while examining & is employed to assess the optical quality of the cornea [15,16]. Activated Keratocytes were found in the eyes of Keratoconus patients treated with CXL when studied under confocal microscopy by Mazzota C, et al. [3]. These activated Keratocytes may have contributed to the development of CXL associated corneal haze. Stromal swelling pressure changes, proteoglycan collagen interactions [17] & Glycosaminoglycan hydration [18] are other factors contributing to stromal haze.

Clinical instruments used to measure haze are custom modified slit lamps, Scheimpflug camera & clinical confocal microscopy. Scheimpflug cameras are noncontact and simple to align, and image acquisition is rapid. Image brightness

is dominated by scatter rather than specular reflection, and the camera assesses the entire cornea in contrast to sampling an area of less than 0.5 mm^2 as sampled by confocal microscopy [19]. An advantage of Scheimpflug cameras over conventional slit-based microscopes is the clear focus through the entire depth illuminated by the slit. This allows precise discrimination of the structures of the entire anterior segment, and with the rotating camera, the anterior segment can be reconstructed in three dimensions. Scheimpflug cameras an excellent instrument for assessing backscattered light from the cornea [20] we determined anterior and posterior corneal HOAs over a range of severity of Fuchs' endothelial corneal dystrophy (FECD. Traditionally, this method has been called "densitometry", which may originate from measurement of density of photographic images from early Scheimpflug cameras. Haze is an important parameter affecting optical quality of the cornea. This corneal haze increases the glare around the bright object due to increased scattering of light going to the retina & increase or decrease in corneal haze can directly affect visual outcome. Thus, we would like to study changes in corneal haze after corneal collagen crosslinking.

Aims & Objectives

- To study the change in preoperative & postoperative corneal densitometry.
- To study the change in corneal densitometry over 6 months duration after the surgery.
- To correlate changes in corneal densitometry with visual acuity.

Material & Methods

- **Study Location:** At Alakh Nayan Mandir eye Institute, Udaipur
- **Study Design:** Prospective interventional
- **Study Duration:** 12 months
- **Study Population:** All the Keratoconus patients who had undergone Collagen crosslinking therapy at Alakh Nayan Mandir eye Institute, Udaipur

Inclusion Criteria

Patients with Progressive Keratoconus [Progressive Keratoconus is defined as 0.5D or more increase in steep K or 10% or more decrease in thinnest pachymetry over the past 6 months [21], who have undergone isotonic collagen crosslinking therapy.

Exclusion Criteria

- Patients with post LASIK ectasia.
- Patients with history of any corneal surgery.
- Patients with any ocular pathology, other than

Keratoconus.

- Patients with history of delayed epithelial healing.

Methodology

This was a prospective interventional. A total of 50 eyes were involved in this study at Alakh Nayan Mandir eye institute from 16/6/2020 to 16/6/2021. Written informed consent was obtained from each patient before the procedures.

Sample Size: Number of patients undergoing CXL at Alakh Nayan Mandir eye institute was around 4-6 per month & sometimes even less due to COVID 19 pandemic. Thus, 50 patients were included over a year in our study as per proforma.

Preoperative Ophthalmological Examination

Before their operations, the eyes of the Keratoconus patients underwent the following:

- Uncorrected visual acuity examination (UCVA) by log MAR
- Best corrected visual acuity examination (BCVA) by log MAR
- Corneal densitometry examination (by Pentacam® Oculus)

Surgical Technique

Using the accelerated protocol, the same surgeon performed all procedures. Accelerated CXL was performed with PESCHKE trade CCL-VARIO Cross linking. It comes with special optics and 1 diode that is homogenising the beam. For accelerated CXL, the "epithelium-off" protocol was followed. Firstly, a speculum was inserted after which a topical anaesthetic (proparacaine - 0.5% eye drops) was instilled on the cornea. Debridement of the epithelium was performed with the help of 20% alcohol for 20-40s under standard hygienic precautions and then, Riboflavin (Peschke M Riboflavin solutions 0.1% riboflavin & 1.0% hydroxypropyl methylcellulose) was applied to cover the exposed corneal stroma and to completely saturate it by reapplying riboflavin at least once every two minutes for a total up to 30 min saturation time. Following the sensitization of corneal stroma by riboflavin, UV-A treatment at 9 mw per cm square for 10 min was given. Riboflavin drops were instilled every 2 minutes during UV-A treatment. Antibiotic and corticosteroid drops were administered after treatment, and a bandage soft contact lens was placed on the eye and removed after epithelialization.

