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ORIGINAL ARTICLE

Effect of Corneal Collagen Cross Linking for Keratoconus on the Ocular Higher Order Aberrations

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Abstract

Background: **Keratoconus (KC) is a noninflammatory progressive central or paracentral thinning of the cornea that leads to poor vision, irregular astigmatism, development of myopia, and rising higher-order aberrations.**

Aim and objectives: **The purpose of this research is to determine the efficacy of corneal collagen cross-linking in addressing higher-order aberrations in keratoconic eyes.**

Patients and methods: **This study was a prospective interventional study. Total 50 eyes diagnosed with KC had originally scheduled corneal collagen Cross-linking.**

Results: **The root mean square of higher order aberrations decreased from 1.62 ± 0.86 to 1.48 ± 0.75, coma decreased from 0.73 ± 0.56 to 0.67 ± 0.49 and spherical aberrations decreased from 0.28 ± 0.28 to 0.23 ± 0.20 before and after surgery, respectively.**

Conclusion: **The only method now available to stop the advancement of KC is corneal cross-linking. Our results demonstrate that corneal cross-linking has positive optical and visual benefits with few side effects.**

Keywords: Corneal collagen cross-linking, Keratoconus, Ocular higher order aberrations

1. Introduction

A degenerative corneal illness, keratoconus (KC) is characterized by thinning of the center or para-central part of the cornea, resulting in uneven astigmatism and impairment of vision. Corneal ectasia has a complicated pathophysiology and etiology, with documented influences from biomechanics, enzymology, proteomics, and molecular genetics, among others. Higher-order aberrations (HOAs) are notably different from the aberrations of a normal cornea and may be induced by corneal thinning and corneal abnormalities in large quantities.[1]

Over 20 years ago, corneal cross-linking (CXL) was developed as a means of halting the advancement of KC. The method employs ultraviolet A (UVA) light and a photosensitizer, riboflavin, to speed up the production of chemical links between the fibers of corneal collagen. Positive effects on vision, topography, and aberrometry have been shown with CXL. After CXL, patients have reported improvements in their uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), maximal keratometry, and several topographic indices.[2]

Clinical indicators, corneal topographic signals, and tomographic signs are often used together to make a diagnosis of KC. The topographic patterns of KC corneas are different in both quality and quantity from those of healthy corneas. Combining topography and wave front analysis may help better identify keratoconic subtypes and increase the sensitivity and specificity of early diagnosis of subclinical KC. Two Zernike polynomials may be used to describe the shape of an aberrated wave front in the pupil of a complex optical system. Each coefficient term in a Zernike polynomial may be uniquely identified by its angular frequency and radial order. The relative importance of each factor in the total

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wave aberration is shown by the magnitude and sign of the coefficient values.[3]

The goal of this research was to assess the efficacy of corneal collagen cross linking in the treatment of KC on the suppression of higher order aberrations in the eye.

2. Patients and methods

This study was approved by the Ethical Committee at the Faculty of Medicine, Al-Azhar University. A written informed consent was submitted by all patients when they were enrolled.

A prospective interventional trial was conducted here. Total 50 eyes diagnosed with KC had originally scheduled corneal collagen Cross-linking.

Slit lamp results, retinoscopy, and concomitant pentacam tomography confirmed the diagnosis of KC. They all have UVA and riboflavin used to stimulate collagen synthesis in the cornea.

Inclusion criteria: 14 years age or older diagnosed as KC patient with higher order aberrations, clean corneas (absence of corneal opacities), minimum corneal thickness was higher than 400 μm at the KC apex, and discontinuation of rigid contact lens usage for at least one month prior to first examination for stage 1 or 2 KC.

Exclusion criteria: Herpetic keratitis, current ocular inflammation, autoimmune illnesses, past ocular operations, severe dry eye, pregnancy, and a history of central or paracentral corneal opacities or scarring are all risk factors.

2.1. Preoperative preparation

Preoperative preparations was included: Patients were subjected preoperatively to the following: Detailed medical and ocular history, systemic evaluations and ocular examination which will include: Slit-lamp biomicroscopy and fundus examination; ocular tomography imaging with a pentacam; simultaneous corneal tomography and scheimpflug camera corneal topography measurements; and wave front aberrometry using an I Design advanced wavescan studio aberrometer.

Fig. 1 showed Operative procedures: the CXL procedure was carried out on the patient while they were under the influence of sedatives and a local anesthetic (Benoxinate HCL drops 0.4 % were administered twice for 2 min). In the operating room, povidone-iodine 5 % was used to disinfect the patient's skin, a lid speculum was inserted, and the middle 8–9 mm of the corneal epithelium was debrided with a hockey knife using the epithelium-off method while using a microscope to make sure there was sufficient stromal riboflavin absorption.

