Corneal Higher-order Aberrations Changes after Accelerated Cross-linking for Keratoconus

Abdelrahman Salman (✉ abd.r.salman10@gmail.com)

Tishreen University

Marwan Ghabra

Whipps Cross University Hospital, Leytonstone, London

Taym Darwish

Tishreen University

Obeda Kailani

Queen Mary's Hospital, King's College Hospital NHS Foundation Trust, London

Hussein Ibrahim

Surgical Eye Hospital, Health Ministry, Damascus

Hakam Ghabra

Harley Street Eye Centre, London

Research Article

Keywords: Keratoconus, Corneal cross-linking, Sirius, Higher order aberrations, Scheimpflug, Topography, Visual acuity

Posted Date: January 24th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1221986/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Aim: To evaluate changes in corneal higher-order aberrations (HOAs) after accelerated corneal cross-linking (A-CXL) and the effect of change in HOAs on visual acuity between baseline and one year after A-CXL.

Methods: In this retrospective case-series, 32 eyes of 24 patients with keratoconus (KC) underwent accelerated corneal cross-linking. The following anterior corneal HOAs: total corneal HOAs, trefoil, secondary trefoil, coma, secondary coma, secondary astigmatism and spherical aberrations were measured and analysed using the Scheimpflug-Placido Sirius (CSO, Italy) topographer at baseline and 12 months after CXL. Multivariate analysis was used to evaluate the independent effect of HOA subtypes on changes in uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA).

Results: At one year post CXL, UDVA and CDVA were significantly improved, -0.13 ± 0.19 LogMar ($P = 0.0005$) and -0.08 ± 0.11 LogMar ($P = 0.0003$), respectively. The mean preoperative trefoil, secondary trefoil, secondary coma and secondary astigmatism were 0.95 ± 0.46 ; μm , 0.20 ± 0.11 ; μm , 0.29 ± 0.19 ; μm and 0.42 ± 0.17 μm , respectively. At one year, the mean values decreased significantly to 0.77 ± 0.47 μm , 0.15 ± 0.11 μm , 0.25 ± 0.18 μm and 0.34 ± 0.18 μm , respectively ($P < 0.05$, for all). While no independent relationship between any HOA changes and change in UDVA was observed, there was a significant effect of the change in secondary coma on the change in CDVA (95% CI 0.01-1.34, $P = 0.048$; $\beta = 0.67$).

Conclusion: Accelerated corneal cross-linking was shown to be effective in improving corneal HOAs in eyes with progressive keratoconus at one year follow-up. A change in secondary coma had a significant and independent effect on CDVA.

Introduction

Keratoconus (KC) is a progressive corneal disease characterized by thinning of the central or para-central portion of the cornea resulting in irregular astigmatism and visual deterioration (1). In KC, corneal thinning causes marked shape changes which induce significant amounts of higher-order aberrations, and differ significantly from the aberrations of the normal cornea (2). Corneal cross-linking was first introduced to halt the progression of keratoconus (3). This procedure increases the rate of formation of chemical bonds between the fibres of corneal collagen by means of a highly localized photopolymerization using ultraviolet A (UVA) light and a photosensitizer, riboflavin (4). Findings in recent studies suggest that CXL can also have useful visual, topographic and aberrometric effect (5, 6, 7). In our previous study, patients had an improvement in uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), maximum keratometry and several topographic indices after CXL(8).

This study was designed to evaluate the effect of accelerated CXL (A-CXL) on anterior corneal HOAs, and to examine the correlation between the change in visual acuity (UDVA and CDVA) and change in corneal HOAs 1 year after CXL.

Patients And Methods

A retrospective case series was conducted at the Department of Ophthalmology, Tishreen University Hospital, Syria. All patients included in this study underwent A-CXL (10 mW/cm² for 9 minutes). This study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics Committee of Tishreen University Hospital, Tishreen University, Syria. Prior to undergoing treatment, written informed consent was obtained from all patients.

