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Clinical Safety Profile of Corneal Collagen Cross-Linking: A Longitudinal Analysis of Endothelial Integrity and Morphological Stability

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Abstract

Background: Keratoconus is a non-inflammatory conical ectasia of cornea that often exhibits bilateral asymmetric progression over time.

Objective: To assess the effectiveness of corneal collagen cross-linking (CXL) on endothelial cell density, endothelial morphology, central corneal thickness, and corneal volume in cases with keratoconus.

Methods: This prospective interventional research involved forty eyes from 22 patients with Stage I and II keratoconus. All patients underwent standard epithelium-off CXL (Dresden protocol). Preoperative and three-month postoperative assessments included non-contact specular microscopy to measure endothelial cell density (ECD), coefficient of variation (CV), hexagonality percentage (HEX%), and central corneal thickness (CCT). Keratometric parameters and corneal volume were also evaluated.

Results: The average preoperative and postoperative values of cell density were 2899.75 ± 299 cells/mm² and 2812.55 ± 218 cells/mm², respectively. Endothelial cell density showed a statistically significant decrease in three months postoperatively (P = 0.001). Coefficient of variation significantly increased (P = 0.001), while hexagonality significantly reduced (P-value equal to 0.001). No substantial difference has been identified in central corneal thickness. Significant reductions were detected in K1, K2, Kmax, and corneal volume. Keratoconus stage showed significant correlations with CCT change, CV change, and HEX change, but not with ECD change. Corneal volume change is related positively with ECD change (P= 0.021) and negatively with HEX change (P= 0.031).

Conclusion: Standard CXL effectively stabilizes early keratoconus, reducing keratometry and volume. Despite minor morphological shifts, endothelial density and corneal thickness remained stable, confirming the procedure's relative safety while necessitating diligent postoperative monitoring for patient safety.

Keywords: Keratoconus; Central corneal thickness; CCT; CXL

Introduction

A bilateral, non-inflammatory, progressive corneal ectasia is known as keratoconus. It causes uneven astigmatism, increased myopia, and corneal thinning and protrusion. Keratoconus is the most common cause of corneal transplant surgery, even though only 26.8 percent of cases require corneal transplantation to restore vision. This condition frequently manifests in adolescents, starting during puberty, progressing throughout the 2nd and 3rd decades of life, and maintaining around the age of forty. The incidence is expected to vary from 1.5 to 25 cases per hundred thousand cases per year, with elevated rates observed in Middle Eastern and Asian populations [1].

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Keratoconus results in visual impairment due to irregular astigmatism,higher-order abnormalities, myopia, and corneal scarring. It manifests throughout puberty and impacts both genders. While its pathophysiology remains unclear, evidence indicates that environmental and genetic factors contribute to the disease's onset. It is marked by alterations in the corneal epithelium's structure and stromal thinning [2]. Keratoconus initially affects only one eye, but it gradually involves both eyes [3].

Corneal collagen cross-linking (CXL) has been initially presented by Wollensak et al. as an effective method to impede or prevent the development of keratoconus [4]. CXL is a recognized method for preventing the development of keratoconus [5,6]. CXL increases the rigidity and elasticity of the ectatic cornea by the chemical interaction of ultraviolet-A radiation (315–400 nanometer) with riboflavin, which induces covalent bond formation among the corneal collagen fibers [7,8]. These cross-links are thought to enhance tissue strength, prevent outward bulging, and ultimately assist cases in maintaining visual acuity [9]. The predominant cross-linking approach is the epithelial off (epi-off) CXL. The 'Dresden protocol' involves the excision of the center eight to nine millimeters of the corneal epithelium, the administration of a 0.1 percent riboflavin solution every five minutes for thirty minutes. and subsequent exposure to UVA (370 nm, three mW/cm²) for thirty minutes. Additional techniques involve accelerated CXL and epithelial-on (epi-on) CXL [10].

Early implementation of CXL may postpone or may obviate necessity for keratoplasty. Nonetheless, CXL was not devoid of problems. UVA radiation employed in process can potentially harm corneal endothelium, resulting in corneal edema. In infrequent instances, this condition may require keratoplasty [11]. CXL was performed when corneal thickness surpasses 400 microns after deepithelization to reduce risk of corneal endothelial cell damage from UV radiation.