Fig. 2: A spatula with a dull edge was used to scrape away the epithelium. Riboflavin infusion (0.1 % riboflavin solution). The stroma was given an injection of riboflavin (5-phosphate) containing 10 mg in 10 ml of a solution containing 20 % dextran-T-500 every 5 min for 30 min, or until a yellow color could be seen in the anterior chamber under a slit lamp biomicroscopy.

UVA (370 nm) radiation was shone on the center 8–9 mm of the cornea at a power density of 3 mW/cm^2 for 30 min. At a distance of 50 mm from the cornea's apex, UVA radiation with a wavelength of 370 nm and an aperture of 9 mm was delivered using the UV-X device (UV-X 1000; IROC, Zurich, Switzerland). Drops of riboflavin 0.1 % were given every 3–5 min during UVA exposure.

The eyes were irrigated with a balanced salt solution.

To ensure complete corneal re-epithelialization, a bandage soft contact lens was inserted and left in place.

The following were administered as postoperative care: All patients were given eye drops containing 1 % prednisolone acetate and 0.5 % moxifloxacin four times daily for 1 week, after which the antibiotic treatments were discontinued. Steroid dosage reduced from four times daily to three times daily, then from three times daily to two times daily, and so on, over the course of 2 weeks. The use of steroids was extended if haze developed, and antibiotic dose reduction was discontinued after a week.

2.2. Postoperative evaluation

On 1 day and 7 days after surgery: Slit lamp examination.

On 6 months after surgery: Refraction by autorefractometer, slit lamp examination and evaluation and recording of wave front aberrometry using I Design advanced wave scan studio aberrometer (Abbott Medical Optics Inc).

Informed consent: Once patients were given information about the potential dangers and advantages of the surgery, they gave their informed permission.

2.3. Ethics of research

Research on human or human products: Prospective study: The patient gave his or her informed permission. When a patient was deemed incapable, parental permission was obtained instead.