The inclusion criteria consisted of patients aged 18 years or older at the time of surgery with progressive KC, clear corneas, minimum corneal thickness of ≥ 400 μ m after removal of the epithelium and a minimum follow up duration of at least 12 months after A-CXL. The diagnosis of KC was established in concordance with the Global Consensus on Keratoconus and Corneal Ectatic Diseases Report (9). Progression of keratoconus was defined as: at least 1 diopter increase in the anterior maximum keratometry or in the manifest refraction spherical equivalent (MRSE), a decrease of 5% in the minimum pachymetry, or loss of at least two lines of the corrected distance visual acuity during the past 12 months (10).

Exclusion criteria included pregnancy, central or paracentral corneal opacities or scarring, a clinical history of herpetic keratitis, evidence of active ophthalmic inflammation, autoimmune disease, severe dry eye, and patients with a history of ocular surgery. Patients who developed postoperative scarring or corneal haze were also excluded from the analysis due to the secondary optical aberrations that result with both scarring and haze (11).

All keratoconic eyes were classified according to Amsler-Krumeich classification (12). Contact lens-wearing patients were asked to discontinue wearing their lenses for 3-weeks and 1-week for rigid and soft contact lenses, respectively.

Evaluation included the measurement of UDVA, CDVA, manifest refraction spherical equivalent (MRSE), slit-lamp biomicroscopy, retinoscopy and fundoscopy. Topography, tomography and aberrometry data were measured at baseline preoperatively and at 12 months postoperatively using the Sirius Sheimpflug-Placido topographer (Costruzioni Strumenti Oftalmici, Florence, Italy). Anterior corneal higher order aberrations were measured at the central 6.0 mm. Three well-focused, aligned and centred images were obtained for each eye. In order to optimise image quality, patients were asked to blink before each image capture to eliminate the effect of corneal surface dryness. Placido disc mires up to the 17th ring had to be continuous to consider the videokeratography to be of good quality and satisfactory for calculation of the Zernike coefficients for a 6.0 mm simulated pupil. Software acquisition was uniform for all data points for consistency (Phoenix v.2.6).

Surgical Procedure:

An epithelium-off A-CXL technique was performed in all subjects. Topical anesthesia consisted of Proparacaine Hydrochloride 0.5% (Proparacain Rama 0.5%, Rama Pharma, Syria) eye drops administered

at 2 minute intervals, starting 10-minutes preoperatively. The central 8-9 mm corneal epithelium was removed using a blunt spatula and dry sponge (without alcohol assistance). Twenty minutes prior to irradiance, Riboflavin with Dextran (0.1% Riboflavin in 20% Dextran. Medio Cross, Germany) solution was applied every 2 minutes. The saturation of the anterior chamber with riboflavin was checked with slit-lamp biomicroscopy. The 32 eyes were irradiated with the Vega C.B.M-X Linker (CSO, Italy) using the A-CXL 10 mW/cm² UVA for 9 minutes to achieve a total energy of 5.4 J/cm². During the 9 minutes of irradiance, riboflavin solution was applied every 2 minutes. At the end of the procedure, the corneal surface was irrigated with balanced salt solution (BSS) and a soft contact lens was applied for 5 days. Topical moxifloxacin 0.5% (Megamox, Rama Pharma, Syria) and fluorometholone 0.1% (Methouflor 0.1%, Diamond Pharma, Syria) eye drops were prescribed for 1 week and 2 weeks, respectively. The surgical protocol utilized for accelerated corneal cross-linking was previously described (8, 13).

Mean Outcomes Measures:

Measurements UDVA, CDVA, MRSE, maximum keratometry, mean keratometry, simulated topographic cylinder, symmetry index front (SIf), total Baiocchi-Calossi-Versaci index (BCV) and minimum corneal thickness (ThkMin). Anterior corneal higher order aberrations were collected from the Sirius over the central 6 mm zone. The Sirius Scheimpflug-Placido topographer provides corneal aberrometry using a special algorithm based on the elevation map. Normalized coefficients were used, expressed in microns of wavefront error (root mean square [RMS]), and labeled with International Organization for Standardization (ISO) standardized double-index Zernike symbols (14). The collected HOAs data included: Root mean square (RMS) total HOAs, RMS trefoil Z (3, ± 3), RMS trefoil II Z (5, ± 3), RMS coma Z (3, ± 1), RMS coma II Z (5, ± 1), RMS astigmatism II Z (4, ± 2), and RMS spherical aberration I Z (4, 0).