Pentacam Imaging

Changes in corneal transparency were measured with backward light scattering as measured by Scheimpflug

tomography (Pentacam HR, Oculus Optikgeräte GmbH). Densitometry values were analysed pre-operatively & at 1 month, 3 month & 6 month postoperatively. Experienced operators performed all measurements in a dark room. Patients were always instructed to blink two times immediately before the measurement and then to open the eye wide without blinking to ensure that the eyelid did not cover the cornea. Only examinations with automatically triggered Scheimpflug scans that revealed the device's software quality check "OK" were used for analysis.

Densitometry is to be measured by grayscale units. The value varies from 0 (i.e.100% transparent) to 100 (0% transparent). One can measure average values of densitometry in four annuli around the apex and in anterior layer (anterior 160µ), central layer & posterior layer (posterior 60µ) (Fig 1). But here, we focused on the measurements at central annuli of 0-2 mm diameter & 2-6 mm diameter because densitometry values were rather more accurate & precise centrally as compared to periphery.

Slit-Lamp Examination (SLE)

As a clinical correlate, corneal haze will be observed at each visit by slit-lamp biomicroscopy by the same investigator and graded on a scale from 1 to 4. The slit-lamp examination grading will be as follows: 0C Z clear cornea; 1C Z focal areas of minimal stromal clouding or reticulation; 2C Z diffuse mild stromal clouding or reticulation; 3C Z diffuse stromal clouding or reticulation somewhat obscuring view of iris details; 4C Z focal or diffuse areas of dense stromal haze obscuring iris detail.

Statistical Analysis

Data were entered into Microsoft Excel 2010 and analysed using EPI INFO.Ver.7 software. Qualitative data is presented as frequency and percentage and compared by chi square test. Quantitative data of two groups was presented with mean and standard deviation and compared by Z test. The "p" values equal to or less than 0.05 were considered as significant.

Observations and Results

A prospective interventional study was carried out on 50 eyes of established cases of Keratoconus undergoing the procedure of CXL at a tertiary eye care centre. The age of the patients ranged from 9-32 years, with mean age of 19.90 ± 4.98 years .Out of 50 patients, 28 (56%) were female and 22 (44%) were male.

In our study, baseline mean log MAR uncorrected visual acuity (UCVA) was 0.63 ± 0.32 SD (Table 1). In 1 month the

mean UCVA decreased to 0.66 ± 0.36 SD which increased to 0.59 ± 0.37 SD. At 6 months, mean UCVA had not changed significantly as shown by $P = 0.564$ (statistically insignificant) (Table 1). Baseline mean BCVA was 0.16 ± 0.15 SD (Table 1). At 6 months mean BCVA decreased to 0.12 ± 0.15 SD. $P = 0.18$ (statistically insignificant). The visual acuity was

	Mean UCVA(log MAR) +/- Std. Deviation	P Value from Baseline for UCVA	Mean BCVA (log MAR) +/- -Std. Deviation	P Value from Baseline for BCVA	Mean SLE Grading +/- Std. Deviation	P Value from Baseline for SLE Grading
BASELINE	0.63 +/-0.32		0.16 +/-0.15		0.32+/-0.32	
1 MONTH	0.66+/-0.36	0.661	0.24+/-0.21	0.031	1.54+/-0.36	<0.001
3 MONTHS	0.61+/-0.36	0.77	0.17+/-0.17	0.756	1.22+/-0.36	<0.001
6 MONTHS	0.59+/-0.37	0.564	0.12+/-0.15	0.186	0.98+/-0.37	<0.001

Table 1: Changes in UCVA, BCVA and SLE grading after CXL.

The mean Km value was 49.10 ± 3.27 SD (pre CXL). It decreased to 48.52 ± 3.39 SD at 1 month and remained to almost at the same level i.e. 48.59 ± 3.39 SD at 3 months and decreased to 47.81 ± 3.53 by 6 months. $P = 0.293$ (statistically insignificant) (Table 2, Figure 1).

	Mean Km	Std. Deviation	ANOVA P Value
BASELINE	49.1	3.27	0.293
1 MONTH	48.52	3.39	
3 MONTHS	48.59	3.23	
6 MONTHS	47.81	3.53	

Table 2: Topographic Indices.