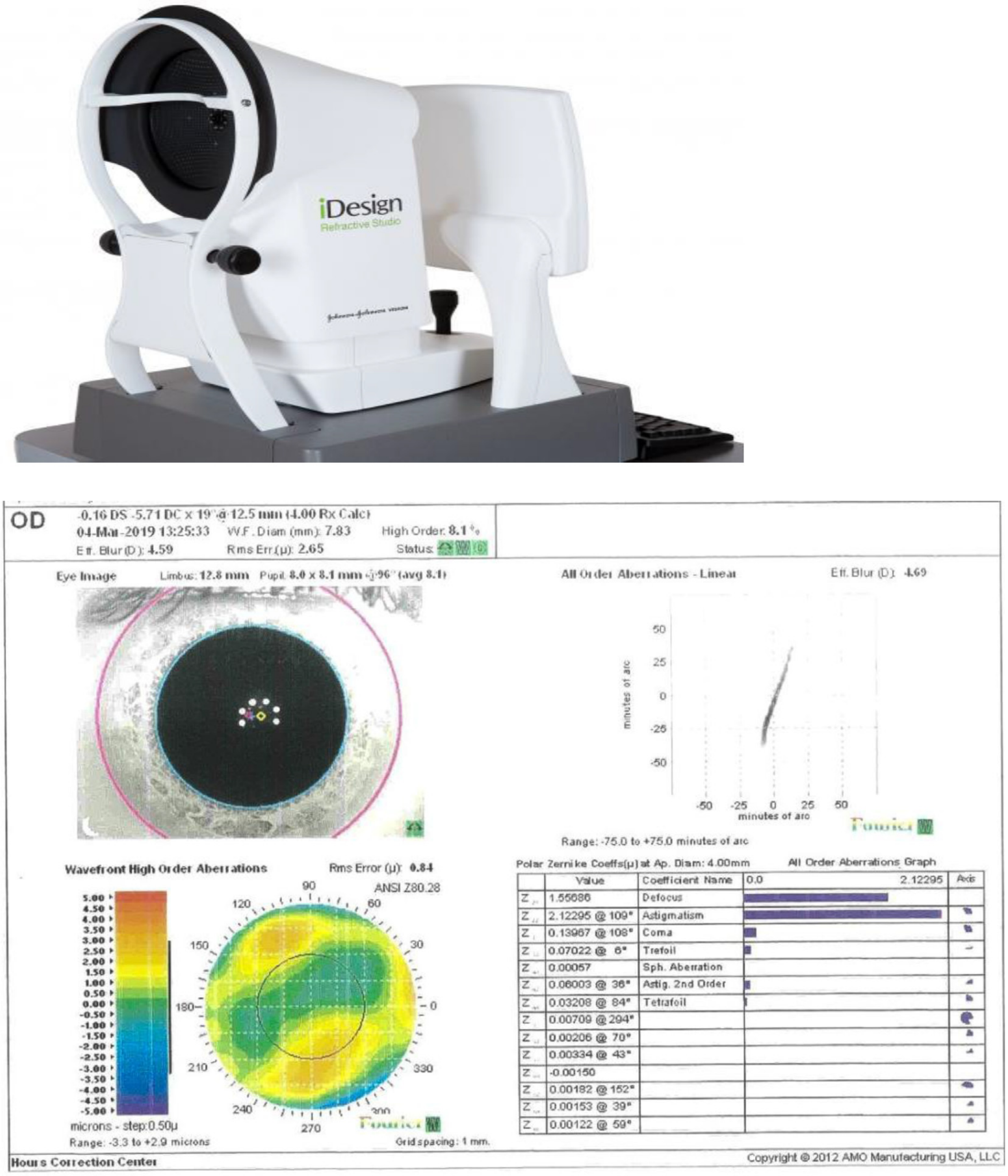

Fig. 1. I Design advanced wavescan studio aberrometer. I Design advanced wavescan studio aberrometer (Abbott Medical Optics Inc) and outprint.

Retrospective study: Confidentiality of record was considered.

2.4. Statistical analysis

All data was statistically evaluated with SPSS 23 software. Data was expressed as mean ± standard deviation (SD). Values are considered significant when *P* less than 0.05, while values are considered highly significant when *P* less than 0.001. Values are considered non-significant when *P* greater than 0.05.

3. Results and discussion

We used an I Design sophisticated wave scan studio Aberrometer to quantify corneal and ocular high-order aberration before and after corneal collagen cross-linking. As a corollary, we may expect to see a correlation between shifts in HOAs and shifts in visual acuity (VA).

Fifty individuals with keratoconic eye conditions were enrolled. Statistics showed that the average age was 23.86 ± 6.28 (range:14.0–38.0 years). A combination of factors, including the widespread

Fig. 2. A spatula with a dull edge was used to scrape away the epithelium. A spatula with a dull edge was used to scrape away the epithelium to apply ribofalvin.

use of corneal topography and scheimpflug based devices in the refractive field today, may account for the very young age at which KC is first diagnosed.[4]

VA is tested in a clinical setting to determine the impact of greater-order aberrations in keratoconic eyes. KC's increased production of HOAs causes a decline in eyesight. As a counter example, using CXL to fix HOAs may boost VA.[5]

By analyzing the point spread function, which is affected by HOA, wavefront technology may determine whether there is a connection between the two factors.

A linear function that accounts for Zernike modes describes the decline in high- and low-contrast acuity as the root-mean-square error (RMS) rises over 0.05 m. The VA may be enhanced by combining these six modes, which differ by two radial orders in the Zernike expansion but possess identical angular frequency. The interplay of modes in the fourth Zernike radial order often has the effect of reducing the clarity of the signal.[5]

According to the results of the current investigation, UCVA significantly improved after surgery. During the 6-month follow-up, patients' average UCVA had increased by 0.04 ± 0.33 Log Mar from its preoperative value of 0.35 ± 0.29 Log Mar to 0.32 ± 0.39 Log Mar. There was also a statistically significant increase in CDVA, from 0.06 ± 0.09 LogMAR before surgery to 0.04 ± 0.07 LogMAR at 6 months ($P < 0.05$). Many additional CXL trials have seen similar postoperative improvements in VA. Enhanced VA might pertain to either improved UCVA or enhanced CDVA, or both.

In EL Ragal et al.,[6] who have described the outcome of CXL in 15 eyes with average follow-up was 6 months, stated that the mean UCVA before surgery was 0.11 ± 0.07, therefore the postoperative improvement is statistically significant (range between 0.05 and 0.3) and changed to 0.15 ± 0.06 (range between 0.1 and 0.3) ($P < 0.05$). While the preoperative mean CDVA was not statistically significant improvement, Also, in Mazzotta et al.,[7] who have described the outcome of CXL in 44 eyes with average follow-up was 12 months, stated that mean BCVA improved 0.75 ± 0.08 Snellen lines. UCVA improved 0.51 ± 0.11 snellen lines.

Vinciguerra et al.[8] also noticed that BCVA got better after surgery. 12 months after surgery, the average BCVA (logMAR) went from 0.28 to 0.14. Significant enhancements in best corrected vision of logMAR 0.08 and 1.34 Snellen lines, respectively, were noted by Raiskup-Wolf et al.10 and Caporossi et al.11; these gains were maintained after 1 year of follow-up in both studies. In people with primary KC who had cross-linking done, they saw a trend towards a smoother corneal surface and an improvement in their ability to see.

