Higher-order aberration 4 years after corneal collagen cross-linking

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Purpose: Corneal collagen cross-linking (CXL) is a treatment strategy used in keratoconic eyes. Evaluation of long-term changes of higher-order aberrations (HOAs) after CXL is useful in understanding the efficacy of this procedure in improving optical, refractive, and visual acuity. This study aims to investigate the long-term effect of CXL on ocular HOA in patients with progressive keratoconus (KC). Methods: Using an OPD-Scan II aberrometer, ocular HOAs measurements of 56 eyes of 56 patients that underwent CXL was evaluated at the baseline, 1, 2, and 4 years after the procedure. All OPD-Scan measurements were decomposed into Zernike coefficients from 3rd to 6th order. Results: The results revealed that except for a few parameters, most of the aberration parameters continuously decreased during the study. In the 4-year postoperative period, a statistically significant improvement in all HOA parameters except 5th order Zernike polynomials (Z4, Z5, Z6, Z7, and Z8) was observed. All the values significantly decreased compared to the preoperative measurements (P < 0.05). The mean ± standard deviation (SD) root mean square of the 3rd, 4th, and the 5th order as well as coma, coma like, and total HOA parameters were significantly decreased compared to both preoperative and previous visits (P < 0.001). There were significant correlations between preoperative measurements of HOAs parameters with best-corrected visual acuity (BCVA) including Z2, Z3, Z4, Z5, Z6, Z7, and Z8. Moreover, all the HOAs parameters in 4 years after the CXL were significantly correlated with BCVA (P < 0.05). Conclusion: CXL is effective in improving HOA parameters in eyes with progressive KC during a long-term follow-up.

Key words: Aberrations, corneal cross-linking, keratoconus, OPD-Scan II, wavefront analysis

Keratoconus (KC) is a progressive corneal ectatic disorder causing corneal thinning, irregular astigmatism, myopia, and increased higher-order aberrations (HOAs) which result in vision deterioration, even blindness. Corneal collagen cross-linking (CXL) is a treatment strategy in keratoconic eyes that was first introduced in 2003. Based on a pathological and biomechanical approach, this method aimed to slow down and possibly arrest the progression of KC and decrease the need for subsequent corneal keratoplasty that was necessary in almost all severe cases of KC. CXL is based on photopolymerization of collagen fibers and increases intra- and inter-fibrillar covalent bonds and improves corneal resistance specifically against stretching. Postoperative studies have also been able to demonstrate the efficacy of this method in improving clinical findings as well as topographical, tomographical and aberrometric indices in adults as well as children and adolescents.

HOAs are among the important refractive and visual quality properties of the human ocular system and the decreased level of some visual features such as contrast sensitivity have been partially attributed to these parameters. Evaluation of long-term changes of HOAs after CXL is useful in understanding the efficacy of CXL on improving optical, refractive, and visual acuity (VA). Researchers have shown a significant reduction in HOA parameters following CXL in patients with progressive KC. This study was designed to evaluate the effect of CXL on ocular HOAs in patients with progressive KC 4 years after the procedure and using OPD-Scan II aberrometer.

Methods

Study design

A prospective study was conducted at the cornea clinic of the AJA University Hospital, Tehran, Iran from 2011 to 2016. The protocols of this study were in accordance with the tenets of the Declaration of Helsinki, and the approval was obtained from the ethics committee of the clinic. After explaining the purpose of the study, signed informed consent was obtained from those who agreed to participate.

