

## Evaluation Of Higher Order Aberrations After Cross-Linking In Patients With Early Keratoconus

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### ABSTRACT

**Background:** Non-inflammatory corneal thinning and steepening are hallmarks of keratoconus (KC), which affects both eyes. The causes of KC are several. If left unchecked, keratoconus typically worsens until the third or fourth decade of life, when it stops growing. The disease may begin later in life and progress or be halted at any point in time. It is possible that it is congenital. To improve corneal tissue's mechanical and chemical stability, corneal collagen cross-linking (CXL) was developed.

**Aim of The Work:** To examine the high-order aberrations in patients with early keratoconus before and after cross-linking.

**Patients and Methods:** From March 2021 to September 2021, 40 eyes that match the inclusion criteria for CXL have been studied in the current prospective comparison study. The study conducted at Nour El Hayah Eye Hospital Cairo Egypt.

**Results:** Preoperative and 6-month examinations showed statistically significant improvements in uncorrected visual acuity and best-corrected visual acuity ( $P<0.001$ ). At six months, there had been a 25 % and an 18 % reduction in total HIGHER ORDER ABERRATIONS (HOAs) and comas, respectively. Spherical aberration was reduced by 8.71 percent ( $P<0.001$ ), showing significant improvement, Trefoil and high-order astigmatism ( $P=0.405$  and  $0.329$ , respectively) showed no significant difference. Preoperative values and 6-month values showed statistically significant differences in apical average (K) values ( $P=0.05$ ).

**Conclusion:** Spherical aberrations, HOAs, and coma diminished with CXL. The improvement in visual function and coma are directly linked.

**Keywords:** Early Keratoconus; Cross-linking; Aberrations .

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### INTRODUCTION

Non-inflammatory corneal thinning and steepening are hallmarks of keratoconus (KC), which affects both eyes.<sup>1</sup>

The causes of KC are several.<sup>2</sup> If left unchecked, keratoconus typically worsens until the third or fourth decade of life, when it stops growing. Although it may begin later in life and progress or stop at any age, it is possible that it is hereditary in some cases.<sup>3</sup>

Most of the time, this disease is limited to the cornea's inferior central two-thirds. There have been reports of corneal steepening that is specific to each keratoconic eye having central, inferior nasal, and inferiorly located cones. There have also been reports of superior cones. More than half of keratoconus patients have cones that are most typically shifted inferior temporally, according to numerous studies.<sup>4</sup>

A wide range of visual issues can be caused by keratoconus, including significant amounts of myopic astigmatism, with blurring and distortion, to ghosting and poor low-contrast acuity. In the severest form of the disease, corneal scarring is common. In keratoconus it is believed that corneal thinning,

protrusion, and scarring causing the loss in visual performance.<sup>5</sup>

In severe stages, KC is rather easy to detect, but in the early stages, where the cornea appears to be healthy, it is more difficult. Astigmatism with an oblique axis, increasing degrees of astigmatism, and advancement in astigmatism and/or spherical refraction are all indications that KC should be considered in patients.<sup>6</sup>

To improve corneal tissue's mechanical and chemical stability, corneal collagen cross-linking (CXL) was developed. The major goal of this treatment is to establish new chemical connections inside the corneal stroma by highly targeted photopolymerization while minimizing exposure to the surrounding eye structure. Free radicals drive the mechanism, which increases covalent bonding within and between collagen fibrils and between collagen molecules. Due to the cornea's structural alterations as well as its biochemical properties and biomechanical, the cornea's collagen fibrils have grown in diameter, making it more resistant to enzyme digestion and hydrothermal shrinking, which indicates better stability.<sup>7</sup>

Preserving current vision and avoiding corneal transplantation are two of the key goals of treatment in terms of clinical outcomes.<sup>8</sup>

### PATIENTS AND METHODS

In this study, 40 eyes evaluated for CXL and meeting the inclusion criteria were compared prospectively.

The study conducted at Nour El Hayah Eye Hospital Cairo Egypt.

All patients provided written informed consent after the nature of the procedure was explained in addition to the benefits and possible risks explained.

Full medical history has been taken and ocular examination done to exclude any other pathology.

Medical /Ophthalmic history was taken including symptoms of HOAs like double vision, halos, glare, night blindness, starburst patterns and blurring.

**Ophthalmologic examination including:** (1) Uncorrected visual acuity (UCVA), Best corrected visual acuity (BCVA). (2) Ocular examination using slit lamp biomicroscopy.

Assessments of corneal topographic changes before and 6 months after CXL.