The collaborative longitudinal evaluation of keratoconus (CLEK) study followed-up on 1209 people with clinically obvious KC every year for 8 years. The flat corneal meridian got worse at a rate of 0.20 D±0.80 D/year, and 24 % of the patients got worse by 3.00 D or more.[9]

In this study, the simulated keratometry of the steep axis went down in a way that was statistically significant (sim K steep), simulated keratometry of the flat axis (sim K flat), minimum keratometry, average corneal power over an area of 6 mm centered over the entrance pupil (APP) reading 6 months after CXL. The preoperative mean sim k steepest was 47.31 ± 2.83 and changed to 46.79 ± 2.64 D (decreased with 0.52 ± 0.79). While SIM K flat was 44.62 ± 1.90 and changed to 44.24 ± 1.84 (decreased with 0.38 ± 0.50) and APP was 46.08 ± 2.31 changed to 45.65 ± 2.17 (decreased with 0.43 ± 0.66) P less than 0.001.

These findings are consistent with those of EL Ragal,[6] who found that, after surgery, the average K levels were lower than they had been before. After surgery, the average K dropped from 49.97 ± 2.81 D (range 47.20–51.75) to 48.34 ± 2.64 D. (range 45.75–50.40).

According to Caporossi et al.,[10] temporary haze and corneal oedema may be to blame for the first deterioration of keratometric values recorded early in the first month. Doors et al.[11] proposed a similar explanation, citing possible corneal remodeling.

Mean spherical error decreased from −0.22 ± 1.91D preoperatively to −0.15 ± 1.84D postoperatively; mean cylindrical error decreased from −2.33 ± 1.41D to −2.27 ± 1.42D; and mean spherical equivalent (SE) error decreased from −1.35 ±±1.84 D to −1.31 1.94 D. Many studies have

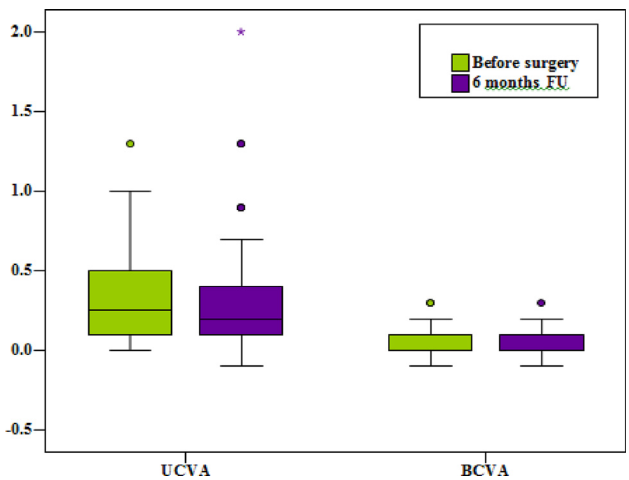

Fig. 3. Comparison between the pre-corneal cross-linking and 6 months post-corneal cross-linking according to uncorrected distance visual acuity and corrected distance visual acuity (n = 50).

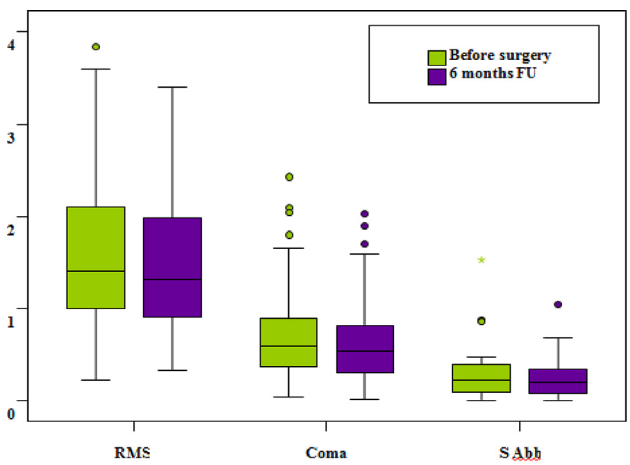

Fig. 4. Comparison between the pre-corneal cross-linkingand 6 months post-corneal cross-linking according to root mean square and higher-order aberrations (n = 50).

shown that refractive errors may be reduced with CXL. Nonrandomized, uncontrolled clinical studies have indicated mean increases of 1.03–2.25 D SE over 6–23 months.[6,10,12] In contrast, Wittig-Silva et al.[13] found no statistically significant difference between treated and control eyes in terms of refractive sphere, astigmatism, or manifest refraction SE values at 6 and 12 months, possibly because CXL is less effective in some patients than in others.

The total high order aberrations RMS were 1.62 ± 0.86 μm, at 6 months, it had reduced to 1.48 ± 0.75 μm ($P < 0.001$). The RMS of total coma aberrations were 0.73 ± 0.56 μm, at 6 months, it had reduced to 0.67 ± 0.49 μm ($P < 0.009$). The spherical aberrations RMS were 0.28 ± 0.28 μm, at 6 months, it had reduced to 0.23 ± 0.20 μm ($P < 0.061$). Our results support those of Caporossi et al.,[10] who found a statistically significant reduction in the total HOA and coma aberration, starting early after treatment and increasing for up to 24 months in 44 eyes.

