

# Epithelial Remodelling After Epithelium-off Continuous Accelerated Corneal Collagen Cross-linking in Progressive Keratoconus

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## Research article

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# Abstract

**Background:** To analyse regional corneal epithelial and stromal remodelling after epithelium-off (epi-off) continuous accelerated corneal collagen cross-linking (CXL) for keratoconus (KC).

**Methods:** In this retrospective study, 20 patients (33 eyes) who were treated with epi-off continuous accelerated CXL (KXL system; Avedro, Inc., Waltham, MA, USA). All treatments were performed with ultraviolet-A (UVA) (energy, 7.2 J/cm<sup>2</sup>; irradiance, 30 mW/cm<sup>2</sup>), using continuous (4 min) illumination. The postoperative changes in corneal biometric and visual outcomes were compared. The corneal thickness changes were evaluated using anterior segment optical coherence tomography (Optovue). All patients were followed up for 12 months postoperatively.

**Results:** Uncorrected distance visual acuity significantly improved from 1.06 ± 0.49 logarithm of the minimum angle resolution (logMAR) to 0.71 ± 0.37 logMAR at 3 months after epi-off continuous accelerated CXL (p<0.001). The corneal epithelial thickness changes were significant in the inner nasal at -1.48 ± 3.65 µm (p=0.024), -1.76 ± 4.21 µm in the inner superior-nasal (p=0.024), -1.52 ± 4.02 µm in the inner superior (p=0.046), -1.97 ± 4.57 µm in the inner superior-temporal (p=0.018), -2.12 ± 4.46 µm in the outer inferior (p=0.014), -2.15 ± 4.82 µm in the outer inferior-nasal (p=0.022), -1.73 ± 4.45 µm in the outer temporal (p=0.019) at 6 months after epi-off continuous accelerated CXL.

**Conclusions:** Significant regional epithelial remodelling occurs after epi-off continuous accelerated CXL; a more regular corneal thickness profile and keratometric variations were observed after treatment.

## Background

Keratoconus (KC) is characterised by biomechanical instability of the cornea, with progressive cone-like bulging that leads to irregular astigmatism and a subsequent gradual decrease in visual acuity [1]. Recently, the Avedro KXL system has been used for various types of corneal collagen cross-linking (CXL) for halting the progression of KC, including LASIK Xtra, epithelium-off (epi-off) accelerated CXL, and trans-epithelial (epi-on) accelerated CXL [2, 3]. Nevertheless, patients treated with accelerated CXL (alone) show minimal visual improvement; subsequently, most patients do not achieve functional visual acuity [4–6].

Moreover, pediatric KC is a distinct entity; it is a more severe disease at the time of diagnosis and has a faster progression as compared to adult KC. Controversial outcomes have been reported on the use of epi-off continuous accelerated CXL treatment in KC [2, 4–6]. Today, the clinical evaluation of corneal epithelial thickness profile is becoming more important in pre-clinical diagnosis and monitoring of KC. It confers benefits, such as timely management of the condition for improved long-term morbidity outcomes [7–9]. A doughnut-like epithelial profile in the peripheral epithelium becomes thinner, and overall thickness regularity improves after conventional CXL [7, 8]. The aim of this retrospective study was to analyse regional corneal epithelial and stromal remodelling after epi-off continuous accelerated CXL.

## Materials And Methods

This retrospective study included 20 patients (33 eyes) diagnosed with KC at the Department of Ophthalmology, Peking Union Medical College Hospital, Beijing, China between July 2016 and November 2019. The study protocol followed the guidelines of the Declaration of Helsinki and the Institutional Review Board for Human Studies and was approved by the Peking Union Medical College Hospital Institutional Ethics Committee. Written informed consent was obtained from all the patients or a parent or guardian on behalf of any participants under the age of 18 before the study was initiated.