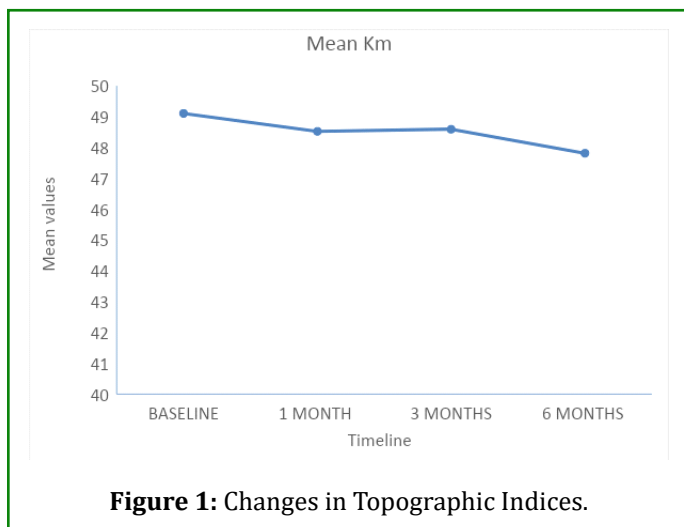


Figure 1: Changes in Topographic Indices.

At baseline, corneal pachymetry was 449.80 ± 43.48 . In 6 months, it decreased to 418.96 ± 48.07 SD.

almost stabilised by 6 months after CXL (Table 1). Almost all patients had low preoperative SLE grading values with a mean of 0.32 ± 0.41 SD. At 6 months, it stabilized to 0.98 ± 0.49 SD. $P < 0.001$ (statistically highly significant). Slit lamp examination had high mean values after 1 month of CXL with a mean of 1.54 ± 0.62 (Table 1).

$P < 0.001$ (statistically highly significant) (Table 3, Figure 2).

	Mean	Std. Deviation	P Value
BASELINE	449.8	43.48	<0.001
1 MONTH	400.2	47.44	
3 MONTHS	407.7	47.72	
6 MONTHS	419	48.07	

Table 3: Pachymetry Pre VS Post Cxl (1 month, 3 months and 6 months follow-up).

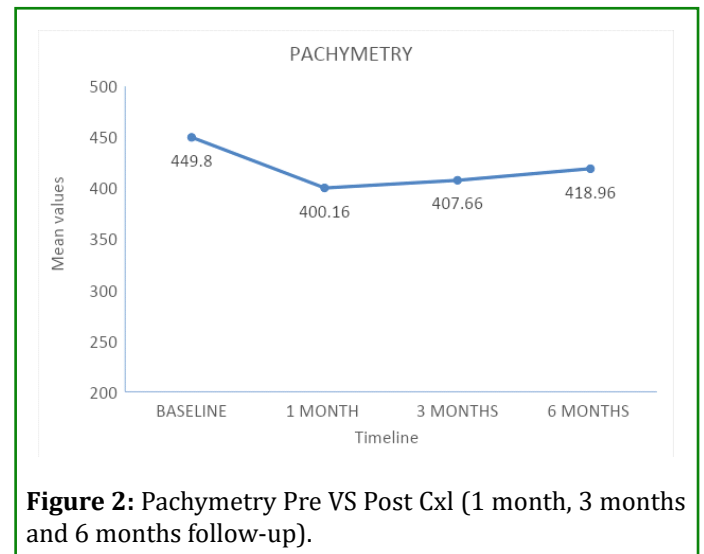


Figure 2: Pachymetry Pre VS Post Cxl (1 month, 3 months and 6 months follow-up).

At baseline, corneal densitometry at 0-2 mm was 16.12 ± 2.08 . In 6 months, it increased to 21.85 ± 8.81 SD. $P < 0.001$ (statistically highly significant) (Table 4, Figure 3).

	Mean	Std. Deviation	P Value
BASELINE	16.12	2.08	<0.001
1 MONTH	28.62	4.55	
3 MONTHS	26.23	4.57	
6 MONTHS	21.85	8.81	

Table 4: Corneal densitometry values at 0-2 mm Pre CXL VS Post CXL (1 month, 3 months and 6 months follow-up).

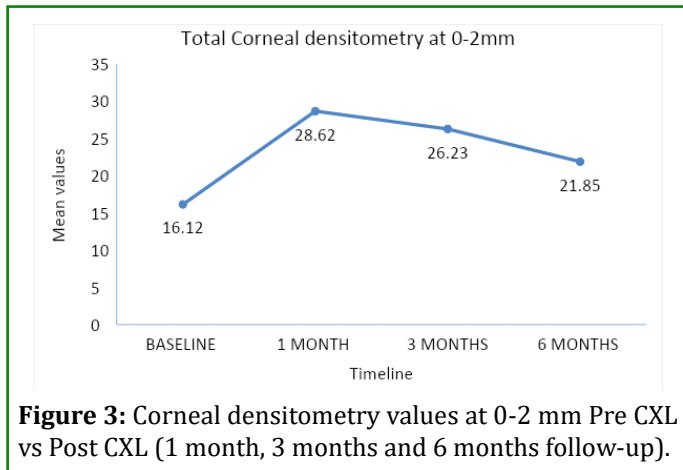


Figure 3: Corneal densitometry values at 0-2 mm Pre CXL vs Post CXL (1 month, 3 months and 6 months follow-up).