Statistical Analysis

Visual acuity was converted to a logMAR notation. A paired t-test was used to test the significance between HOAs at baseline and HOAs 1 year after A-CXL. Multivariate regression analysis was used to identify the factors associated with changes in UDVA and CDVA. This analysis was performed using generalized estimating equations to correct for patients in whom both eyes were included in the dataset. Analyses were performed using SPSS software (version 21.0, International Business Machines Corp.). P-values of less than 0.05 were considered significant.

Results

A total of thirty-two eyes of 24 patients were included in this analysis. The mean age was 24.7 ± 6.7 years. Sixteen (66.67%) patients were females. According to the Amsler-Krumeich classification, 24 eyes had stage I KC and 8 eyes had stage II KC. Furthermore, all 32 eyes had central KC, with an apex within a central 2 mm radius.

Visual, Refractive and Topographic Outcomes

The LogMAR UDVA and CDVA were significantly improved (-0.13 ± 0.19 and -0.08 ± 0.11 respectively, $P < 0.05$ for both) at one year postoperatively. The mean values of MRSE, sphere and manifest astigmatism were significantly improved, 0.52 ± 0.63 D, 0.39 ± 0.61 D and 0.26 ± 0.46 D, respectively ($P < 0.05$ for all). While the values of mean keratometry, simulated cylinder, Sif and BCV were not significantly changed ($P > 0.05$ for all), the maximum keratometry significantly decreased from their baseline line values of 54.62 ± 4.13 D to 54.0 ± 4.63 D at one year post CXL. The mean values of ThkMin were significantly decreased (-11.09 ± 19.60 μ m, $P < 0.05$). Table 1 shows the visual, refractive and topographic outcomes.

At 1 year-follow-up, one eye (3.12%) lost 1 Snellen line of the CDVA, 14 (43.75%) had no change and 17 (53.13%) eyes gained one line or more. The maximum keratometry was decreased or unchanged in 29 eyes and increased by more than 1 D in 3 eyes.

Change in Higher-Order Aberrations

Total HOAs, coma and spherical aberrations values were not significantly changed at one year post CXL ($P > 0.05$ for all). However, trefoil, trefoil II, coma II and astigmatism II decreased significantly at one year compared to baseline values ($P < 0.05$ for all). Table 2 shows the anterior corneal aberrations changes in the study population.

Multivariate Analysis

Table 3 shows the results of the multivariate analysis of CDVA and UDVA. The calculated effects of the baseline confounders: visual acuity, mean keratometry, simulated cylinder, Sif, BCV, ThkMin and HOAs subtypes and the change in HOA subtypes, were given for both determinants. The confounders, CDVA and Sif at baseline were strongly related to a change in CDVA. An independent significant effect of the change in coma II was observed in the changes seen in CDVA ($P = 0.048$, $\beta = 0.67$). While no independent relationship between any changes in HOAs and UDVA were observed, astigmatism II at baseline was significantly related to the change in UDVA ($P = 0.03$, $\beta = -0.95$).

Discussion

While corneal cross-linking that was first introduced to halt the progression of KC, it has also been found to improve visual acuity and corneal topography characteristics (5, 6, 15). Several studies have found increased higher-order aberrations in keratoconic corneas (16, 17), suggesting that these eyes may have poorer retinal images than a normal eye, leading to reduced visual acuity (2). This study was designed to report on HOAs 1 year following accelerated-CXL performed to treat KC, and to determine whether changes in HOAs are associated with a change in visual acuity.

