



The Effect of Corneal Collagen Cross-Linking on Higher Order Aberrations in Keratoconus

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Authors' contributions

This work was carried out in collaboration among all authors. Author AMM designed the study, wrote the protocol and wrote the first draft of the manuscript. Author MMK performed the statistical analysis. Author HAS managed the analyses of the study. Authors MMK and HAS managed the literature searches. All authors read and approved the final manuscript.

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Case Study

ABSTRACT

Purpose: To assess the changes in ocular high order aberrations after collagen cross linking for keratoconus.

Patients and Methods: This study included 30 eyes with confirmed KCN. Baseline evaluation focused on: UDVA and BSCVA using logMAR notation, MRSE, corneal topography using Orbscan IIZ and wave-front aberrometry using Zywave II. CXL was performed per 'Dresden protocol' through a 30-minutes exposure to 370 nm UVA with an irradiance of 3 mW/cm². Patients had comprehensive ophthalmic evaluation after 6 months with special attention to: UDVA, BSCVA, MRSE, corneal topography and wave-front aberrometry changes.

Results: The mean age was 25.5±5.84 (20:31) years. After 6 months, there was a significant decrease in corneal thickness from 493.2± 24.17μ to 486.7±24.26μ (P<0.05) and a significant decrease in K max from 47.4±1.17D to 46.1±1.17D (P<0.05). BSCVA improved from preoperative value (0.00:0.5 logMAR (median 0.3)) to 6 months' value (0.1:1.00 logMAR (median 0.2) (P <0.05). Preoperative MRSE was -7.25: -0.5D (median -2.85D) and at 6 months was -6.25: -0.5D (median -

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2.125D) ($P < 0.05$). A significant correlation was found at 6 months between changes in both BSCVA and: K max ($P < 0.001$), corneal thickness ($P < 0.05$), vertical coma ($P < 0.001$) and trefoil ($P < 0.001$).

Conclusions: Improvement in HOA was detected after CXL for KCN. The changes in total, vertical coma and vertical trefoil aberrations were significantly correlated with postoperative improvement in BSCVA. Thus, improvement in HOA profile after CXL is one of the explanations of improvement in visual function after CXL in KCN.

Keywords: Corneal Collagen; Keratoconus; visual acuity.

1. INTRODUCTION

Keratoconus is a progressive, often bilateral but asymmetric and non-inflammatory corneal ectasia. The incidence of keratoconus in general population is 1 per 2,000 [1]. Diminished number of keratocytes that undergo apoptosis, together with loss of collagen lamellae result in corneal thinning and reduction of biomechanical stability of the cornea [1,2].

To reach the diagnosis of keratoconus, ophthalmologists combine clinical signs and corneal tomographic changes that differentiate these corneas from normal ones [3].

Standard treatment for keratoconus has included rigid contact lens, intracorneal ring segments, and penetrating keratoplasty in attempt to improve visual acuity in these cases. On the other hand, corneal collagen cross-linking (CXL) was introduced lately to increase the rigidity of corneas to prevent keratoconus disease progression [4-7].

Both lower and higher order aberrations (HOAs) have influence on retinal image quality in human eyes. In keratoconic eyes, the abnormal corneal shape causes about 5-6 times increase in higher order root-mean-square error (RMS) than normal eyes for a 6-mm pupil [8]. In patients with keratoconus, the anterior corneal surface is the most important source of optical errors; especially vertical coma aberrations [9].

Zernike polynomials are beneficial to describe the shape of an aberrated wavefront in terms of basic mathematical subtypes. The interaction of these Zernike aberrations can be additive or subtractive to each other. In KC, the increased corneal HOAs; particularly spherical aberration and coma, contribute to the increase in total ocular HOAs and reduction of visual function [10].

The aim of our study is to assess the changes in ocular HOAs and examine the correlation between these changes, visual changes and tomographic changes after CXL for KC.

2. CASE STUDY

This is a prospective, unmasked, interventional case series that was conducted between April 2018 and March 2019 at Nour El Ain Eye Hospital, Tanta, Egypt. The study included patients with confirmed KCN based on their clinical and topographic findings. The inclusion criteria included clear corneas, with a minimal corneal thickness of 400 μ and age range between 20 and 35 years for all candidates of CXL. The exclusion criteria were pregnancy and lactation, presence of corneal opacities, history of herpetic keratitis or autoimmune diseases, active ophthalmic inflammation, severe dry eye and previous ocular surgeries.