Certain studies suggest that corneal thickness may significantly diminish during operation due to corneal dryness, potentially resulting in endothelial cell injury [12]. In addition, Sykakis et al. [13] evaluated three randomized controlled trials to determine whether there is evidence that corneal cross-linking is an effective intervention compared to no treatment for preventing the course of keratoconus. Nonetheless, their Cochrane review could not do a quantitative synthesis of the data due to the limited number of RCTs. The present research is intended to assess the impact of corneal collagen cross-linking on the corneal endothelium and central corneal thickness in cases with keratoconus.

Materials and Methods

This prospective interventional research was conducted from February 2023 to November 2023 at Ibn Al-Haitham Eye Teaching Hospital. All techniques have been conducted by the same surgeon to ensure standardization of the surgical technique and minimize operator-related variability.

Study Population

The research involved 40 eyes from 22 cases diagnosed with keratoconus who have been scheduled for corneal collagen cross-linking (CXL) during the study period. Each patient was evaluated preoperatively and at three months postoperatively. Specular microscopic examination was performed before CXL and repeated three months after the procedure to assess endothelial parameters.

Inclusion Criteria

Cases with keratoconus categorized as grade I & grade II regarding Amsler–Krumeich classification, who exhibited proven clinical deterioration, instrumental progression. Diagnosis of keratoconus progression was determined regarding criteria set out by global agreement on keratoconus ectatic disorders [14]. Eligible participants were aged between 14 and 30 years, had a CCT greater than four hundred μm, and presented with completely clear corneas.

Exclusion Criteria

Cases where corneal thickness at narrowest point was below four hundred μm. A history of herpetic keratitis, concurrent corneal infections, preexisting autoimmune disorders, severe allergic conjunctivitis, acute hydrops, keratoconus cataracts, glaucoma, diffuse central corneal opacity, significant dry eye, advanced and vitreoretinal conditions. Also, people with mental instability, those who recently used contact lenses and those who were pregnant or nursing.

Preoperative Assessment

All cases received a thorough ocular assessment prior to surgery, which included:

- A thorough history assessment that included personal demographic information, presenting complaints, both current and past medical conditions to exclude individuals with collagen disorders & diabetes mellitus, or hormonal changes such as pregnancy.
- Ophthalmic history [Prior ocular injuries, surgical procedures, allergies and a history of wearing glasses or contact lenses (all individuals with a history of contact lens use were advised to stop lens usage for a minimum of two weeks prior to assessment)].
- Comprehensive ophthalmic examination included: External assessment for identification of pathologies such as ptosis, lid hemangioma, UCVA, BCVA, IOP measurement via applanation tonometry, posterior segment evaluation for abnormalities using indirect ophthalmoscopy and slit lamp biomicroscopy with an auxiliary contact lens.

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- Corneal assessment employing corneal tomography to evaluate CCT, corneal endothelial cell analysis through noncontact specular microscopy NIDEK CEM-530, concentrating on following parameters: Coefficient of variation (CV percent) of cell size, ECD, percentage of HEX prior to and one month following CXL.

Surgical technique

A 0.1% riboflavin solution was produced by diluting a 0.5% solution of vitamin B2 riboflavin-five phosphate with dextran T500. Solution has been protected from light & employed within twelve hours. A topical anaesthetic was applied before treatment with benoxinate eye drops. Corneal epithelium was manually dissected over an eight-millimeter diameter area utilizing a blunt tool (Hokey knife), a 0.1% riboflavin solution was intermittently supplied for roughly thirty minutes. Corneal penetration, presence of riboflavin in anterior chamber (riboflavin shielding) were assessed using slit lamp examination with a blue filter. UVA irradiation was conducted utilizing an optical system (Kohler illumination) comprising a light source consisting of seven UV diodes (365 nm; Nichia, Nuernberg, Germany) and a series potentiometer for voltage adjustment. Before treatment, a target irradiance of three mW/cm² (5.4 J/cm² surface dosage) has been calibrated with a UVA meter (LaserMate-Q; LASER 2000, Wessling, Germany) at a distance of one centimeter. Irradiance has been administered for thirty minutes at a power density of three mW/cm², resulting in a total dosage of 5.4 J/cm². Throughout treatment, riboflavin solution was administered every three minutes to ensure full saturation of cornea with riboflavin. Following therapy, a bandage contact lens was employed till corneal epithelium was fully regenerated, often within three days. Postoperatively, cases received topical antibiotics along with artificial tear substitutes.