Preoperative and postoperative examinations included a slit-lamp examination, best spectacle-corrected visual acuity with and without a pinhole, uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) using a Snellen chart, corneal topography (TMS-4N; TOMEY, Erlangen, Germany), dual Scheimpflug Imaging System (Gallilei; Ziemer Ophthalmology, Port, Switzerland), and ultrasonic pachymetry (TOMEY Ltd, Aichi, Japan) of the central cornea. Goldmann applanation tonometry and an Ocular Response Analyzer (Reichert Technologies; Depew, New York, USA) were used to measure intraocular pressure and corneal biomechanical properties. The corneal demarcation line and the corneal epithelial and stromal thicknesses were measured and evaluated using anterior segment optical coherence tomography (AS-OCT) (Optovue RTVue XR, Optovue; Fremont, California, USA). Corneal epithelial and stromal thickness profiles were obtained at the thinnest part of the central cornea using 16 peripheral measurements on the corneal vertex; measurements and statistical analyses for the central 6-mm zone of corneal apex (inner areas, 3 mm of corneal apex; outer areas, 6 mm of corneal apex) were performed and measured [8]. For ultrasound pachymetry, the average measurements of the corneal thickness values were chosen (each single measurement represented the mean of five consecutive measurements).

Inclusion criteria for the study were as follows: documented progressive KC, patient age > 10 years, corneal thickness  $\geq 400 \mu\text{m}$ , no other ocular pathologic signs (such as ocular surface infection or allergy), and no pregnancy or lactation. KC stage was determined according to the Amsler-Krumeich classification preoperatively.[1]

All patients underwent uneventful epi-off continuous accelerated CXL treatment with the use of a new high-intensity ultraviolet-A (UVA) illuminator (CCL-365; Peschke Meditrade GmbH; Huenenberg, Switzerland). All of the patients' eyes underwent continuous (4 min) light illumination with an irradiation of  $30 \text{ mW/cm}^2$ .

### Surgical technique

All procedures were performed by one experienced surgeon (Y.L.) using a high-intensity UVA illuminator (KXL I, Avedro; Waltham, Massachusetts, USA) under sterile conditions. After topical anaesthesia with 0.5% proparacaine (Alcaine, Alcon-Couvreur; Puurs-Sint-Amands, Belgium, USP), the corneal epithelium was mechanically removed with an 8.0–9.0 mm diameter cut using a crescent knife. After epithelial removal, a solution of 0.1% riboflavin and 1% hydroxypropyl methylcellulose (Vibex Rapid, Avedro) was

instilled on the centre of the cornea and was allowed to soak for 10 min. After completing the riboflavin soak, the solution was rinsed from the eye with a balanced salt solution. Next, UVA energy was applied at 7.2 J/cm<sup>2</sup> with an irradiance of 30 mW/cm<sup>2</sup> to the eye underwent continuous (4 min) light illumination for epi-off continuous accelerated CXL. Finally, the eye was rinsed with a balanced salt solution again, and a bandage contact lens (PureVision; Bausch & Lomb, Rochester, New York, USA) was applied to the cornea until complete re-epithelialisation was achieved.

After surgery, all patients were administered with topical 0.5% levofloxacin four times daily for 2 weeks, 0.5% corticosteroid loteprednol etabonate (Lotemax; Bausch & Lomb, Tampa, Florida, USA) and preservative-free artificial tears four times daily for one month, and 0.2% carbomer eye gel (Liposic; Bausch & Lomb, Brunsbütteler Damm, Berlin, Germany) once daily at night for one month.

Patients were examined before surgery and at 3, 6, and 12 months postoperatively. Postoperative evaluation included UDVA, corneal biomechanical parameters, corneal topography, and corneal thickness profiles (epithelial and stromal) using AS-OCT.

### **Statistical analysis**

Data were recorded into a Microsoft Excel spreadsheet (Microsoft; Redmond, Washington, USA), and statistical analysis was performed using SPSS for MAC, version 25.0 (IBM SPSS, Armonk, New York, USA). The normality of the data was tested with the Shapiro-Wilk test. A paired t-test was performed to analyse postoperative changes. If the data were not normally distributed, the Wilcoxon rank-sum test was performed. Friedman analysis of variance (ANOVA) with the Bonferroni correction was applied in case data did not show normal distribution. *P* values less than 0.05 were considered statistically significant.

## **Results**

In total, 33 eyes from 20 patients were enrolled in this retrospective study. The mean age at the time of the procedure was 22.33 ± 5.15 years (range, 10–33 years). Among the 20 patients, 18 eyes (55%) had stage I KC, 9 eyes (27%) had stage II KC, 3 eyes (9%) had stage III KC, and 3 eyes (9%) had stage IV KC. Bilateral epi-off continuous accelerated CXL was performed in 13 patients, among whom 12 patient (15 eyes) had stage I KC, 7 patient (7 eyes) had stage II KC, and 10 patients (10 eyes) had dominant eyes with a more severe KC stage compared to the non-dominant eyes (Table 1).