Study population

Fifty-six eyes of 56 patients aged 18–50 years with progressive KC were enrolled in the study. The diagnosis of KC was based on corneal topographic map and anterior and posterior elevation pattern by optical path difference Scan II (OPD-Scan II; Nidek Co., Ltd., Gamagori, Japan) as well as at least one of the clinical diagnostic signs such as Fleischer ring, Vogt’s striae, Munson’s sign, Rizzuti’s sign, conjugal protrusion of the cornea at the apex, or corneal thinning by means of slit-lamp biomicroscopy. KC progression was defined as an increase in the level of some visual features such as contrast sensitivity.
of 1.00 diopter (D) or more in the steepest keratometric measurement, an increase of 1.00 D or more in manifest cylinder, or an increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE) in a 24-month period. Patients with thinnest corneal thickness <400 µm, history of ocular trauma or surgery, corneal scarring or corneal opacities, history of any concurrent ophthalmic disorders such as glaucoma, severe dry eye, or corneal infections, history of autoimmune or connective tissue disorders, patients with pregnancy or nursing women, and patients with poor compliance were excluded from the study.

Data collection
All participants underwent extensive ocular examinations, including uncorrected visual acuity (UCVA), and best-spectacle corrected visual acuity (BCVA), MRSE, Goldmann tonometry, slit-lamp biomicroscopy, ultrasound pachymetry, and topographic and tomographic imaging. The right eye of each participant was included in this study. The main outcome measures were HOA parameters which were evaluated along with mean keratometry (K), central corneal thickness (CCT), MRSE, UCVA, and BCVA at the baseline (preoperative), and then, at 1, 2, and 4 years after the treatment.

Aberrometry and wavefront analysis
Aberrometry and wavefront measurement were performed using OPD-Scan II. The OPD-Scan II aberrometer using placido-based topography and principle of scanning retinoscopy/skiascopy measures corneal, and whole eye aberrations. Patients-wearing contact lenses were asked to stop using them at least 3 weeks before the aberrometry. To avoid any possible diurnal variations, the examinations were performed between 9 am and 12 pm. All OPD-Scan measurements were performed under dark examination (2.2 Lux) over a 6 mm diameter zone centered on the corneal vertex, after 2 min of dark adaptation, three consecutive measurements were taken, and the average values were decomposed into Zernike coefficients. The Zernike coefficients for corneal first surface aberrations parameters from 3rd to 6th order were studied. Moreover, root mean square (RMS) value for primary coma aberration \( Z_{5}^{2} \)), and coma-like aberration (primary and secondary coma aberration \( Z_{5}^{2} \) and \( Z_{7}^{2} \)), and total HOA from third- to sixth-order were calculated. The detailed information regarding the Zernike polynomials has been discussed elsewhere.16,17

Corneal cross-linking procedure
The CXL procedure was performed according to the protocol described by Wollensak et al. with the following details.18 After the administration of tetracaine hydrochloride for topical anesthesia, a 10% alcohol-saturated sponge was applied to the central cornea for 30 s, and the corneal epithelium was removed over the central 9.0 mm by mechanical debridement with a Hockey knife. Then, every 2 min, two drops of riboflavin 0.1% with dextran 20% solution was instilled onto the cornea for 30 min until the stroma was completely penetrated, and the aqueous was stained yellow. Subsequently, a 9.0 mm diameter circular beam of ultraviolet A (UVA) irradiation which was emitted from a solid-state device (UV-X System, Peschke Meditrade GmbH, Huenenberg, Switzerland), 5 cm from the corneal apex with a wavelength of 370 ± 5 nm and an irradiance of 3 mW/cm² or 5.4 J/cm² was applied to the cornea for 30 min. During the UV exposure, one drop of riboflavin solution was again applied every 2 min. Antibiotic and corticosteroid drops were administered after the procedure, and a therapeutic contact lens was placed on the eye for 7 days. Patients were visited on the 7th day to remove the contact lenses and evaluate epithelial healing.

Statistical analysis
Statistical analysis was performed using IBM SPSS Statistics software (Version 22; IBM Inc., Armonk, New York, USA). The data are presented as mean ± standard deviation (SD). The normal distribution of the data was confirmed using the Kolmogorov–Smirnov test. Comparison of the measurements was performed using the repeated measures analysis of variance with Bonferroni adjustment for multiple comparisons. Pairwise comparisons were performed using paired t-test. The Pearson correlation analysis was performed to evaluate the relationship between HOAs parameters and UCVA and BCVA. \( P < 0.05 \) was considered statistically significant.