Alio et al.,[14] reported that there was a significant increase in total corneal wavefront HOAs at a 6 mm optical zone in keratoconic eyes compared with normal eyes (RMS 3.14 μm compared with 0.52 μm, respectively), with the largest individual increase in Zernike values seen with coma (RMS 2.90 μm–0.35 μm, respectively) and spherical aberrations (RMS 1.06 μm–0.38 μm, respectively).

Barbero et al.,[15] Coma aberration was found to be 3.74 times greater in eyes with KC compared with normal controls, as reported by Barbero et al.[16] Higher order wavefront aberrations in early and probable KC were also reported to be abnormal by Jafri et al.,[17] Patients with suspected and early KC had a greater vertical coma and higher RMS values.

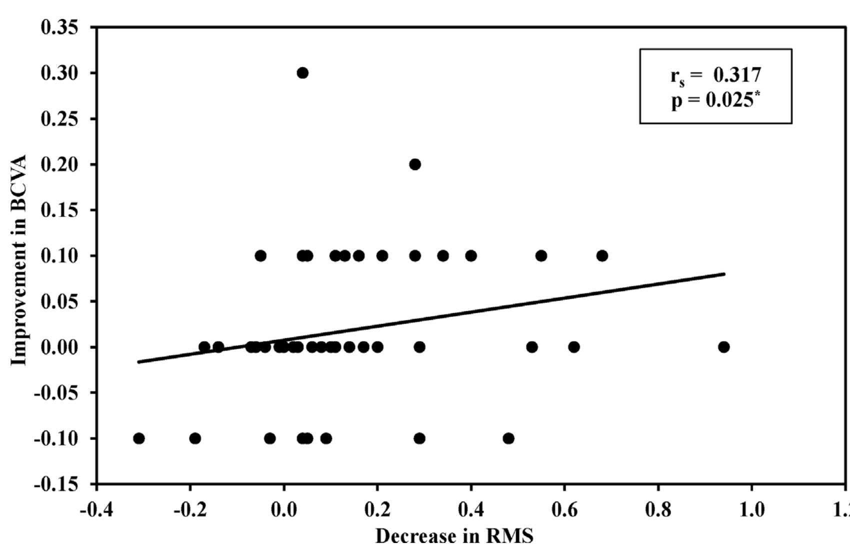

Fig. 5. Correlation between improvement in corrected distance visual acuity and root mean square (n = 50).