Table 1  
Preoperative Patient Demographic Data

Parameter	Epi-off Continuous Accelerated CXL
Eyes/Patients (n)	33/20
Age (y)	22.33 ± 5.15
Sex (M/F)	14/6
MRSE (D)	-7.44 ± 4.16
K <sub>max</sub> (D)	51.42 ± 6.18
K <sub>mean</sub> (D)	48.79 ± 5.00
K <sub>ast.</sub> (D)	5.24 ± 3.24
UDVA (logMAR)	1.06 ± 0.49
CDVA (logMAR)	0.23 ± 0.19
Grade of KC	
I	18 (55%)
II	9 (27%)
III	3 (9%)
IV	3 (9%)
<p>Epi-off = epithelium-off; CXL = corneal collagen crosslinking; M = male; F = female; D = diopters; MRSE = manifest refraction spherical equivalent; K<sub>max</sub> = maximum keratometry; K<sub>mean</sub> = front average keratometry; K<sub>ast.</sub> = keratometric astigmatism; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; logMAR = logarithm of the minimum angle of resolution; KC = keratoconus.</p> <p>*KC stage according to the Amsler-Krumeich classification.<sup>1</sup></p>	

The differences between preoperative and postoperative values were statistically significant in epithelial thickness changes at 12 months after epi-off continuous accelerated CXL. Regarding the changes in corneal stromal thickness, the mean between preoperative and postoperative CCT values were 480.58 ± 35.40 μm, 476.97 ± 32.75 μm and 481.12 ± 33.90 μm (p = 0.923), respectively; further details are shown in Table 2. Moreover, the changes in corneal epithelial thickness was statistically significant thinner in the inner nasal, -1.48 ± 3.65 μm (p = 0.024); inner superior-nasal, -1.76 ± 4.21 μm (p = 0.024); inner superior, -1.52 ± 4.02 μm (p = 0.046); inner superior-temporal, -1.97 ± 4.57 μm (p = 0.018); outer inferior, -2.12 ± 4.46 μm (p = 0.014); outer inferior-nasal, -2.15 ± 4.82 μm (p = 0.022); outer temporal, -1.73 ± 4.45 μm (p =

0.019) at 6 months after epi-off continuous accelerated CXL. The changes in corneal epithelial profiles are shown in Fig. 1.

Table 2  
Mean Corneal Thickness Changes After Epi-off Continuous Accelerated CXL

<b>Mean ± SD</b>				
Parameter	Pre-op	6-month Post-op	12-month Post-op	<i>P</i> value
Stromal thickness (µm)				
Central	480.58 ± 35.40	476.97 ± 32.75	481.12 ± 33.90	0.923
Inner Inferior	495.42 ± 24.76	490.88 ± 26.99	494.82 ± 22.31	0.774
Inner Inferior-nasal	514.82 ± 23.65	510.42 ± 23.10	512.88 ± 20.26	0.813
Inner Nasal	528.76 ± 27.04	527.64 ± 23.77	530.24 ± 22.47	0.910
Inner Superior-nasal	539.94 ± 27.50	540.42 ± 25.32	541.48 ± 23.85	0.892
Inner Superior	539.73 ± 29.20	540.06 ± 27.37	542.24 ± 25.47	0.914
Inner Superior-temporal	524.94 ± 31.58	523.79 ± 30.47	528.09 ± 28.85*	0.869
Inner Temporal	497.67 ± 33.36	495.64 ± 32.01	502.79 ± 32.93*	0.822
Inner Inferior-temporal	471.79 ± 75.95	481.36 ± 29.38	489.52 ± 35.18	0.744
Outer Inferior	541.97 ± 29.52	537.09 ± 32.42	543.97 ± 23.77	0.545
Outer Inferior-nasal	552.52 ± 30.71	548.12 ± 29.22	550.39 ± 23.10	0.746
Outer Nasal	559.36 ± 29.82	557.39 ± 28.06	558.97 ± 22.40	0.998
Outer Superior-nasal	569.79 ± 28.31	570.24 ± 25.40	569.21 ± 22.24	0.959
Outer Superior	571.55 ± 29.54	572.42 ± 27.46	575.36 ± 25.65	0.737
Outer Superior-temporal	555.52 ± 30.36	555.97 ± 29.21	557.70 ± 25.29	0.964
Outer Temporal	529.39 ± 35.71	530.06 ± 31.41	533.42 ± 29.10	0.953
Outer Inferior-temporal	524.73 ± 31.23	523.82 ± 29.30	529.91 ± 35.00	0.881
Epithelial thickness (µm)				
Central	50.58 ± 5.61	49.70 ± 5.29	51.06 ± 5.79	0.779
Inner Inferior	50.27 ± 4.69	49.64 ± 4.31	50.97 ± 4.78	0.413
Inner Inferior-nasal	54.91 ± 4.77	53.48 ± 4.34	54.12 ± 4.74	0.470
Inner Nasal	57.18 ± 5.66	55.70 ± 4.04*	55.94 ± 4.18	0.578
Inner Superior-nasal	57.70 ± 4.81	55.94 ± 3.51*	56.55 ± 3.95	0.322
Inner Superior	56.45 ± 4.95	54.94 ± 3.53*	55.70 ± 4.40	0.346