Evaluation of HOAs by Shack-Hartmann aberrometry ( Bausch & Lomb Zywave III) before and 6 months after CXL.

### The Technique of CXL:

The technique was performed under topical anaesthesia under sterile condition. Riboflavin is injected into the corneal stroma after the corneal epithelium is removed using a blunt spatula.

Before and after the treatment, 0.1 percent riboflavin eye drops are used(Riboflavin eye drops 0.1% are applied to exposed stromal surface five minutes prior to the CXL procedure and then every five minutes

during the treatment) exposure to UVA radiation (370nm) at 3mW/cm<sup>2</sup> for 30 minutes on the cornea's surface. If the cornea is thicker than 400 micrometers, the method is safe and does not cause endothelium toxicity. When riboflavin is used at this low riboflavin content at this UV wavelength and energy level.

Postoperatively, antibiotic drops in the form of moxifloxacin and corticosteroid drops in the form of prednisolone acetate 1% were administered four times per day for one week. A bandage lens is placed over the cornea. The patients were also prescribed lubricant gel that was administered four times per day for one week.

Slit-lamp examinations were performed on all patients on the day of surgery, as well as one week and one month thereafter. All patients have had corneal topography and Zy wave aberrometers done six months after CXL to examine changes in the HOAs before and after the procedure.

SPSS application was used to enter, validate, and analyze the acquired data (Statistical Package for Social Science).

Tables and graphs of collected data are examined using proper statistical procedures by computer software.

### Statistical methods:

SPSS version 18 was used to analyze the collected data (SPSS Inc., Chicago, IL, USA). Statistics such as mean and standard deviation (SD) were used for quantitative information, and percentages were used for qualitative information. On the other hand, the Chi square or Fisher's exact test was employed to establish whether or not the difference was statistically significant for quantitative variables. It was considered statistically significant when the P-value was 0.05 or lower.

### RESULTS

#### Study population:

The study included 40 eyes of 40 patients.

All patients completed their six months follow-up period.

Studied patients (N = 40)			
Age (years)	Mean ± SD	$28.1 \pm 5.2$	
	Min - Max	18 – 35	
Sex	Male	17	42.5%
	Female	23	57.5%

**Table 1:** All patients studied had their age and sex documented.

	Pre-op (N = 40)	Post-op (N = 40)	MW	P-value
RMS HOA (5 mm)	Mean	1.34	<b>470.5</b>	<b>0.002 S</b>
	±SD	0.29		
RMS HOA (6 mm)	Mean	1.70	<b>398</b>	<b>&lt; 0.001 HS</b>
	±SD	0.37		

**Table 2:** Comparison between pre-operative and post-operative Root mean square (RMS) Higher Order Aberration (HOA) in studied patients.

There was statistically significant ( $p$ -value = 0.002) decreased RMS HOA (5mm) post-operatively ( $1.11 \pm 0.36$ ). There was highly statistical significant ( $p$ -value < 0.001) decreased RMS HOA (6mm) post-operatively ( $1.29 \pm 0.41$ ).

		Pre-op (N = 40)	Post-op (N = 40)	MW	P-value
<b>Horizontal Trefoil</b>	<b>Mean</b>	0.261	0.246	626	0.91 NS
	<b>±SD</b>	0.037	0.035		
<b>Vertical Trefoil</b>	<b>Mean</b>	0.293	0.311	624.5	0.089 NS
	<b>±SD</b>	0.049	0.040		
<b>Horizontal coma</b>	<b>Mean</b>	0.601	0.494	123	< 0.001 HS
	<b>±SD</b>	0.053	0.052		
<b>Vertical coma</b>	<b>Mean</b>	1.64	1.42	37.5	< 0.001 HS
	<b>±SD</b>	0.08	0.07		
<b>Spherical aberrations</b>	<b>Mean</b>	0.520	0.406	119	< 0.001 HS
	<b>±SD</b>	0.061	0.051		
<b>2<sup>nd</sup> horizontal trefoil</b>	<b>Mean</b>	0.042	0.039	537.5	0.011 S
	<b>±SD</b>	0.006	0.008		
<b>2<sup>nd</sup> vertical trefoil</b>	<b>Mean</b>	0.078	0.074	592.5	0.044 S
	<b>±SD</b>	0.008	0.008		
<b>2<sup>nd</sup> horizontal coma</b>	<b>Mean</b>	0.126	0.094	335.5	< 0.001 HS
	<b>±SD</b>	0.025	0.032		
<b>2<sup>nd</sup> vertical coma</b>	<b>Mean</b>	0.378	0.286	188	< 0.001 HS
	<b>±SD</b>	0.059	0.047		

**Table 3:** Comparison of pre- and post-operative Higher Order Aberration (HOA) levels in the patients being studied.

#### This table shows:

Neither horizontal nor vertical trefoil had statistical significance ( $p$ -value 0.05) before or after surgery.