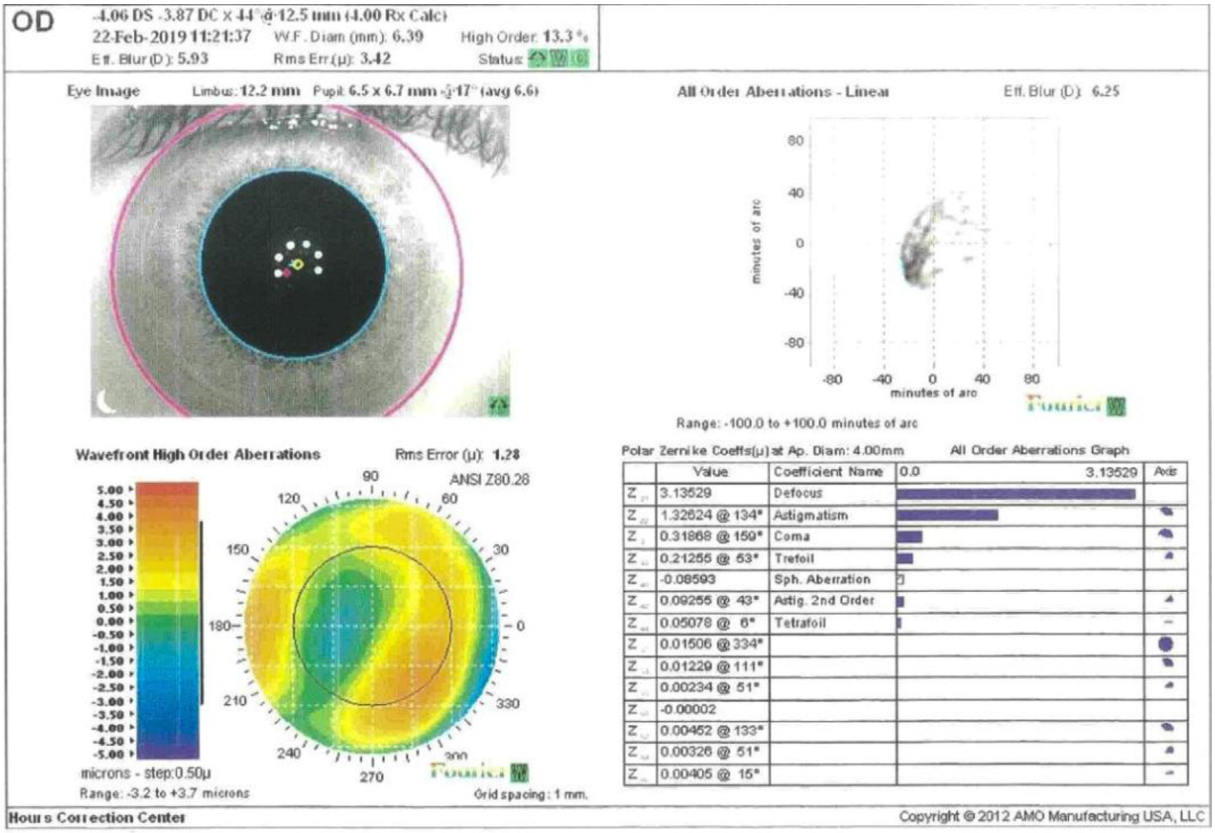

Fig. 6. Patient X postoperative Zernike analysis showing: root mean square 1.18, Coma aberration 0.22122, Spherical aberration - 0.06507.

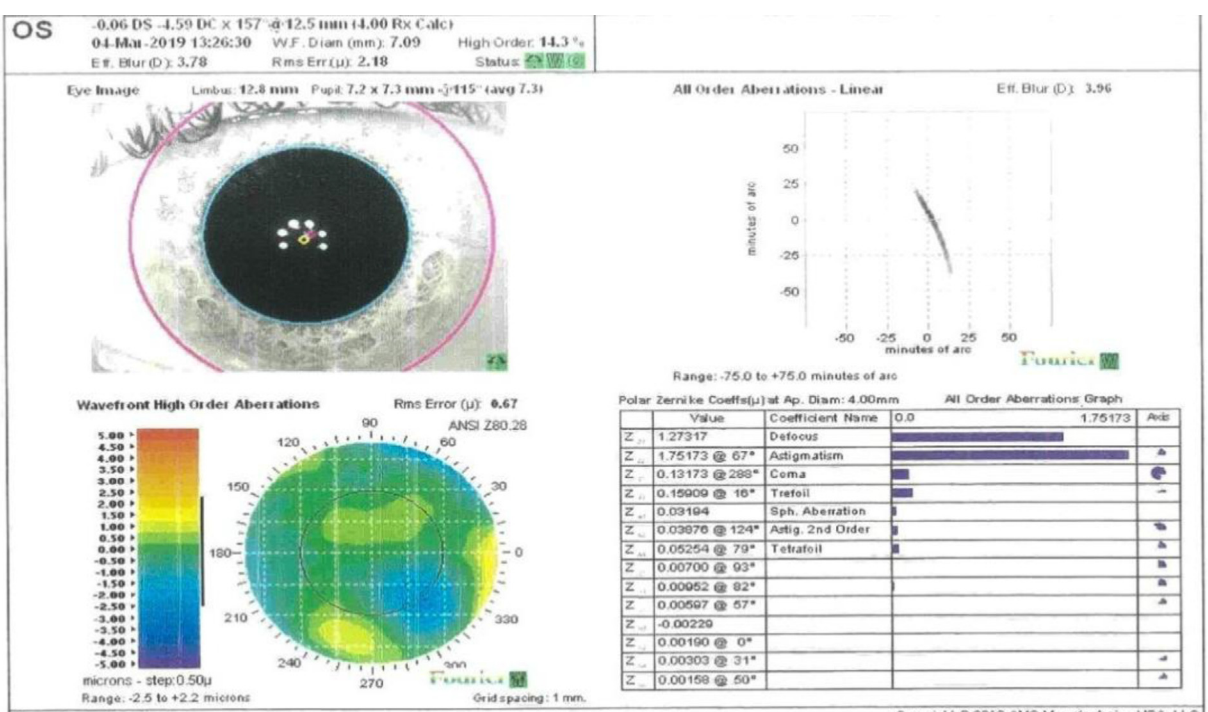

Fig. 7. Patient Y preoperative Zernike analysis showing: root mean square 0.67, Coma aberration 0.13173, Spherical aberration 0.03194.

Table 1. Distribution of the studied cases according to demographic data (n = 50).

	No. (%)
Sex	
Male	35 (70.0)
Female	15 (30.0)
Age (y)	
Minimum–maximum	14.0–38.0
Mean ± SD	23.86 ± 6.28
Median (IQR)	24.0 (20.0–26.0)

IQR, Inter quartile range; SD, Standard deviation.

in either UDVA or CDVA, as shown in the present study. The only significant ($P < 0.05$) trend was a decrease in the percentage of change in CDVA compared with the percentage of change in overall aberrations ($P = 0.025$ $r_s = 0.317$), SE ($P = 0.587$ $r_s = 0.105$), and Coma aberrations ($P = 0.005$ $r_s = -0.508$). The degree to which a patient's coma changed after surgery was shown to be highly and statistically significantly correlated with the degree to which their VA improved.