At baseline corneal densitometry at 2-6 mm was 13.94 ± 1.61 . In 6 months, it increased to 15.89 ± 5.61 SD. $P < 0.001$ (statistically highly significant) (Table 5, Figure 4).

	Mean	Std. Deviation	P Value
BASELINE	13.94	1.61	<0.001
1 MONTH	20.38	2.99	
3 MONTHS	18.7	3.1	
6 MONTHS	15.89	5.61	

Table 5: Corneal densitometry at 2-6 mm Pre CXL vs Post CXL (1 month, 3 months and 6 months follow-up).

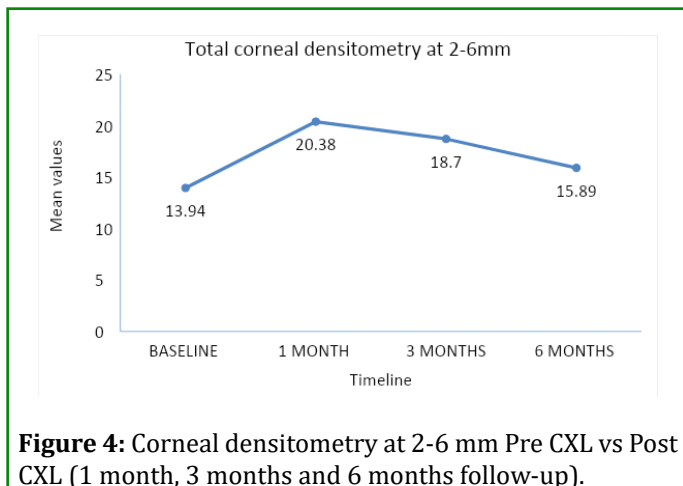


Figure 4: Corneal densitometry at 2-6 mm Pre CXL vs Post CXL (1 month, 3 months and 6 months follow-up).

Discussion

Corneal haze is an inevitable adverse reaction that occurs after CXL which is temporary. Many studies tried to explain the changes and mechanisms causing this corneal collagen crosslinking associated haze. This study was aimed at objectively studying changes in this corneal haze (corneal densitometry) & its effect on visual outcome.

Study was a prospective interventional time bound including a total 50 eyes of 39 patients and was carried out over the period of 12 months from 16th June 2020 to 16th June 2021. The age of the patients ranged from 9-32 years, with mean age of 19.90 ± 4.98 years. Out of 50 eyes, 28 (56%) were of female patients and 22 (44%) were of male patients. There was almost equal prevalence of Keratoconus in both genders.

In this study, the pre CXL mean log MAR visual acuity (UCVA) was 0.63 ± 0.32 SD. At 1 month it was 0.66 ± 0.36 SD with p value 0.661 (statistically insignificant), at 3 months it was 0.61 ± 0.36 SD with p value 0.771 (statistically insignificant) and 0.61 ± 0.36 SD at 6 months with p value 0.564 (statistically insignificant).

Mean log MAR visual acuity (BCVA) was 0.16 ± 0.15 SD before corneal collagen crosslinking. At 3 months it was 0.24 ± 0.21 SD with p value 0.031 (statistically insignificant). At 6 months it stabilized to 0.12 ± 0.15 with p value 0.186 (statistically insignificant). The visual acuity was almost stabilised by 6 months after CXL. Similar study was conducted by Agrawal V [22] on 41 patients with progressive Keratoconus over period of 1 year showed that BCVA improved at least one line in 54% (20/37) of eyes and remained stable in 28% (10/37) of eyes ($P = 0.006$). Hashemi H, et al. [23] conducted the study on 62 eyes (31 patient) in 2 groups found that the mean changes in uncorrected ($P = 0.733$) and corrected ($P = .646$) distance visual acuities and manifest refraction spherical equivalent ($P = 0.598$) did not differ statistically significantly between the 2 groups.