Results
A total of 56 eyes of 56 patients with progressive KC were enrolled in this study. No patients were lost to follow-up, and all patients completed the examination sessions. No patients suffered postoperation or long-term complication. The mean age of the study population was 31 ± 6 years. There were 31 male (55.3%) and 25 female (44.7%). All keratoconic eyes had stage 2 of KC severity according to Amsler–Krumeich classification.19,20 Preoperative and postoperative follow-up findings of the patients with KC are shown in Table 1. Significant decreases in mean K, MRSE, UCVA, and BCVA, and a significant increase in CCT was observed in the KC patients during the study (\( P < 0.001 \), all comparisons).

| Parameter                  | Preoperative | 1st year | 2nd year | 4th year | \( P \)   |
|----------------------------|--------------|----------|----------|----------|---------|
| Mean keratometry (diopter) | 50.6±3.3     | 49.1±3.5 | 48.7±3.6 | 48.4±3.5 | <0.001  |
| CCT (µm)                   | 438±23       | 444±26   | 447±25   | 450±25   | <0.001  |
| MRSE (diopter)             | −7.91±3.78   | −7.25±3.65 | −7.01±3.61 | −6.87±3.55 | <0.001  |
| UCVA (LogMAR)              | 0.76±0.35    | 0.65±0.31 | 0.59±0.29 | 0.53±0.27 | <0.001  |
| BCVA (LogMAR)              | 0.45±0.17    | 0.31±0.20 | 0.24±0.18 | 0.19±0.18 | <0.001  |

Data are presented as mean±SD. *P values were based on multiple comparisons of four examinations and were calculated using repeated measure ANOVA with Bonferroni adjustment for multiple comparisons. BCVA: Best-spectacle corrected visual acuity, CCT: Central corneal thickness, LogMAR: Logarithm of minimum angle of resolution, MRSE: Manifest refraction spherical equivalent, UCVA: Uncorrected visual acuity, SD: Standard deviation, ANOVA: Analysis of variance.
Comparison of the HOA parameters at the baseline and 1st, 2nd, and 4th year after CXL are demonstrated in Table 2. The results revealed except a few parameters most of the aberration parameters were continuously decreased during the study. Analysis of the HOA parameters at the 4-year postoperation has shown statistically significant improvement in all HOA parameters (P < 0.001, all comparisons) except 5th order Zernike polynomials (Z_5^1, Z_5^{-1}, Z_5^{3}, Z_5^{-3}, Z_5^{5}, Z_5^{-5}, P > 0.05). All the values significantly decreased compared to the preoperative measurements (P < 0.05). The mean ± SD RMS of the 3rd, 4th, and the 5th order as well as coma, coma-like, and total HOA parameters were significantly decreased compared to both preoperative and previous visits (P < 0.001).

There were significant correlations between preoperative measurements of HOAs parameters with BCVA including Z_1^1 (P < 0.001, r = 0.741), Z_3^{-3} (P = 0.002, r = 0.653), Z_5^{11} (P < 0.001, r = 0.625), Z_7^{11} (P = 0.012, r = 0.541), and Z_9^{3} (P = 0.025, r = 0.482). Moreover, all of the HOAs parameters in 4 years after the CXL were significantly correlated with BCVA (P < 0.05). The highest correlations were found in Z_1^1 (P < 0.001, r = 0.765), Z_3^{-3} (P ≤ 0.001, r = 0.701), total HOA (P < 0.001, r = 0.688), Z_5^{11} (P < 0.001, r = 0.650), and Z_7^{11} (P = 0.008, r = 0.555).