Postoperative Assessment

Subsequent to surgery, patients received ciprofloxacin 0.3% eye drops each four hours for one week and dexamethasone 0.1percent eye drops every four hours for one week. It has been recommended to deliver preservative-free artificial tears four times daily for one month. Bandage contact lens was extracted upon completion of epithelialization, often after four days. After one month, we re-examined all cases utilizing same instruments by specular microscopy. Following removal of contact lens, cases were prescribed a topical mixture of steroid and antibiotic to be administered six times daily, with a gradual reduction over subsequent six weeks, in conjunction with a topical lubricant substitute.

Ethical Considerations

Ethical approval has been collected from the Arab Board of Medical Specialization Committee and the Scientific Department of Ibn Al-Haitham Eye Teaching Hospital. Verbal informed consent has been collected from all cases before enrollment in the research, in agreement with institutional ethical standards.

Statistical analysis

Data entry and analysis were conducted using Microsoft Excel 2021 and SPSS 26 (Statistical Package for Social Sciences). Continuous variables have been stated as range (minimum and maximum), mean ± standard deviation, while categorical variables have been presented as frequencies and percentages. Paired sample t-tests have been utilized to compare preoperative and postoperative measurements. Pearson's correlation coefficient has been applied to evaluate correlations between keratoconus stage, corneal volume changes, and endothelial parameter changes. A P-value < 0.05 was measured statistically significant.

Results

The mean age was 19.23 ± 3.5 years (minimum age: 14, maximum age: 28). A majority of the participants were females, constituting 14 individuals (63%). Regarding keratoconus staging, 17 eyes (42.5%) were classified as Stage I and 23 eyes (57.5%) as Stage II as demonstrated in Table 1.

Table 1: Cases Characteristics in the examined Group.

Age (years) Mean ± SD		19.23 ± 3.5
Sex	Male	8 (36.4%)
	Female	14 (63.3%)
Keratoconus Stage	Stage I	17 (42.5%)
	Stage II	23 (57.5%)

The mean ± SD preoperative and postoperative values of cell density were 2899.75 ± 299 cells/mm² and 2812.55 ± 218 cells/mm², correspondingly. There was a significant distinct between preoperative and decreased postoperative cell density (P value equal to 0.001), as clarified in (Table 2). The mean ± (SD) preoperative and postoperative values of central corneal thickness were 465.10 ± 28.89 µm and 461.85 ± 31.30 µm, correspondingly. There was no significant change among preoperative and postoperative central corneal thickness (P value equal to 0.23). The mean ± (SD) preoperative and postoperative values of coefficient variation were 26.65 ± 2.7 and 31.55 ± 4.40, respectively. There was a significant elevation in postoperative coefficient of changes compared to the preoperative value (P value = 0.001), as explained in (Table 2). The mean ± SD preoperative and postoperative values of hexagonality were 68.50 ± 5.5 and 64.33 ± 5.3, respectively. There was a significant decrease in postoperative hexagonality than the preoperative value (P value = 0.001), as clarified in Table 2.

The mean ± (SD) preoperative and postoperative values of K1 were 44.62 ± 1.84 D and 43.48 ± 1.92 D, correspondingly.

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There was a significant decrease in postoperative K1 value compared to preoperative measurements (P value < 0.001), as demonstrated in (Table 3), the mean ± (SD) preoperative and postoperative values of K2 were 49.85 ± 2.76 D and 48.31 ± 2.64 D, respectively. A statistically significant reduction was observed postoperatively (P value below 0.001), as demonstrated in (Table 3). The mean ± (SD) preoperative and postoperative values of Kmax were 53.90 ± 4.88 D and 52.20 ± 4.15 D, respectively. There was a significant reduction in postoperative Kmax values (P value equal to 0.009), as clarified in (Table 3). The mean ± (SD) preoperative and postoperative values of corneal volume were 57.10 ± 1.88 mm^3 and 56.52 ± 1.71 mm^3, respectively. There was a significant postoperative decrease in corneal volume (P value equal to 0.006) (Table 3).

Table 2: Comparison of Endothelial Parameters Pre-operative and 3 Months Post-operative.

Variables	Minimum-Maximum		Mean ± SD		P-value
	(Pre)	(Post)	(Pre)	(Post)	
Cell density (c/mm^2)	2277–3626	2385–3548	2899.75 ± 299	2812.55 ± 218	0.001
Central corneal thickness (CCT)	405–521	401–557	465.10 ± 28.89	461.85 ± 31.30	0.23
Coefficient of variation (CV%)	20–31	22–39	26.65 ± 2.7	31.55 ± 4.40	0.001
Hexagonal %	55–77	51–79	68.50 ± 5.5	64.33 ± 5.3	0.001

Table 3 : Keratometric & Corneal Volume Analysis Pre-operative and 3 Months Post-operative.