Consistent with previously reported studies (5, 6, 18), our results showed significant improvements in MRSE, UDVA and CDVA at one year after cross-linking. The factors responsible for improving visual acuity after cross-linking are not yet clear. Kirgiz et al. postulated that anterior corneal flattening and

posterior corneal steepening after cross-linking are important factors in the stabilization of keratometric values and improvement of visual outcomes (19).

In this analysis, the Sirius Scheimpflug-Placido tomographer was used to measure the anterior corneal aberrations, in light of the finding that the anterior corneal surface contributes to approximately one half of the total aberrations of the eye (20). We opted to evaluate changes in corneal HOAs after CXL treatment rather than measuring whole-eye HOAs. We also excluded any cases with apparent corneal haze from our analysis. The repeatability of anterior corneal aberrations with the Sirius is high (20). Furthermore, we paid special attention to the anterior corneal HOAs that are most relevant to clinical practice (i.e. coma, trefoil, and spherical aberration) (2).

Our results showed significant improvement in trefoil, secondary trefoils, secondary coma and secondary astigmatism ($P < 0.05$ for all) one year after CXL. We found similarities in our findings to those reported by other studies. Ghanem et al. reported a significant decrease in coma, trefoil, secondary astigmatism, secondary coma and secondary trefoil 2 years after CXL. The improvement in HOAs in KC eyes was attributed to the flattening of the corneal apex caused by the effect of CXL (21). In this study, the significant flattening in the apical keratometry may explain the significant improvement in HOAs after CXL. However, in our previously reported study that compared an accelerated CXL irradiation protocol (10 mW/cm² for 9 minutes) with the standard Dresden protocol (3 mW/cm² for 30 minutes), the standard protocol resulted in significantly greater anterior corneal flattening than the accelerated protocol (8). Furthermore, we found that the impact of each treatment on the anterior HOAs was different; anterior trefoil was significantly decreased in the accelerated CXL group, whereas anterior total HOAs and coma were significantly decreased in the standard CXL group. Wisse et al. reported significant improvement in spherical aberrations 1 year after standard CXL (11). Mazzotta et al. found significant improvement in coma 5 years after accelerated CXL (9mW/cm² for 10 minutes) (15). Caporossi et al. reported a statistically significant reduction in coma aberrations between preoperative and 1-month postoperative values with a sustained effect 4 years after standard CXL (22). However, they found no significant change in spherical aberration. These findings are consistent with ours; we found no significant change in mean spherical aberrations values at one year after CXL. In their study, Greenstein et al. reported a significant improvement in total HOAs and coma when derived from the cornea alone and when measured as total ocular aberrations 1 year after standard CXL (22). They found that total corneal HOAs worsened by more than 1.0 μm only in one eye (out of 31 keratoconus eyes). In contrast, although we did not observe significant changes in total anterior HOAs, none of the 32 eyes showed an increase of 1.0 μm or more at 1-year follow-up.

Previous studies have demonstrated that the Zernike polynomials have a different impact on visual function (2). Wisse et al. found that horizontal coma had the strongest relationship with change in UDVA (11). In contrast, Greenstien et al. found no significant correlation between improvement in HOAs values and improvement in UDVA and CDVA after CXL (23). Ghanem et al. found no correlations between changes in individual corneal aberrations and visual acuity after CXL (21). On the contrary, our

multivariate analysis demonstrated that coma II had the strongest relationship with changes in CDVA. However, no correlation was observed between HOAs subtypes changes and change in UDVA.

Several limitations to our study may have affected the results. The retrospective nature of the study is designed to analyse pre-existing data and is subject to bias. In addition, we were unable to evaluate total ocular HOAs as a wavefront device was not used in this study. We used the Sirius Scheimpflug tomography software program, which calculates optical aberrations (based on elevation maps) rather than using an aberrometer, which measures optical aberrations. Further studies with a larger sample size to evaluate wavefront aberrations in addition to Scheimpflug-based aberrations are needed.

Conclusion

This study demonstrated that anterior corneal HOAs, in particular trefoil, trefoil II, coma II and astigmatism II, improved after accelerated CXL. Only changes in coma II had a significant and independent effect on corrected distance visual acuity.