**Discussion**

CXL is a treatment recommended for patients with progressive KC and is the only available approach that relies on pathophysiological bases of the disease. Longitudinal and long-term follow-up studies have shown an acceptable safety for this technique, and extremely rare complications have been reported in patients.\textsuperscript{[21-25]} CXL that was originally introduced to slow or ideally prevent further progression of KC has shown to be efficient in improvement of clinical, topographical, and aberrometric indices.\textsuperscript{[8,11,13]} As with most of the studies in the literature, we found a significant improvement in mean K, CCT, MRSE, UCVA, and BCVA 4-year-postoperation, which indicates the corneal stability induced by CXL.\textsuperscript{[21-25]}

One of the optical sequelae of KC is increased HOAs that results in vision deterioration and visual dysfunction.\textsuperscript{[26]} In this study, we found that all ocular aberrations except 5th order Zernike polynomials significantly decreased in the course of the study. These findings are in agreement with those of other studies. A decrease in total HOAs, total spherical aberration, and total coma after CXL was reported by previous studies that used Nidek OPD-Scan.\textsuperscript{[8,13]} Ghanem et al.\textsuperscript{[21]} reported a significant reduction in coma, trefoil, secondary astigmatism, quadrefoil, secondary coma, and secondary tetrafoil 2 years after CXL. In a study by Greenstein et al.,\textsuperscript{[20]} on 96 eyes in a 12-month follow-up, researchers reported a significant reduction of total anterior corneal HOAs, total coma, 3rd order coma, and vertical coma. In our study, total anterior corneal HOAs, total HOAs, total coma, coma like, 3rd, 4th, and 5th order coma showed significant reduction in the first 12 months. However, most of

| Parameter | Preoperative | Mean±SD RMS | 1st year | 2nd year | 4th year | Difference (1st-4th year) | P* |
|-----------|-------------|-------------|---------|---------|---------|--------------------------|---|
| Z_1^1      | 0.43±0.20   | 0.42±0.20   | 0.36±0.17 | 0.32±0.15 | 0.11±0.05 | <0.001                  |
| Z_3^{-3}   | 1.43±0.57   | 1.38±0.56   | 1.16±0.47 | 1.06±0.43 | 0.36±0.14 | <0.001                  |
| Z_5^{11}   | 0.49±0.22   | 0.47±0.21   | 0.40±0.18 | 0.37±0.17 | 0.11±0.05 | <0.001                  |
| Z_2^{11}   | 0.57±0.27   | 0.56±0.27   | 0.52±0.25 | 0.44±0.21 | 0.13±0.06 | <0.001                  |
| Z_4^{11}   | 0.50±0.22   | 0.50±0.31   | 0.40±0.17 | 0.36±0.16 | 0.14±0.06 | <0.001                  |
| Z_5^{11}   | 0.42±0.16   | 0.43±0.29   | 0.38±0.14 | 0.35±0.13 | 0.08±0.03 | <0.001                  |
| Z_6^{11}   | 0.27±0.12   | 0.25±0.18   | 0.22±0.10 | 0.20±0.09 | 0.07±0.05 | <0.001                  |
| Z_7^{11}   | 0.36±0.11   | 0.37±0.21   | 0.33±0.15 | 0.30±0.10 | 0.06±0.02 | <0.001                  |
| Z_8^{11}   | 0.17±0.06   | 0.17±0.10   | 0.14±0.05 | 0.13±0.05 | 0.04±0.01 | <0.001                  |
| Z_9^{11}   | 0.10±0.03   | 0.10±0.05   | 0.08±0.02 | 0.08±0.02 | 0.02±0.00 | 0.153                   |
| Z_10^{11}  | 0.32±0.17   | 0.33±0.30   | 0.28±0.15 | 0.27±0.15 | 0.04±0.02 | 0.123                   |
| Z_11^{11}  | 0.13±0.07   | 0.13±0.12   | 0.11±0.06 | 0.10±0.06 | 0.03±0.01 | 0.483                   |
| Z_12^{11}  | 0.25±0.13   | 0.25±0.23   | 0.20±0.10 | 0.19±0.10 | 0.06±0.02 | 0.089                   |
| Z_13^{11}  | 0.11±0.05   | 0.12±0.10   | 0.10±0.05 | 0.09±0.04 | 0.02±0.01 | 0.531                   |
| Z_14^{11}  | 0.14±0.08   | 0.15±0.13   | 0.12±0.07 | 0.12±0.07 | 0.02±0.01 | 0.419                   |
| Z_15^{11}  | 0.46±0.20   | 0.42±0.35   | 0.34±0.14 | 0.30±0.13 | 0.13±0.05 | <0.001                  |
| 3rd order  | 1.74±0.54   | 1.69±0.49   | 1.44±0.40 | 1.31±0.37 | 0.43±0.12 | <0.001                  |
| 4th order  | 0.86±0.17   | 0.86±0.16   | 0.73±0.13 | 0.67±0.12 | 0.20±0.04 | <0.001                  |
| 5th order  | 0.51±0.14   | 0.52±0.21   | 0.44±0.14 | 0.43±0.13 | 0.08±0.02 | 0.023                   |
| Coma       | 1.51±0.55   | 1.47±0.53   | 1.23±0.34 | 1.13±0.30 | 0.38±0.14 | <0.001                  |
| Coma-like  | 1.57±0.53   | 1.52±0.51   | 1.28±0.42 | 1.18±0.39 | 0.38±0.13 | <0.001                  |
| HOA        | 2.04±0.44   | 1.99±0.42   | 1.70±0.35 | 1.55±0.32 | 0.49±0.11 | <0.001                  |