In this study, the mean Km value was 49.10 ± 3.27 (baseline Km value). It was 48.53 ± 3.39 SD for 1 month, 48.59 ± 3.23 SD by 3 months and 47.81 ± 3.53 SD ($P = 0.293$ statistically insignificant). Agrawal V [22] showed that mean Km decreased by a mean of 2.73D in 66% of eyes and remained stable in 22% of eyes over period of 2 years. Similar study by Caprossi A, et al. [13], demonstrated the long-term stabilization of Keratoconic corneas without significant side-effects in 44 eyes for up to 48 months after CXL, accompanied by a reduction in the mean Km value by 2 diopters.

In this study, pachymetry reduced significantly at 1 month postoperatively (baseline pachymetry was 449.80 ± 43.48 & at 1 month 400.16 ± 47.44 with p value being < 0.001)

which coincided with the increase in corneal densitometry (baseline corneal densitometry value was 16.2 ± 2.08 & at 1 month total corneal densitometry at 0-2 mm was 28.62 ± 4.55) which was followed by a gradual return to a near baseline level (At 6 months it corneal pachymetry increased to 418.96 ± 48.07) coinciding with the decrease in densitometry (i.e. 21.85 ± 8.81). These concomitant changes in corneal pachymetry and corneal densitometry support a suggestion that changes in corneal stromal lamellar spacing and arrangement may increase light scattering, thus leading to corneal haze.

In the current study, there was a significant increase in the corneal haze, peaking at 1 month postoperatively. Then, there was a gradual reduction of the corneal haze as measured objectively using Pentacam densitometry. 6 months after the procedure, the values of corneal densitometry did not reach baseline levels. The mean corneal densitometry remained higher than the baseline level, with an increase of 2.08 ($P = <0.001$). These changes are in accordance with the changes in the Keratoconus subgroup of the study conducted by Greenstein et al., where the baseline mean corneal densitometry was 14.9 ± 1.93 (SD) [24]. In their study, the increase in the mean densitometry between baseline and 1 month 23.4 ± 4.40 ; $P < 0.001$ was statistically significant. There was a little change at 3 months (mean 22.4 ± 4.79 ; $P = .06$) and then followed by decreased corneal densitometry at 6 and 12 months in their study. They reported that even though the mean densitometry decreased significantly between 6 and 12 months postoperatively, it remained elevated compared with baseline values ($P < 0.001$). This course of increased postoperative haze at 1 month, which was then followed by a gradual decrease, but not returning to the baseline level at 6 month also, is in accordance with that reported by Gutiérrez R, et al. [4]. This may be due to the higher baseline corneal stromal haze in their series resulting from more advanced KC. There was no correlation found between corneal haze (i.e. Corneal densitometry) & BCVA at 1 month ($r=0.04$). Whereas there is moderately inverse correlation between corneal densitometry & corneal pachymetry ($r = -0.29$) at 1 month which is in accordance to study by Helaly HA, et al. [25] where they found strong inverse correlation between this two variables ($r = -0.72$).

Slit lamp evaluation of the stromal haze followed a similar course, peaking at 1 month postoperatively, which was then followed by gradual decrease. At 6 months postoperatively, it was higher than the baseline level (0.32 ± 0.41 vs. 0.98 ± 0.49), with an increase of 0.49 ($P < 0.001$). This course also is in accordance with that reported by Greenstein et al. in the KC subgroup of their study, where a baseline clinical haze was 0.3 ± 0.73 and a 12-month postoperative clinical haze was 0.7 ± 0.91 . Greenstein SA, et al. [24] found that clinically, the corneal stromal haze after CXL is different from that

occurring after excimer laser photorefractive keratotomy. The haze after PRK had a more reticulated appearance limited to the subepithelial area and that after CXL had a dust-like change in the corneal stroma or a mid stromal demarcation line (up to 60% of the stromal depth) [26].

Regarding the thinnest pachymetry, the mean decreased markedly at 1 month postoperatively by 49.64. It increased gradually to reach a near baseline level at 6 months postoperatively (418.96 ± 48.07). This is in agreement with a previous report on transient thinning of the cornea with ultrasound pachymetry after CXL treatment [7]. Changes in the corneal thickness seem to reflect a compactness of the corneal stroma.

Conclusion

The current study demonstrated that after isotonic CXL:

- There was no significant decrease in the topographic and keratometric indices at the end of 6 months following the procedure.
- There was reduction in pachymetry at the end of 1 month which was then stabilised by 6 month.
- Postoperative changes in corneal densitometry do not affect the final visual outcome.
- The Scheimpflug corneal densitometry and clinical corneal haze peaked at 1 month followed by a gradual decline.
- There was inverse correlation found between corneal pachymetry & corneal densitometry.

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