Highly statistical significant ( $p$ -value < 0.001) decreased post-operative Horizontal coma ( $0.494 \pm 0.052$ ) when compared with pre-operative Horizontal coma ( $0.601 \pm 0.053$ ).

Highly statistical significant ( $p$ -value < 0.001) decreased post-operative Vertical coma ( $1.42 \pm 0.07$ ) when compared with pre-operative Vertical coma ( $1.64 \pm 0.07$ ).

Highly statistical significant ( $p$ -value < 0.001) decreased post-operative spherical aberrations ( $0.406 \pm 0.051$ ) when compared with pre-operative spherical aberrations ( $0.520 \pm 0.061$ ).

Statistically significant ( $p$ -value = 0.011) decreased post-operative 2<sup>nd</sup> horizontal trefoil ( $0.039 \pm 0.008$ ) when compared with pre-operative 2<sup>nd</sup> horizontal trefoil ( $0.042 \pm 0.006$ ).

Statistically significant ( $p$ -value = 0.044) decreased post-operative 2<sup>nd</sup> vertical trefoil ( $0.074 \pm 0.008$ ) when compared with pre-operative 2<sup>nd</sup> vertical trefoil ( $0.078 \pm 0.008$ ).

Highly statistical significant ( $p$ -value < 0.001) decreased post-operative 2<sup>nd</sup> horizontal coma ( $0.094 \pm 0.032$ ) when compared with pre-operative 2<sup>nd</sup> horizontal Coma ( $0.126 \pm 0.025$ ).

Highly statistical significant ( $p$ -value < 0.001) decreased post-operative 2<sup>nd</sup> vertical coma ( $0.286 \pm 0.047$ ) when compared with pre-operative 2<sup>nd</sup> vertical Coma ( $0.378 \pm 0.059$ ).

		Pre-op (N = 40)	Post-op (N = 40)	MW	P-value
<b>K1</b>	<b>Mean</b>	43.8	42.9	700	0.333 NS
	<b>±SD</b>	4.4	3.9		
<b>K2</b>	<b>Mean</b>	49.5	49.8	775	0.808 NS
	<b>±SD</b>	4.0	4.0		

**Table (4):** Pre and postoperative K values in the patients investigated are compared.

## DISCUSSION

A new treatment for keratoconus called corneal collagen crosslinking (CXL) has recently been introduced. Strengthening the cornea using cross-linking is an easy, non-invasive technique aimed to arrest the advancement of keratoconus.<sup>9</sup>

In recent times, evidence has shown that collagen crosslinking (CXL) with riboflavin drops increases the biomechanical strength and stability of the cornea.<sup>10</sup>

Long-term follow-up studies have indicated adequate safety for this procedure, and exceedingly rare problems have been recorded in these patients.<sup>11</sup>

In our study we aimed at assessing the effect of epithelium off (Photo-oxidative Collagen Cross-linking with Riboflavin and Ultraviolet light) technique on corneal higher order aberrations over the 6month follow-up. None of the patients showed either a complication or deterioration that required further intervention during the follow-up period.

There are many studies about the effect of epithelium off CXL technique on HOAs.

Our study showed statistically significant improvement in HOAs indicated by the improvement of RMS HOAs (5mm) ( $p$ -value = 0.002) and Highly

statistical significant RMS HOA (6mm) ( $p$ -value < 0.001).

The forty eyes included in the study showed this improvement after the 6-month follow-up period.

There are many reports on the effect of CXL using epithelium removal or epithelium-off (epi-off) technique. Most of those studies also show results consistent with our results.

Greenstein et al. reported having improvement in 74% of 96 eyes in a 1-year follow-up study ( $P < 0.05$ ). This lower percentage of improvement may be attributed to their inclusion of post- LASIK ectasia patients in their study, who tend to have the poorer response to CXL.<sup>12</sup>

Kocamis et al. conducted on 37 eyes showed statistically significant improvement ( $p=0.001$ ) of corneal HOAs after 18 months follow-up.<sup>13</sup>

In a 12-month follow-up study, Vinciguerra et al. did an examination of 28 eyes utilizing the epi off method. Improvements in HOAs were shown to be statistically significant.<sup>14</sup>

Vinciguerra et al. in 2012 conducted another study on 41 eyes of patients of younger population of less than eighteen years of age. A statistically significant improvement in corneal HOAs was found during a 24-month follow-up.<sup>15</sup>