Variables	Minimum- Maximum		Mean ± SD		P-value
	(Pre)	(Pre)	(Pre)	(Post)	
K1 (D)	41.20 – 48.10	40.50 – 46.90	44.62 ± 1.84	43.48 ± 1.92	<0.001
K2 (D)	44.30 – 55.80	43.10 – 53.90	49.85 ± 2.76	48.31 ± 2.64	<0.001
Kmax (D)	46.80 – 63.40	45.90 – 60.70	53.90 ± 4.88	52.20 ± 4.15	0.009
Corneal Volume (mm^3)	53.40 – 60.80	52.90 – 59.90	57.10 ± 1.88	56.52 ± 1.71	0.006

Regarding correlation analysis, keratoconus stage demonstrated a statistically significant relation with CCT change (r = 0.312, P value = 0.049), CV change (r = −0.336, P value equal to 0.033), and HEX change (r = 0.421, P value equal to 0.007). However, no significant relation was found among keratoconus stage and ECD change (P value = 0.592), as shown in Table 4.

Corneal volume change demonstrated a statistically significant positive association with ECD change (r equal to 0.382, P value equal to 0.021), and a significant negative relation with HEX change (r = −0.355, P value equal to 0.031). Insignificant correlation was detected among corneal volume change and CV or CCT changes (P –value above 0.05), as showed in Table 5.

Table 4: Correlation of Keratoconus Stage with endothelial parameters after CXL.

Variables	r	P-value
ECD change	-0.088	0.592
CCT change	0.312	0.049
CV change	-0.336	0.033
HEX change	0.421	0.007

Table 5: Correlation among corneal volume change and endothelial parameters after CXL.

Variables	r	P-value
(ECD) change	0.382	0.021
(CV) change	0.267	0.094
(HEX %) change	–0.355	0.031
(CCT) change	–0.118	0.468

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Discussion

The current study evaluated the impact of CXL on the corneal endothelium and CCT in cases with keratoconus. Our results demonstrated that the mean ECD significantly decreased from 2899.75 ± 299 cells/mm² preoperatively to 2812.55 ± 218 cells/mm² postoperatively (P = 0.001). Our results were parallel to Razmjoo et al. [15] which compared the findings of endothelial specular microscopy in 68 keratoconic eyes before and 1 year after CXL. Their results showed that there was a significant reduction in ECD (~60 cells; 2753±230 cells/mm², preoperatively, and 2699±210 cells/mm², postoperatively, with *P*=0.004). However, our results disagreed with the study done by Elsayed et al. [16] which aimed to document temporary alterations in corneal endothelium subsequent to CXL for keratoconus management. They reported that one month after CXL, the mean ECD increased from 2740.87 ± 202.56 cells/mm² to 2751.20 ± 226.35 cells/mm² but with no statistically significant differences.

Similarly, Elgazzar et al. [17] evaluated the corneal endothelial variations subsequent to CXL therapy for keratoconus, as assessed by specular microscopy. The average preoperative endothelial cell density (CD) was 2963.1±364.1 cells per square meter, while the average after one month postoperatively was 2956.96±363 cells/mm², indicating a statistically insignificant change. Additionally, Abdel-Radi et al. [18] evaluate changes in corneal endothelial cells subsequent to the novel accelerated pulsed high-fluence protocol of epithelium-off corneal cross-linking for the management of mild to moderate keratoconus. The mean preoperative endothelial cell density of 2944.6±247.41 cell/mm² exhibited a non-significant decrease at three and six months postoperatively, measuring 2931.03±253.82 and 2924.7±224.88 cells per square meter, respectively (P-value=0.361).