Table 2. Comparison between the pre-corneal cross-linking and 6 months post-corneal cross-linking according to refraction (n = 50).

	Before surgery	6 months FU	Change	Z	*P*
S			**Improvement**		
Minimum–maximum	−8.0–3.0	−8.0–3.0	−2.50–4.25		
Mean ± SD	−0.22 ± 1.91	−0.15 ± 1.84	0.07 ± 1.08	0.639	0.523
Median (IQR)	0.0 (−1.0–0.75)	0.0 (−0.75–1.0)	0.25 (−0.50–0.50)		
C			**Improvement**		
Minimum–maximum	−6.25–0.0	−6.00–0.0	−2.50–2.25		
Mean ± SD	−2.33 ± 1.41	−2.27 ± 1.42	0.06 ± 0.91	0.502	0.616
Median (IQR)	−2.25 (−3.50 to −1.0)	−2.25 (−3.0 to −1.0)	0.0 (−0.50–0.50)		
SE			**Improvement**		
Minimum–maximum	−8.38–1.50	−8.13–1.63	−3.38–3.0		
Mean ± SD	−1.35 ± 1.84	−1.31 ± 1.94	0.04 ± 0.95	0.743	0.457*
Median (IQR)	−1.0 (−1.75 to −0.25)	−1.0 (−2.0 to −0.13)	0.12 (−0.26–0.62)		

IQR, Inter quartile range; SD, Standard deviation; Z, Wilcoxon signed ranks test.
P: *P* value for comparing between the two studied periods.
*: Statistically significant at *P* less than or equal to 0.05.

Although CXL seems to boost VA in most cases, the reason for this increase in clarity is still a mystery. Clinical features that correlate with post-CXL changes in VA have not been identified, despite examinations of topography, pachymetry, corneal haze, and corneal biomechanics after CXL.

However, Reductions in total ocular aberrations following CXL tend to correlate with enhancements

O'Brart et al.[18] reported on a randomized, prospective, bilateral trial of 22 patients with proven keratoconic progression, and they found that all eyes treated stabilized, with improvements in CDVA, corneal power measures, and higher order aberrations. However, over the 18-month follow-up period, 14 % of untreated eyes showed advancement.

Table 3. Comparison between the pre-corneal cross-linking and 6 months post-corneal cross-linking according to simulated keratimetric reading (n = 50).

	Before surgery	6 months FU	Decrease	t	*P*
SIMK1_D					
Minimum–maximum	42.88–57.30	42.24–54.44	−1.11–2.86		
Mean ± SD	47.31 ± 2.83	46.79 ± 2.64	0.52 ± 0.79	4.688[a]	<0.001[a]
Median (IQR)	47.07 (45.30–49.20)	46.68 (44.88–48.15)	0.37 (0.0–0.90)		
SIMK2_D					
Minimum–maximum	40.81–48.98	40.81–48.21	−0.52–1.65		
Mean ± SD	44.62 ± 1.90	44.24 ± 1.84	0.38 ± 0.50	5.412[a]	<0.001[a]
Median (IQR)	44.41 (43.27–45.86)	44.21 (42.99–45.55)	0.35 (0.0–0.67)		
APP_6 mm					
Minimum–maximum	41.95–52.08	41.85–49.90	−0.69–2.24		
Mean ± SD	46.08 ± 2.31	45.65 ± 2.17	0.43 ± 0.66	4.618[a]	<0.001[a]
Median (IQR)	45.76 (44.45–47.71)	45.74 (43.90–47.42)	0.38 (−0.06–0.70)		

IQR, Inter quartile range; SD, Standard deviation; SIMK, Simulated keratimetric reading; t, Paired *t*-test.
P: *P* value for comparing between the two studied periods.
[a] Statistically significant at *P* less than or equal to 0.05.

Table 4. Comparison between the pre-corneal cross-linking and 6 months post-corneal cross-linking according to root mean square and higher-order aberrations (n = 50).

	Before surgery	6 months FU	Decrease	Z	*P*
RMS					
Minimum–maximum	0.23–3.84	0.33–3.40	−0.31–0.94		
Mean ± SD	1.62 ± 0.86	1.48 ± 0.75	0.14 ± 0.23	3.975[a]	<0.001[a]
Median (IQR)	1.40 (1.0–2.10)	1.32 (0.91–1.99)	0.08 (0.0–0.21)		
Coma					
Minimum–maximum	0.04–2.43	0.01–2.03	−0.28–0.53		
Mean ± SD	0.73 ± 0.56	0.67 ± 0.49	0.06 ± 0.15	2.618[a]	0.009[a]
Median (IQR)	0.59 (0.37–0.90)	0.54 (0.30–0.82)	0.04 (−0.03–0.13)		
S Abb					
Minimum–maximum	0.0–1.53	0.0–1.04	−0.23–0.49		
Mean ± SD	0.28 ± 0.28	0.23 ± 0.20	0.04 ± 0.14	1.873	0.061
Median (IQR)	0.23 (0.10–0.39)	0.20 (0.08–0.34)	0.02 (−0.03–0.10)		

IQR, Inter quartile range; S Abb, spherical abberations; SD, Standard deviation; Z, Wilcoxon signed ranks test.
P: *P* value for comparing between the two studied periods.
[a] Statistically significant at *P* less than or equal to 0.05.