Baseline evaluation included: UDVA and BSCVA using logMAR notation, manifest refractive spherical equivalent (MRSE), slit lamp examination, dilated fundus examination, corneal topography using Orbscan IIZ (Bausch & Lomb, Technolas GmbH, Germany) and wave-front aberrometry using Zywave II (Bausch & Lomb, Technolas GmbH, Germany).

Epithelium-off cross-linking procedure was performed under topical anaesthesia per "Dresden protocol" through removal of the central 8mm of corneal epithelium, applying one drop of 0.1% riboflavin ophthalmic solution (Ribocross, Sunway PVT. LTD, India) over the cornea for 30 minutes and then exposing the cornea to 370 nm UVA with an irradiance of 3 mW/cm² for 30 minutes. The post-operative regimen of treatment included moxifloxacin 0.5% eye drops (Fortymox; Orchidia Pharmaceutical Ind., Cairo, Egypt) four times daily, prednisolone acetate 1% eye drops (Orchapred; Orchidia Pharmaceutical Ind., Cairo, Egypt) four times daily and artificial tears (Cornetears, Orchidia Pharmaceutical Ind., Cairo, Egypt) four times daily and when needed

for any foreign body or burning sensation for at least 3 months. A therapeutic soft contact lens was used till the corneal surface was totally re-epithelialized.

All patients had comprehensive ophthalmic evaluation after six months with special attention to: visual acuity assessment (UDVA, BSCVA and MSE), slit lamp examination, corneal topography changes and wave-front aberrometry.

Pre-operative demographic data (age, sex), pre-operative and 6 months post-operative BSCVA, keratometry, pachymetry, MRSE, HOAs (total and individual) were entered in a spreadsheet before further statistical analysis.

3. STATISTICAL ANALYSIS

Statistical presentation and analysis of the present study were conducted, using the range, median, mean, standard deviation, Mann-Whitney U Test, paired t-test and Spearman correlation by SPSS V20 (IBM, Chicago, USA). P value of ≤ 0.05 was used as a cut off value for significance of results.

4. RESULTS

A total of 30 eyes of 19 patients with progressive KC were enrolled in this study and all underwent epi-off CXL with no intra-operative or post-operative complications recorded. The mean age of the study population was 25.5 ± 5.84 years.

There was a statistically significant improvement in BSCVA at 6 months after CXL ($P < 0.05$) as shown in Table 1. The range of pre-operative spherical equivalent was $[(-7.25) - (-0.5)]$ with -2.85 median. Post-operative spherical equivalent range at 6 months was $[(-6.25) - (-0.5)]$ with -2.125 median as shown in Table 1. The difference between the values was statistically significant ($P < 0.05$).

There was a significant decrease in the K max readings from the pre-operative values (47.4 ± 1.17 D) to the 6 months' post-operative values (46.1 ± 1.17 D) ($P < 0.05$); and there was a significant decrease in corneal pachymetry from the pre-operative values (493.2 ± 24.17 μ) to 6 months' postoperative values (486.7 ± 24.26 μ) ($P < 0.05$) Table 2.

Analysis of the HOA parameters at 6 months post-operatively indicates a significant improvement in all HOA parameters in

comparison to preoperative values ($P < 0.05$). The pre-operative range of vertical coma was (0.19 – 1.28, median 0.375); while at 6 months post-operatively; the range was (0.08 – 1.16, median 0.215); and the pre-operative range of vertical trefoil was $[(-0.76) - 0.03]$, median (-0.135); while at 6 months post-operatively; the range was $[(-0.59) - 0.06]$, median (-0.025) Table 3.

A significant correlation was found at 6 months between changes in both BSCVA and: K max ($P < 0.001$), corneal thickness ($P < 0.05$), vertical coma ($P < 0.001$) and trefoil ($P < 0.001$) Table 4.

5. DISCUSSION

CXL is a minimally invasive procedure that many studies have reported its efficacy and safety in preventing progression of early to moderate KC. [11] The principal aim of this study was to determine changes in HOAs at 6 months after CXL using the Epi-off Dresden protocol to treat KC; and after recording these changes, we ran a correlation with visual acuity changes, with special attention to the HOA subtypes that are most relevant to clinical practice: coma and trefoil.