Our results showed that the mean CCT demonstrated a slight decrease from 465.10 ± 28.89 µm preoperatively to 461.85 ± 31.30 µm postoperatively; though, this change wasn't statistically significant (P –value equal to 0.23). Regarding endothelial morphology, we found that the coefficient of variation significantly increased from 26.65 ± 2.7 preoperatively to 31.55 ± 4.40 postoperatively (P = 0.001). We found that the percentage of hexagonal cells significantly decreased from 68.50 ± 5.5 preoperatively to 64.33 ± 5.3 postoperatively (P = 0.001), reflecting increased pleomorphism Similarly, our findings were consistent with Mohamed et al. [19] which evaluate the CXL safety with epithelial debridement for the management of keratoconus on the corneal endothelium by utilizing endothelial specular microscope. They revealed that there was no significant distinct between pre-and postoperative CCT but coefficient of variation increased significantly after corneal collagen cross-linking. They found a significant reduction in hexagonal cell percentage (HEX), with mean preoperative and postoperative hexagonal cell percentage values of 41.73 ± 5.08% & 38.13 ± 5.24% respectively (P < 0.05). Also, Elgazzar et al. [17] revealed that the mean preoperative CCT was 477.5±35.57 µm, whereas the mean value at one month postoperatively was 477.9±36.88 µm, with statistically insignificant difference between the two values. The mean preoperative coefficient of variation (CV%) was 36.3±5.9%, whereas 1 month after operation, it was 36.2±5.6%, with a statistically insignificant difference.

In addition, our results were parallel to Wen et al. [7]which found that the CCT had no significant change (470±40 µm, preoperatively and 469.8±42 µm, postoperatively, with *P*=0.591). The preoperative percentage of Hex., demonstrating pleomorphism, was 54.14±6%, while the postoperative percentage was 54.55% (*P*=0.517), demonstrating no significant variation in cellular morphology. The coefficient of variation (CV%) indicated a considerable increase in cell size (polymegathism). (32.72±10.14%, preoperatively, and 40.21±9.7%, postoperatively, with *P*=0.021). Furthermore, Abdel-Radi et al. [18] reported that there were insignificant variations were seen in the mean coefficient of difference, percentage of hexagonal cells, or the average, minimum, and maximum diameters of endothelial cells at three and six months of age post pl-ACXL. Their findings indicated that corneal endothelium alterations following accelerated pulsed high-fluence corneal collagen cross-linking were minimal, with a stable endothelial cell count and insignificant morphological variations.

As well, Lamiaa et al. [20] assessed the alterations in corneal endothelial cells subsequent to CXL for the management of progressive keratoconus utilizing corneal specular microscopy. They reported a mean CV% of 29.43 ± 5.35% preoperatively & 30.03 ± 6.01% 1 months postoperatively with no significant distinct (P-value equal to 0.38). Their also results demonstrated that there were statistically insignificant variations in corneal endothelial counts involve CCT, endothelial cell density, hexagonal cells %, after cross linking technique in keratoconic cases through one-month follow-up.

In the present study, significant reductions were observed in keratometric parameters (K1, K2, K max) and corneal volume, reflecting corneal flattening and structural stabilization. In the current study, correlation analysis revealed that keratoconus stage had a statistically significant positive association with CCT change (r = 0.312, P-value equal to 0.049) and HEX change (r = 0.421, P-value equal to 0.007), and a significant negative association with CV change (r = −0.336, P-value equal to 0.033). However, no significant correlation has been presented between keratoconus stage and ECD change (r = −0.088, P-value equal to 0.592).

Furthermore, corneal volume change demonstrated a statistically significant positive relation with ECD change (r = 0.382, P-value equal to 0.021) and a significant negative relation with HEX change (r = −0.355, P-value equal to 0.031). No significant relation was observed between corneal volume change and CV change (r = 0.267, P-value equal to 0.094) or CCT change (r = −0.118, P-value equal to 0.468).

The study done by Kobashi et al. [21] evaluated the effectiveness of collagen cross-linking one year after treatment of keratoconus, as contrast to no treatment, by synthesizing RCT utilizing a systematic review. Their findings indicated that all trials had a decrease in Kmax over the one-year observation time. They determined that CXL could effectively slow the evolution of keratoconus for a minimum of one year under specific conditions. Li et al.'s [22] meta-analysis evaluated the effectiveness of corneal collagen cross-linking in treating keratoconus. Their research demonstrated that CXL was both safe and effective in stabilizing keratoconus. The findings indicated a statistically significant increase in Kmean, Kmax, and Kmin within the CXL treated group. A substantial quantity of published clinical trials has demonstrated a therapeutic impact of corneal collagen cross-linking in keratoconus. Significant decreases in Kmax, Kmin, and Kmean have been observed following the CXL operation. The enhancement in Kmaxhas been observed at -2.05 D in the corneal collagen cross-linking group relative to the control group.