	<b>Mean ± SD</b>			
Inner Superior-temporal	56.00 ± 6.30	54.03 ± 4.42*	54.58 ± 4.50	0.295
Inner Temporal	50.82 ± 5.84	49.94 ± 4.65	50.42 ± 5.72	0.872
Inner Inferior-temporal	47.45 ± 4.68	48.21 ± 3.89	48.82 ± 3.99	0.220
Outer Inferior	55.18 ± 6.86	53.06 ± 6.81*	55.58 ± 5.26	0.337
Outer Inferior-nasal	58.15 ± 5.55	56.00 ± 3.77*	57.12 ± 4.19	0.184
Outer Nasal	56.73 ± 5.71	55.79 ± 3.44	56.24 ± 3.65	0.838
Outer Superior-nasal	55.85 ± 5.13	54.76 ± 3.91	54.82 ± 3.79	0.570
Outer Superior	54.48 ± 5.14	53.64 ± 4.14	53.97 ± 4.25	0.750
Outer Superior-temporal	56.91 ± 5.36	55.67 ± 3.23	56.15 ± 3.65	0.475
Outer Temporal	56.33 ± 6.68	54.61 ± 4.12*	54.45 ± 5.09	0.507
Outer Inferior-temporal	52.70 ± 6.28	52.18 ± 4.40	53.55 ± 5.14	0.542
Epi-off = epithelium-off; CXL = corneal collagen crosslinking; SD = standard deviations; Pre-op = preoperative; Post-op = postoperative.				
*Wilcoxon rank-sum test was performed.				

UDVA improved significantly at 3 months after epi-off continuous accelerated CXL. The mean value changes in UDVA were  $0.71 \pm 0.37$  logarithm of the minimum angle of resolution (logMAR),  $0.68 \pm 0.37$  logMAR, and  $0.67 \pm 0.32$  logMAR, respectively, during the 12 months follow-up (all  $p < 0.001$ ). Corneal compensated intraocular pressure (IOPcc) and goldmann-correlated intraocular pressure (IOPg) were significantly increased at 3 months after epi-off continuous accelerated CXL; the mean value changes in IOPcc was  $14.69 \pm 2.33$  mmHg and IOPg was  $11.54 \pm 3.19$  mmHg, respectively, during the 12 months follow-up ( $p = 0.017$  and  $p = 0.004$ ). At the last follow-up, there were no statistically significant decreased corneal keratometry (Ks, Kf, and AveK) or reduced simulated keratometric cylinder (Cyl) (all  $p > 0.05$ ). More details are shown in Table 3.

Table 3

Changes in UDVA, IOP, and Corneal Biomechanical Parameters After Epi-off Continuous Accelerated CXL