*P values were based on multiple comparisons of four examinations and were calculated using repeated measure ANOVA with Bonferroni adjustment for multiple comparisons. †Statistically significant change compared with preoperative measurements by paired t-test. ‡Statistically significant change compared with the previous measurement by paired t-test. ANOVA: Analysis of variance, SD: Standard deviation, RMS: Root mean square, HOA: Higher-order aberrations
the other aberration parameters showed significant reduction only after 24 months.

Caporossi et al. [22] found a statistically significant reduction in coma aberration between preoperative and 1-month postoperative values which was extended up to 4-year-follow-up. They reported 100% corneal stability among their patients in a 4-year follow-up after CXL. However, they did not observe any significant changes in spherical aberration. O’Brart et al. [23] in 2013 reported a significant decrease in secondary astigmatism, coma, and pentafoil in the 1st year postoperative compared with preoperative values. They also found that after 4-6 years follow-up, only secondary astigmatism and coma were significantly decreased compared with preoperative values. [24] They further extended their follow-up to 7 years after CXL and reported a significant decrease in secondary astigmatism and coma compared to preoperative values. [25] The improvement in HOAs parameters in patients with KC is attributed to the corneal flattening of the cone apex and reduced steepening of the cornea caused by CXL. [11]

In our study, there was a significant correlation between preoperative and postoperative HOAs and BCVA. Nevertheless, no significant correlation was observed between the improvement in HOAs values and VA. This finding has been reported in other studies. [10,11] However, our findings were similar to Ghanem et al. [11] reported a significant correlation between postoperative BCVA and corneal HOAs. Greenstein et al. [10] found no significant correlation between improvement in HOAs parameters and improvement in UCVA and BCVA after CXL.

Study limitations
This study has some limitations. Unfortunately, we did not have access to anterior and posterior corneal HOAs, which made a comparison of these aberrations with similar studies impossible. Another limitation is that we measured HOAs parameters only with an OPD-Scan, and we could not evaluate the patients with other devices, therefore, our results may be limited to only OPD-Scan II aberrometer and could not be generalized to other devices.

Conclusion
Our study showed continuous decrease in ocular HOAs during the long-term follow-up after CXL in patients with KC. It would be suggested that CXL is an effective procedure in correcting aberration parameters in KC patients.

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Conflicts of interest
There are no conflicts of interest.

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