Similar results have been found in a prior investigation by Wollensak et al., which recorded a decrease in the maximal keratometry value of 2.01 D. The research conducted by Arbelaez et al. [23] indicated a reduction in the average keratometry measurement of 1.36 D after a period of twelve months. Moreover, Henriquez et al. [24] observed a significant decrease in Kmax of 2.21 D in the control group after 12 months. The systematic review and meta-analysis by Chunyu et al. [4] determined that corneal collagen cross-linking effectively limits the development of keratoconus for a minimum of one year.

In contrast, our results disagreed with Elsayed et al. [16] which found no statistically significant correlation among keratoconus stage & changes in CCT, HEX and CV. Alterations in ECD exhibited a statistically significant correlation with stage of keratoconus.

This research has multiple strengths. Its prospective design allowed for systematic data collection and minimized bias. All techniques were performed by a single experienced surgeon using a standardized protocol, which reduced variability in surgical technique and enhanced internal consistency. Objective assessment tools, including non-contact specular microscopy and corneal tomography, were used to obtain reliable quantitative measurements of endothelial parameters and corneal thickness. Furthermore, the study did not limit its evaluation to simple pre- and postoperative comparisons but also investigated correlations between keratoconus stage, corneal volume changes, and endothelial parameters, providing deeper insight into possible associations.

Although its benefits, the research possesses specific limitations. The limited sample size may restrict the generalizability of the results. The follow-up duration of three months is relatively short and may not adequately reflect long-term endothelial safety or recovery. Also, the research has been performed at a single center, which may limit external validity. The lack of a control group restricts the capability to compare the detected changes with the natural progression of keratoconus.

Based on the findings of this research, corneal Collagen Cross-Linking (CXL) seems to be an effective and nearly safe therapeutic alternative for cases with early-stage keratoconus and adequate corneal thickness. Nevertheless, strict patient selection remains essential, particularly with regard to maintaining a minimum stromal thickness threshold to protect the corneal endothelium from potential ultraviolet-A toxicity. Routine preoperative and postoperative evaluation using specular microscopy is recommended to monitor endothelial cell density and morphology, especially in younger patients and in corneas approaching the lower safety thickness limit. Additionally, Extended follow-up durations are necessary to identify whether the observed endothelial morphological changes are transient or persistent. Future multicenter research with larger sample sizes and end of more progressed keratoconus stages are encouraged to provide more comprehensive safety data and allow comparison between different cross-linking protocols.

Conclusion

This study demonstrated that CXL in cases with Stage I and II keratoconus leads to significant developments in keratometric parameters and a reduction in corneal volume, confirming its efficacy in inducing corneal flattening and structural stabilization. Although a statistically significant reduction in ECD and alterations in endothelial morphology (increased CV and decreased hexagonality) were observed at three months postoperatively, central corneal thickness remained stable, and endothelial cell counts stayed within physiological limits. These findings suggest that standard epithelium-off CXL is relatively safe for the corneal endothelium in early-stage keratoconus when appropriate safety protocols are followed. Nevertheless, endothelial morphological changes warrant careful postoperative monitoring, particularly in thinner corneas. Additional long-term, large-scale research is recommended to evaluate the persistence and clinical relevance of endothelial changes following CXL.

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Author Contributions

Conceptualization, Sabah Lafta Ashash, Hussein Abdulhadi Mohammed, Furkaan Majied Hamied; Formal analysis, Sabah Lafta Ashash, Hussein Abdulhadi Mohammed, Furkaan Majied Hamied; Investigation, Sabah Lafta Ashash, Furkaan Majied Hamied; Project administration, Sabah Lafta Ashash, Hussein Abdulhadi Mohammed, Furkaan Majied Hamied Software, Sabah Lafta Ashash, Hussein Abdulhadi Mohammed; Validation, Sabah Lafta Ashash, Hussein Abdulhadi Mohammed, Furkaan Majied Hamied; Visualization, Sabah Lafta Ashash, Hussein Abdulhadi Mohammed, Furkaan Majied Hamied; Writing—original draft, Sabah Lafta Ashash; Writing—review, editing, and provided critical feedback to help shape the research, analysis, and manuscript, Sabah Lafta Ashash; All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests: The authors declare no competing interests.

Consent to participate: Not applicable.

Consent for Publication: Not applicable

Ethics Approval: Ethical approval has been collected from the Arab Board of Medical Specialization Committee and the Scientific Department of Ibn Al-Haitham Eye Teaching Hospital. Verbal informed consent has been collected from all cases before enrollment in the research, in agreement with institutional ethical standards.

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