It is a common clinical practice to use visual acuity testing to assess the impact of HOAs. (10) So, it is expected that the increased figures of HOAs caused by KC would reduce visual performance; thus, correcting HOAs by CXL could improve visual acuity.

The present study found a significant improvement in the BSCVA post-operatively from pre-operative values (0.00 – 0.5 logMAR, median 0.3) to 6 months' post-operative values (0.1 – 1.00 logMAR, median 0.2) ($p < 0.05$).

Other studies had reported improvement of visual acuity after CXL as well. Derakhshan et al. [12] reported significant improvement in UCVA and BCVA, and reduction in SE and K readings after CXL. They found that the improvement in vision started after the first month in most of their patients, and continued to improve till the third month [12]. Also, Vinciguerra et al. [13] reported an improvement in mean best-corrected vision (log MAR) from 0.28 to 0.14 at 12 months after CXL for KC [13].

Chang et al. [14] found in their review on CXL that the mean BCVA improved more than 1 line (from 0.35 ± 0.24 to 0.23 ± 0.21 logMAR) at 1 year after CXL. [14] Raikup-Wolf et al. [15] and

Caporossi et al. [16] reported significant improvements in CDVA that continued to improve even 1 year after CXL, and they noticed a trend towards a more regular cornea.

In theory, factors affecting the improvement in visual acuity after corneal collagen crosslinking can be attributed to changes in corneal biomechanics, topographic changes and reduction in HOAs after CXL.

In this study, the range of pre-operative SE was (-7.25: -0.5) with (- 2.85) median. Post-operative SE range at 6 months was (-6.25: -0.5) with (-2.12) median. There was a significant reduction in the mean SE from -3.1 ± 1.71 D to -2.5 ± 1.54 D at 6 months post-operatively.

Improvement in error of refraction after CXL has been reported in many studies: Caporossi et al. [16] showed that the mean SE went through almost 2 D hyperopic shift from the first year after CXL. (6) Similarly, Razmjoo et al. [17] found a significant difference in SE at 12 months post-operatively of 0.62 ± 0.37 D ($P = 0.006$) [17].

On the other hand, Marie Eve Legare et al. [18] found a non-significant change in the mean spherical equivalent at 24 months after CXL despite presence of a significant improvement in uncorrected distant VA [18]. However, they reported a trend towards improvement in best corrected distant VA (BDVA) in patients with worse preoperative BDVA, which possibly explains this contradiction; since their study had had a better preoperative BDVA (0.11 ± 0.20 logMar, range -0.1 : 0.6), in comparison to the worse preoperative BSCVA in our study (median 0.3 logMar, range 0 : 0.5).

In our study, there was a significant reduction in Kmax value. The preoperative mean K max was 47.4 ± 1.17 D and changed to 46.1 ± 1.17 D at 6 months post-operatively. Reduction of Kmax after corneal collagen crosslinking was associated with flattening of the cornea. In our study, we found a significant correlation between changes in Kmax and changes in BSCVA, which suggests that reduction of Kmax was associated with improvement in BSCVA.

This finding was also addressed by Caporossi et al. [16] who recorded mean reduction in the dioptric power of 2.1 ± 0.13 D after CXL. In addition, Raikup-Wolf et al. [19] stated that the improvement in visual acuity after CXL is

attributed to reduction in corneal curvature and increased stiffness of cornea by CXL.

Corneal thickness was recorded throughout our study. Initially, the mean corneal thinnest location was 493.2 ± 24.17 μ m and at 6 months post-operatively, the mean corneal thinnest location became 486.7 ± 24.26 μ m.

In theory, corneal thinning after CXL can be explained by: corneal de-epithelialization during the Epi-off CXL procedure that increases the rate of evaporation from the corneal stroma, keratocyte apoptosis, changes in corneal collagen fibrils and extracellular matrix in the anterior stroma or a temporary increase in endothelial pump activity that is induced by exposure to UVA.

In our study, we found a significant correlation between changes in corneal thickness and changes in BSCVA. As the corneal thickness decreased after CXL in all cases, we can assume that these changes are signs of improvement if there is no associated increase in k values.