From the results of this research, we can deduce that crosslinking is a successful therapy for eyes with progressive KC since both VA and field of view improved. This study's results corroborate what was already known about the cumulative HOA improving following CXL.

3.1. Conclusions

HOA contribute significantly to the decreased visual quality seen by those with KC. Our results imply that the quality of vision for individuals with KC may be greatly improved by treating HOA, particularly coma.

Further studies with larger samples and longer follow-up period are recommended to confirm the presented study Figs. 3–7, Tables 1–4.

Consent for publication

Not applicable.

Availability of data and materials

Data and materials were available.

Author declaration of funding statement

No specific grant was given to this study by funding organizations in public, private, or not-for-profit sectors.

Author Contribution

The conception and design of the study was done by Mohamed Abd El-Hamid Abo El-Enin, acquisition of data, or analysis were done by Abd El-Maged Mohamed Tag El-Din and interpretation of data was done by Ahmed Shaker Abu-Elkhier Zordok, Each author was responsible for either writing the article, reviewing it extensively for both style and substance, or giving final approval of the version to be submitted.

Conflict of Interest

Authors claim to have no conflicts of interest.

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References

1. Mohamed MK, Ahmed MM, Khaled A, Hisham A. Changes in ocular higher-order aberrations after corneal collagen cross-linking for keratoconus. *Med J Cairo Univ*. 2021;89:1367–1371.
2. Hamed M, Abo El Enine M, Tawfik A. Evaluation of higher order aberrations after cross-linking in patients with early keratoconus. *Al-Azhar Int Med J*. 2022;3:70–74.
3. Fasciani R, Crincoli E, Fedeli C, et al. Binocular visual function changes after corneal collagen cross-linking in patients with keratoconus. *Cornea*. 2023;42:176–180.
4. Villavicencio OF, Gilani F, Henriquez MA, Izquierdo L, Ambrósio RR. Independent population validation of the Belin/Ambrosio enhanced ectasia display: implications for keratoconus studies and screening. *Int J Keratoconus Ectatic Corneal Dis*. 2014;3:1–8.
5. Applegate RA, Marsack JD, Ramos R, Sarver EJ. Interaction between aberrations to improve or reduce visual performance. *J Cataract Refract Surg*. 2003;29:1487–1495.
6. El-Raggal TM, Riboflavin-Ultraviolet A. Corneal cross-linking for keratoconus. *Middle East Afr J Ophthalmol*. 2009;16:256–259.
7. Mazzotta C, Caporossi T, Denaro R, et al. Morphological and functional correlations in riboflavin UV A corneal collagen cross-linking for keratoconus. *Acta Ophthalmol*. 2012;90:259–265.
8. Vinciguerra P, Albè E, Trazza S, et al. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes

undergoing corneal cross-linking. *Ophthalmol Times*. 2009;116: 369−378.
9. Wagner H, Barr JT, Zadnik K. Collaborative longitudinal evaluation of keratoconus (CLEK) study: methods and findings to date. *Contact Lens Anterior Eye*. 2007;30:223−232.
10. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. *J Cataract Refract Surg*. 2006;32:837−845.
11. Doors M, Tahzib NG, Eggink FA, Berendschot TT, Webers CA, Nuijts RM. Use of anterior segment optical coherence tomography to study corneal changes after collagen cross-linking. *Am J Ophthalmol*. 2009;148:844−851.
12. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34: 796−801.
13. Wittig-Silva C, Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. *J Refract Surg*. 2008;24:S720−S725.
14. Barbero S, Marcos S, Merayo-Lloves J, Moreno-Barriuso E. Validation of the estimation of corneal aberrations from videokeratography in keratoconus. *J Refract Surg*. 2002;18: 263−270.
15. Alió JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg*. 2006;22:539−545.
16. Barbero S, Marcos S, Merayo-Lloves J, Moreno-Barriuso E. Validation of the estimation of corneal aberrations from videokeratography in keratoconus. *J Refract Surg*. 2002;18: 263−270.
17. Jafri B, Li X, Yang H, Rabinowitz YS. Higher order wavefront aberrations and topography in early and suspected keratoconus. *J Refract Surg*. 2007;23:774−781.
18. O'Brart DP, Chan E, Samaras K, Patel P, Shah SP. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. *Br J Ophthalmol*. 2011;95:1519−1524.