Declarations

Ethics approval and consent to participate

This study was approved by the research ethics committee of Tishreen University in accordance with tents of the Declaration of Helsinki. Informed consent, in Arabic language, to participate in this study was obtained from all participants.

Consent of publication

Consent for publication, was obtained from all study subjects.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due their containing information that could compromise the privacy of research participants, but are available from the corresponding author (Abdelrahman Salman) on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None

Acknowledgement

None

Author's contributions

AS was the major contributor, interpreted the data. AS and OK wrote the manuscript. MG, TD, HI and HG reviewed the manuscript.

References

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998 Jan-Feb;42(4):297-319. (Pubmed)
2. Jinabhai A, Radhakrishnan H, O'donnell C. (2009). Higher-Order Aberrations in Keratoconus: A Review. *Optometry in Practice*, 10, 141–160. (Link)
3. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003 May;135(5):620–7. (Pubmed)
4. Arbelaez MC, Sekito MB, Vidal C, Choudhury SR. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One-year results. *Oman J Ophthalmol*. 2009;2(1):33–38. (Link)
5. Artieda, June & Mahillo-Fernández, Ignacio & Morote, Ignacio & Alba, Nicolás. (2020). Analysis of visual, refractive, topographic and aberrometric changes in different uncommon accelerated cross-linking protocols in keratoconus: A 12 month follow-up. *Journal of EuCornea*. 9. 1–6. 10.1016/j.xjec.2020.08.001. (Link)
6. Kirgiz A, Eliacik M, Yildirim Y. Different accelerated corneal collagen cross-linking treatment modalities in progressive keratoconus. *Eye Vis (Lond)*. 2019 Jun 3;6:16. (Pubmed)
7. Singal N, Ong Tone S, Stein R, Bujak MC, Chan CC, Chew HF, El-Defrawy S, Jin Y, Kranemann C, Rabinovitch T, Rootman DS, Slomovic AR, Cohen A, Dai D, Hatch W. Comparison of accelerated CXL alone, accelerated CXL-ICRS, and accelerated CXL-TG-PRK in progressive keratoconus and other corneal ectasias. *J Cataract Refract Surg*. 2020 Feb;46(2):276–286. (Pubmed)
8. Salman AM, Darwish TR, Haddad YH, Shabaan RH, Askar MZ. Accelerated versus Standard Corneal Cross-linking for Progressive Keratoconus in Syria. *J Ophthalmic Vis Res*. 2021 Jul 29;16(3):338–348. (Pubmed)
9. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, Malecaze F, Nishida K, Sangwan VS; Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. Global consensus on keratoconus and ectatic diseases. *Cornea*. 2015 Apr;34(4):359–69. (Pubmed)
10. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *J Cataract Refract Surg*. 2011 Jan;37(1):149–60. (Pubmed)
11. Wisse RP, Gadiot S, Soeters N, Godefrooij DA, Imhof SM, van der Lelij A. Higher-order aberrations 1 year after corneal collagen crosslinking for keratoconus and their independent effect on visual acuity. *J Cataract Refract Surg*. 2016 Jul;42(7):1046–52. (Pubmed)
12. AMSLER M. Kératocône classique et kératocône fruste; arguments unitaires [Classic keratocene and crude keratocene; Unitary arguments]. *Ophthalmologica*. 1946 Feb-Mar;111(2-3):96-101. French.

(Pubmed)