Mean ± SD				
Parameter	Pre-op	3-month Post-op	6-month Post-op	12-month Post-op
UDVA (logMAR)	1.06 ± 0.49	0.71 ± 0.37*	0.68 ± 0.37*	0.67 ± 0.32*
Ks (D)	51.42 ± 6.18	51.26 ± 6.30	51.07 ± 5.88	51.75 ± 6.75
Kf (D)	46.17 ± 4.13	46.13 ± 4.36	45.91 ± 3.63	46.67 ± 4.51*
AveK (D)	48.79 ± 5.00	48.38 ± 4.91	48.08 ± 4.26	49.18 ± 5.41
Cyl (D)	5.24 ± 3.24	5.13 ± 3.41	5.14 ± 3.49	5.02 ± 3.27
IOPcc (mmHg)	13.86 ± 2.02	14.69 ± 2.33*	14.66 ± 2.91	14.62 ± 2.19
IOPg (mmHg)	10.22 ± 2.66	10.74 ± 2.78	11.54 ± 3.19*	10.99 ± 3.11
CRF (mmHg)	6.92 ± 1.62	6.78 ± 1.77	7.52 ± 1.83*	7.09 ± 1.89
CH (mmHg)	8.16 ± 1.27	7.81 ± 1.49	8.38 ± 1.58	8.07 ± 1.40
UDVA = uncorrected distance visual acuity; IOP = intraocular pressure; Epi-off = epithelium-off; CXL = corneal collagen crosslinking; SD = standard deviations; Pre-op = preoperative; Post-op = postoperative; logMAR = logarithm of the minimum angle of resolution; Ks = simulated keratometry of the steep meridian; Kf = simulated keratometry of the flat meridian; AveK = average of simulated keratometry; Cyl = simulated keratometric cylinder; D = diopters; IOPcc = corneal compensated intraocular pressure; IOPg = goldmann-correlated intraocular pressure; CRF = corneal resistance factor; CH = corneal hysteresis; mmHg = millimeters of mercury.				
*P value was statistically significant differences between postoperative and baseline.				

## Discussion

Successful treatments of KC should address two distinct factors: the optical inefficiency of corneal irregularity and the disease progression of corneal bulging; these may be required for corneal transplantation [10]. Recently, CXL performed with the Avedro KXL system has been established as an effective therapeutic technique for halting the progression of KC [2, 4–6]. To our knowledge, this study is the first to retrospectively evaluate the regional corneal epithelial and stromal remodelling after epi-off continuous accelerated CXL with AS-OCT.

A doughnut-like epithelial profile showed an attenuation of peripheral thinning after CXL [7]. Atia et al. [8] explained the mechanism of epithelial compensation, wherein the epithelium layer appears to undergo remodelling to reduce the bulging of the anterior stromal surface and to render the anterior corneal surface more regular. However, it is important to evaluate the corneal epithelial and stromal thickness profile of KC in pre-clinical diagnosis and to monitor the progression of KC after treatment [7–9]. Rocha et al. [7] and Atia et al. [8] investigated the corneal epithelial and stromal remodelling after conventional CXL (3 mW/cm<sup>2</sup> for 30 min, total energy 5.4 J/cm<sup>2</sup>). However, the regional epithelial thickness profile was

significantly thinner in the inner areas (within 2.5 mm of corneal apex) after conventional CXL [7]. Other groups [8] reported both inner areas (3 mm of corneal apex) and outer areas (6 mm of corneal apex) of the corneal epithelial remodelling were significantly thinner after conventional CXL with no evidence of KC progression during the 6 months follow-up. Regarding our results, more significant changes were investigated in the mean value of corneal regional epithelial remodelling in the inner areas (3 mm of corneal apex) than the outer areas (6 mm of corneal apex) and the regional thickened corneal epithelium in 12 (36.4%) eyes at 6 months after epi-off continuous accelerated CXL (30 mW/cm<sup>2</sup> for 4 min, total energy 7.2 J/cm<sup>2</sup>).

Hersh et al. [11] suggested that the improvement in CDVA after CXL is probably related to the remodelling in both corneal epithelia and stroma. Mita et al. [12] investigated the time course of keratocytes repopulation in the corneal stroma following corneal wound healing after accelerated CXL (30 mW/cm<sup>2</sup> for 3 min, total energy 5.4 J/cm<sup>2</sup>) over the 6 months postoperative period. Moreover, the increase in corneal densitometry following epi-off continuous accelerated CXL was not associated with a change in visual acuity, and an improvement of visual acuity reported in the previous study [2, 4–6]. Ozgurhan et al. [5] reported UDVA improved or remained stable in 41 (93.1%) eyes at 24 months after treatment for paediatric KC with a mean improvement of 0.13 logMAR. In current study, UDVA significantly improved at 3 months after treatment, and UDVA improved or remained stable in 17 (51.5%) eyes at 12 months after treatment with a mean improvement of 0.16 logMAR. A reduction in the keratometric values may be used to assess the efficacy of the procedure [6]. Ağca et al. [6] reported the mean reductions in mean K ( $K_{\text{mean}}$ ) and maximum K ( $K_{\text{max}}$ ) were less than 0.25 D, and  $K_{\text{max}}$  decreased  $\geq 1.00$  D in 38 (33.6%) eyes during the 5 years follow-up. Most of the literatures reported that the  $K_{\text{mean}}$  values were significant decreased from 0.13 D to 0.62 D [2, 4, 5]. Regarding our results, the mean value of corneal keratometry changes in Ks and AveK was 0.35 D, and the mean reduction in Cyl was 0.22 D; the differences were not statistically significant. Ks and AveK decreased or remained stable in 10 (30.3%) eyes, and Cyl was reduced  $\geq 0.50$  D in 12 (36.4%) eyes. The primary goal of CXL was to strengthen the corneal collagen adjacent fibres and to stabilize the cone-like bulging cornea, rather than improve its shape [6].