Agrawal reported in his study that was conducted on 37 eyes statistically significant improvement of total HOA 12 to 16 months after the procedure.<sup>16</sup>

Naderan and Jahanrad in their study that was conducted on 56 eyes found statistically significant improvement in corneal HOA after 1 year follow-up. This improvement continued till 4 years of follow-up with  $p < 0.001$ .<sup>17</sup>

Ghanem et al.'s study that included 42 eyes showed statistically significant improvement of corneal HOAs 6 months after epi-off CXL. This improvement continued over the two-year follow-up period of this study.<sup>18</sup>

Our study was initially designed to have a follow-up corneal topography at 3 months, but analyzing the early data from the first 10 patients done showed mixed results. Some patients showed initial deterioration in HOAs and other corneal parameters. The rest didn't show significant improvement. This led to omitting the 3-month corneal topography. These findings were consistent with findings from other studies.

Kosekahya et al. showed similar results in their study that was conducted on 93 eyes using epi- off technique. In their study the difference in RMS HOAs was statistically insignificant after 3 months follow-up. It became statistically significant at 6 months and remained almost stable till 1 year follow-up.<sup>19</sup>

There were some other studies that stated that CXL doesn't affect HOAs, it just stabilizes them. In those studies the postoperative values of HOAs were slightly lower, but the difference was statistically insignificant.

Wisse et al. in a study including 187 eyes using epi-off technique showed slightly lower values of corneal HOAs with no statistically significant change ( $P=0.272$ ) in HOAs after a 1-year follow-up.<sup>20</sup>

We couldn't find any previous study that states that CXL increases corneal or total ocular HOAs.

Our study compared the pre- and postoperative values of the following elements of HOAs: horizontal trefoil, vertical trefoil, horizontal coma, vertical coma, spherical aberrations, 2nd horizontal trefoil, 2nd vertical trefoil, 2nd horizontal coma, 2nd vertical coma.

These subtypes were chosen because it was reported that they are the most affected by keratoconus.<sup>21</sup>

In the study by Caporossi et al. coma aberrations showed no statistically significant change. Spherical aberrations increased at 24 months.<sup>22</sup>

Greenstein et al. found that there is a statistically significant improvement in Horizontal Coma, Vertical Coma, spherical aberrations and total coma (summation of third order and fifth order coma). The trefoil improvement was statistically insignificant.<sup>12</sup>

In Ghanem's et al. study, significant reduction in coma ( $P = 0.016$ ), trefoil ( $P = 0.018$ ), fifth order coma ( $P < 0.001$ ), and fifth order trefoil ( $P = 0.001$ ) was found. They didn't comment on spherical aberrations.<sup>18</sup>

Naderan and Jahanrad in their study found statistically significant improvement in vertical coma and spherical aberrations only, at the 1-year follow-up. Over the second, third and fourth year follow-ups all the other elements showed statistically significant improvement. At the 4-year follow-up, the  $p$  value was less than 0.001 for Horizontal trefoil, vertical trefoil, horizontal coma, vertical coma and spherical aberrations. As for the 2nd horizontal trefoil, 2nd vertical trefoil, 2<sup>nd</sup> horizontal coma and 2nd vertical coma the  $p$  values were 0.483, 0.089, 0.153 and 0.123 respectively.<sup>17</sup>

This contradiction may be attributed to the method they used (OPD-Scan) in measuring HOA. There is a difference in this system accuracy in estimating both total and corneal HOAs.

Vertical coma and spherical aberration values considerably improved at postoperative 6 months ( $p = 0.001$  and  $p = 0.003$  respectively) in the study done by Kosekahya et al. and did not alter between the 6th and 12th months. The vertical trefoil did not differ significantly ( $p = 0.96$ ). HOAs in general were not discussed in the study.<sup>19</sup>

According to Wisse et al., the highest K value had reduced or remained steady in 164 of 187 eyes at the 1-year follow-up visit. A mean rise in maximal K was seen in 16 eyes with keratoconus that had advanced by greater than 1.00 D.<sup>20</sup>

Most of the studies showed that K1 and K2 improve after CXL, but there was disagreement whether this improvement is statistically significant or not.

Patient's with higher order keratoconus undergoing corneal collagen crosslinking was the primary focus of our research, which was completed successfully.

### CONCLUSION

After CXL, the overall number of, spherical aberrations, total coma, and HOAs decreased significantly. The coma is the most common ailment. Ocular aberrations have a significant impact on the quality of the retinal image. Resolving HOAs may improve vision aberration in people with KC.

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