13. Salman A, Darwish T, Ghabra M, Kailani O, Khalil H, Shaaban R. Clinical Outcomes of Accelerated Corneal Cross-Linking for Pediatric Keratoconus. *J Ophthalmol*. 2021 Nov 18;2021:1851883. (Pubmed)
14. International Organization for Standardization (ISO). *Ophthalmic Optics and Instruments-Reporting Aberrations of the Human Eye*. Geneva, Switzerland, ISO, 2008: (ISO 24157:2008). (Link)
15. Mazzotta C, Raiskup F, Hafezi F, Torres-Netto EA, Armia Balamoun A, Giannaccare G, Bagaglia SA. Long term results of accelerated 9 mW corneal crosslinking for early progressive keratoconus: the Siena Eye-Cross Study 2. *Eye Vis (Lond)*. 2021 May 1;8(1):16. (Pubmed)
16. Alió JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg*. 2006 Jun;22(6):539–45. PMID: 16805116. (Pubmed)
17. Shneor E, Piñero DP, Doron R. Contrast sensitivity and higher-order aberrations in Keratoconus subjects. *Sci Rep*. 2021 Jun 21;11(1):12971. (Pubmed)
18. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011 Jul;37(7):1282–90. (Pubmed)
19. Kırgız A, Atalay K, Çabuk KŞ, Kaldırım H, Taşkapılı M. Factors affecting visual acuity after accelerated crosslinking in patients with progressive keratoconus. *Arq Bras Oftalmol*. 2016 May-Jun;79(3):151–4. (Pubmed)
20. Bayhan HA, Aslan Bayhan S, Muhafız E, Can I. Repeatability of aberrometric measurements in normal and keratoconus eyes using a new Scheimpflug-Placido topographer. *J Cataract Refract Surg*. 2014 Feb;40(2):269–75. (Pubmed)
21. Ghanem RC, Santhiago MR, Berti T, Netto MV, Ghanem VC. Topographic, corneal wavefront, and refractive outcomes 2 years after collagen crosslinking for progressive keratoconus. *Cornea*. 2014 Jan;33(1):43–8. (Pubmed)
22. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. *Am J Ophthalmol*. 2010 Apr;149(4):585–93. (Pubmed)
23. Greenstein SA, Fry KL, Hersh MJ, Hersh PS. Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. *J Cataract Refract Surg*. 2012 Feb;38(2):292–302. (Pubmed)

Tables

Table 1. Patients Characteristics at Baseline and at 1 Year after Cross-Linking.

	Preoperative		Postoperative		Change		
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	p value
LogMAR UDVA	0.63	0.43	0.50	0.40	-0.13	0.19	0.0005
LogMAR CDVA	0.30	0.25	0.22	0.20	-0.08	0.11	0.0003
MRSE (D)	-2.64	2.45	-2.12	2.29	0.52	0.63	0.0001
Sphere (D)	-1.03	2.42	-0.64	2.22	0.39	0.61	0.001
Cylinder (D)	-3.21	1.46	-2.95	1.37	0.26	0.46	0.0032
Mean keratometry (D)	46.78	2.00	46.81	2.37	0.03	1.85	0.9296
Maximum Keratometry (D)	54.62	4.13	54.00	4.63	0.61	1.41	0.029
Simulated Cylinder (D)	-3.32	1.68	-3.47	2.16	-0.15	0.90	0.3484
Slf (D)	5.84	3.02	5.45	3.19	-0.39	1.33	0.1072
BCV (D)	3.01	2.44	2.51	1.26	-0.50	2.25	0.2109
ThkMin (μm)	432.19	27.04	421.09	26.42	-11.09	19.60	0.0032

UDVA= uncorrected distance visual acuity; CDVA= corrected distance visual acuity; MRSE= manifest refraction spherical equivalent; D= diopter; Slf= symmetry index front; BCV= Baiocchi-Calossi-Versaci; ThkMin= minimum corneal thickness; μm= micron. P. Chi-squared test. Statistically significant values (P < 0.05). Values in bold are statistically significant.

Table 2. Changes in Anterior Corneal HOAs One Year after A-CXL.

	Preoperative		Postoperative		Change		
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	p value
Total HOAs	2.40	1.28	2.24	1.17	-0.16	0.55	0.1032
Z (3, ± 3) trefoil	0.95	0.46	0.77	0.47	-0.18	0.28	0.0014
Z (5, ± 3) trefoil II	0.20	0.11	0.15	0.11	-0.05	0.12	0.0356
Z (3, ± 1) coma	2.10	1.13	1.95	1.22	-0.14	0.46	0.0846
Z (5, ± 1) coma II	0.29	0.19	0.25	0.18	-0.05	0.10	0.0113
Z (4, ± 2) astigmatism II	0.42	0.17	0.34	0.18	-0.08	0.15	0.0056
Z (4, 0) spherical aberration I	0.10	0.35	0.07	0.32	-0.03	0.17	0.302

HOAs= higher-order aberrations; Z= Zernike. P. Chi-squared test. Statistically significant values (P < 0.05). Values in bold are statistically significant.