The application of CXL is based on significantly stiffening the corneal stroma by photochemically cross-linking the individual corneal collagen fibres [12]. These reactive oxygen species cause new covalent bonds to form across adjacent collagen strands in the stromal layer of the cornea. Mita et al. [12] reported that the variations in corneal biomechanical parameters were not significant over the time course of corneal wound healing after accelerated CXL. In our study, we found that the mean biomechanical values (corneal resistance factor and corneal hysteresis) were not significantly changed during the 12 months follow-up. This increased stiffness and rigidity stabilised the cornea and halted or slowed the progression of keratoconus [6, 12]. On the other hand, the factors influencing IOP measurements in CXL are the improvement in corneal biomechanical properties (corneal strengthening), corticosteroids administration, sex, and preoperative CCT less than 450  $\mu\text{m}$  [13]. It was noted that the IOP values throughout the 12 months follow-up period was significantly higher than the preoperative IOP values.

Accelerated CXL might halt the progression of KC, and in some cases restore the corneal geography, in accordance with previous reports in the literature [2, 4–6]. Moreover, the application of CXL in paediatric KC showed controversial outcomes, and there are still controversies regarding the corneal thickness changes in epi-off continuous accelerated CXL [2, 5, 6]. Uçakhan et al. [14] reported equally effective outcomes in both paediatric and adult patients with KC after conventional CXL over a 3 years follow-up, whereas another group reported higher failure rates in paediatric KC compared to adults after conventional CXL over a 10 years follow-up [15]. In addition, both accelerated CXL and conventional CXL provided superior postoperative outcomes and more significant changes in keratometry values. Corneal biomechanical stability was less in conventional CXL than accelerated CXL (total energy 5.4 J/cm<sup>2</sup>) [16]. The main limitation of this study was its retrospective design. A large sample size to achieve more power and indication expansion is needed for further investigation.

In conclusion, CXL has become a commonly used therapeutic technique for halting the progression of KC. Our results indicated that corneal epithelial remodelling occurred more significantly in the inner areas compared to the outer areas after treatment. Epi-off continuous accelerated CXL is a safe and effective surgical option for both paediatric and adult KC with no evidence of subsequent keratoconic progression during the 12 months follow-up.

## Abbreviations

KC: keratoconus; UVA: ultraviolet-A; epi-off: epithelium-off; logMAR: logarithm of the minimum angle of resolution; CCT: central corneal thickness; CXL: corneal collagen cross-linking (CXL); UDVA: uncorrected distance visual acuity; CDVA: corrected distance visual acuity; AveK: average of simulated keratometry; Ks: simulated keratometry of the steep meridian; Kf: simulated keratometry of the flat meridian; Cyl: simulated keratometric cylinder; D: diopters; epi-on: Trans-epithelial; IOPcc: corneal compensated intraocular pressure; IOPg: goldmann-correlated intraocular pressure; CRF: corneal resistance factor; CH: corneal hysteresis

## Declarations

### **Ethics approval and consent to participate:**

This study was approved by the Ethics Committee of the Peking Union Medical College Hospital (China) and followed the tenets of the Declaration of Helsinki. A written and informed consent was obtained from all participants or a parent or guardian on behalf of any participants under the age of 18.

### **Consent for publication:**

Not applicable.

### **Availability of data and materials:**

The datasets obtained and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:**

The authors declare that they have no competing interests.

**Funding:**

Not applicable.

**Authors' contributions:**

Conceived and designed the experiments: J.P., Y.L., C-K.J. and G.Y.

Performed the experiments: Y.L.

Collected and analyzed the data: J.P., M.W. and S.J.K.

Contributed reagents/materials/analysis tools: J.P., Y.L., and C-K.J.

Wrote the paper: J.P.

Critical revision of the manuscript: J.P.

All the authors have read and approved the final manuscript.

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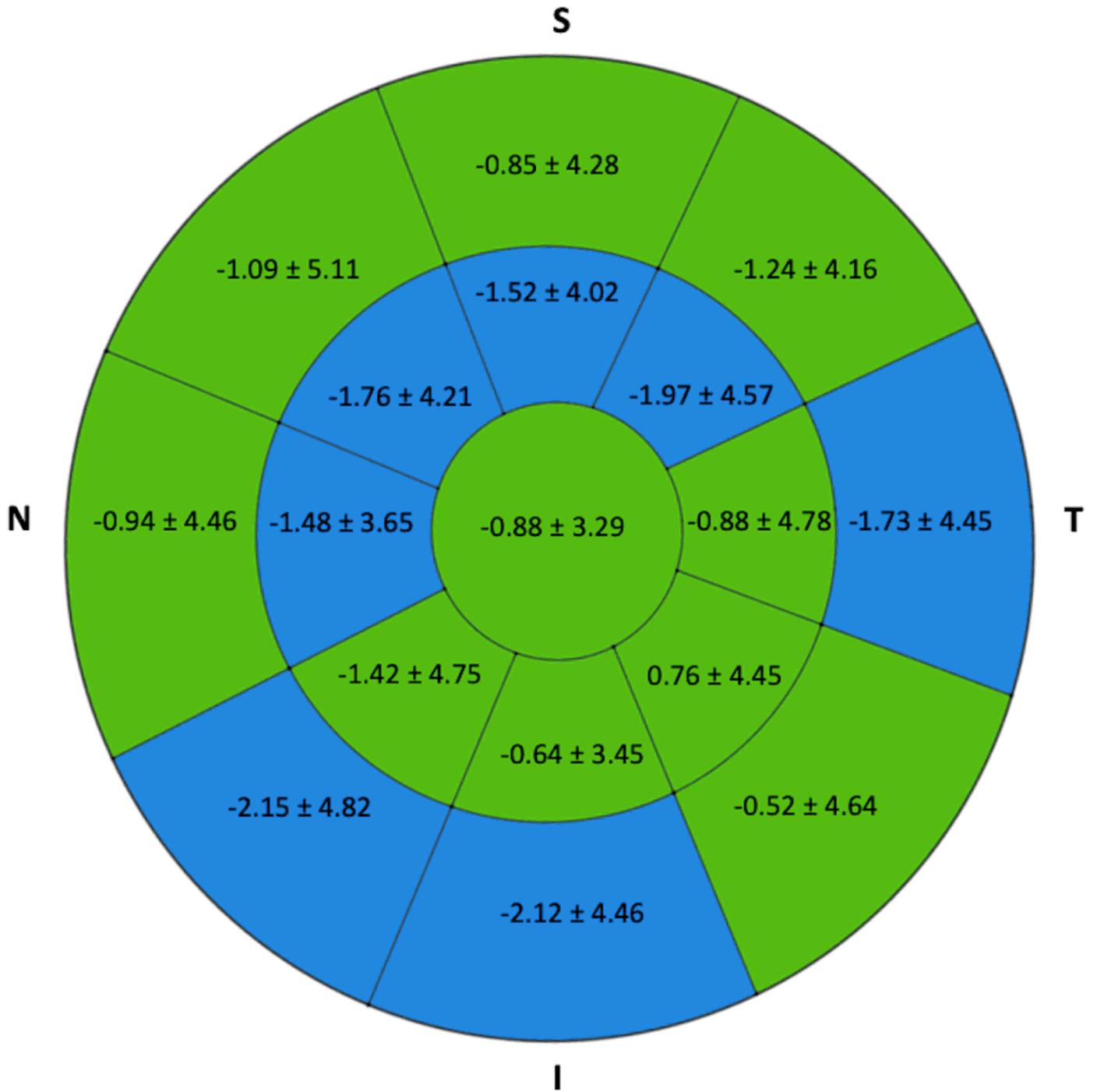
Not applicable.

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## Figures



**Figure 1**

Mean changes in epithelial thickness distribution at 6 months after epi-off continuous accelerated corneal collagen cross-linking (CXL). Values in blue indicate a significant change after surgery ( $p < 0.05$ ). S: superior; I: inferior; T: temporal; N: nasal