Table 3. Multivariable Analysis of the Effect of a Change in Topographic Parameters and Optical Aberrations on CDVA and UDVA 1 Year after Cross-Linking.

Δ= changes in variables after cross-linking; CDVA= corrected distance visual acuity; CI= confidence interval; HOA= higher-order aberration; UDVA= uncorrected distance visual acuity; Slf= symmetry index front; BCV= Baiocchi-Calossi-Versaci; ThkMin=minimum corneal thickness; Z= Zernike; HOAs= higher-order aberrations; UDVA= uncorrected distance visual acuity; * Statistically significant.

Δ CDVA		β Coefficient	[95% Conf. Interval]		p value
Baseline Confounder	CDVA	-0.33	-0.57	-0.09	0.012*
	Mean keratometry	0.02	0.00	0.05	0.061
	Simulated cylinder	-0.07	-0.22	0.08	0.328
	SIf	-0.07	-0.13	-0.01	0.027*
	BCV	-0.02	-0.07	0.03	0.448
	ThkMin	0.00	0.00	0.00	0.054
	Z (3, $\pm$ 3) trefoil	0.02	-0.15	0.20	0.786
	Z (3, $\pm$ 1) coma	0.08	-0.03	0.19	0.156
	Z (4, 0) spherical aberration I	0.15	-0.09	0.39	0.204
	Z (4, $\pm$ 2) astigmatism II	0.13	-0.25	0.51	0.454
	Z (5, $\pm$ 3) trefoil II	0.41	-0.56	1.38	0.372
	Z (5, $\pm$ 1) coma II	0.02	-0.83	0.87	0.964
	Δ Z (3, $\pm$ 1) coma	-0.06	-0.18	0.07	0.334
Change in HOAs Subtype	Δ Z (5, $\pm$ 1) coma II	0.67	0.01	1.34	0.0480*
	Δ Z (3, $\pm$ 3) trefoil	0.08	-0.17	0.34	0.488
	Δ Z (5, $\pm$ 3) trefoil II	-0.10	-0.95	0.74	0.795
	Δ Z (4, 0) Spherical Aberration I	0.08	-0.21	0.37	0.559
Δ UDVA		β Coefficient	[95% Conf. Interval]		p value
Baseline Confounder	UDVA	-0.19	-0.46	0.08	0.151
	Mean keratometry	0.03	-0.03	0.09	0.258
	Sim Cylinder	-0.20	-0.57	0.17	0.254
	SIf	-0.03	-0.16	0.10	0.611
	BCV	0.00	-0.13	0.12	0.942
	ThkMin	0.00	-0.01	0.00	0.388
	Z (3, $\pm$ 3) trefoil	0.03	-0.41	0.47	0.887
	Z (3, $\pm$ 1) coma	0.00	-0.26	0.27	0.986

	Z (4, 0) Spherical Aberration I	0.18	-0.31	0.68	0.425
	Z (4, ± 2) astigmatism II	-0.95	-1.78	-0.11	0.03*
	(5, ± 3) trefoil II	1.57	-0.70	3.85	0.153
	(5, ± 1) coma II	-0.46	-2.42	1.50	0.611
Change in HOAs Subtype	Δ Z (3, ± 1) coma	-0.16	-0.47	0.15	0.285
	Δ Z (5, ± 1) coma II	0.32	-1.32	1.96	0.676
	Δ Z (3, ± 3) trefoil	-0.23	-0.75	0.29	0.349
	Δ Z (5, ± 3) trefoil II	1.09	-0.97	3.16	0.266
	Δ Z (4, 0) Spherical Aberration I	-0.02	-0.71	0.67	0.947