Postoperative corneal thinning was reported in numerous CXL studies. Greenstein et al. [20] stated that after CXL, corneal thinning occurred initially, followed by recovery towards baseline thickness. The mean preoperative thinnest pachymetry was 440.7 ± 52.9 μ m; at 1 month after CXL, the corneas thinned out by -23.8 ± 28.7 μ m; and from 1 to 3 months by -7.2 ± 20.1 μ m; and then the corneal thickness recovered between 3 months and 6 months after CXL with an average change of 20.5 ± 20.4 μ m; however, the thinnest pachymetry remained slightly decreased from baseline [20].

Not all HOAs have significant influence on visual performance. [10,21] By using wavefront technology, we can examine the point spread function (PSF) to evaluate the quality of retinal image under the influence of HOAs that affects the quality of visual performance. In KC, PSF tends to be large and blurred in comparison to normal eyes where PSF is small and round [22].

In our study, preoperative HOA range was 0.32: 1.52, median 0.575, that decreased at 6 months postoperatively to 0.19: 1.41, median 0.395. Also, we found an improvement in vertical coma after the CXL from a pre-operative range of (0.19: 1.28, median 0.375) to 6 months' post-operative range of (0.08 – 1.16, median 0.215).

Table 1. BSCVA improvement after 6 months

Groups		Range	Median	Mann-Whitney U Test	P value
BSCVA (LogMAR)	Preoperative (n=30)	0.00 : 0.5	0.3	Z score	0.00985*
	Postoperative 6 months (n=30)	0.1 : 1.00	0.2	2.29364	
SE (D)	Preoperative (n=30)	(-7.25) : (-0.5)	-2.75	Z score	0.02743*
	Postoperative 6 months (n=30)	(-6.25) : (-0.5)	-2.125	-1.92022	

BSCVA, best spectacle corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; SE, spherical equivalent; D, diopters

**Significant at the <0.05 level*

Table 2. K max and thinnest location pachymetry changes after 6 months

Groups		Mean ± SD	Paired t test	P value
K max (D)	Preoperative (n=30)	47.4 ± 1.17	31.504	<0.001*
	Postoperative 6 months (n=30)	46.1 ± 1.17		
Thinnest location pachymetry (µm)	Preoperative (n=30)	493.2 ± 24.17	21.695	<0.001*
	Postoperative 6 months (n=30)	486.7 ± 24.26		

K max, maximum keratometric reading; D, diopters

** Significant at the <0.05 level*

Table 3. High order aberrations changes after 6 months

Groups		Range	SD ± Mean	Mann-Whitney U Test	P value
6 mm Higher order aberrations	Preoperative (n=30)	0.32 : 1.52	0.8 ± 0.38	Z score	0.00427*
	Postoperative 6 months (n=30)	0.19 : 1.41	0.6 ± 0.40	2.62974	
Vertical coma aberrations	Preoperative (n=30)	0.19 : 1.28	0.6 ± 0.37	Z score	0.0044*
	Postoperative 6 months (n=30)	0.08 : 1.16	0.4 ± 0.37	2.62424	
Vertical trefoil aberrations	Preoperative (n=30)	(-0.76) – 0.03	-0.2 ± 0.25	Z score	0.00144*
	Postoperative 6 months (n=30)	(-0.59) – 0.06	-0.1 ± 0.21	-2.97906	

**Significant at the <0.05 level*

Table 4. Correlation between BSCVA and: K max, corneal thickness, vertical coma and trefoil

	BSCVA (LogMAR)	
	r_s	P
K max (D)	0.696	0.00037*
Corneal thickness	0.358	0.002*
Vertical coma	0.855	<0.0001*
Vertical trefoil	0.445	<0.001*

r_s , Spearman correlation

*Significant at the <0.05 level

Another improvement was recorded in vertical trefoil aberrations that dropped from pre-operative range of (-0.76: 0.03, median -0.135) to 6 months' post-operative range of (-0.59: 0.06, median -0.025).

Moreover, we found a strong significant correlation between changes in BSCVA and changes in both vertical coma and vertical trefoil aberrations. This strong correlation proves the effect of vertical coma and vertical trefoil aberrations on visual acuity. Reduction of these aberrations was accompanied by a significant improvement in the visual acuity.

Many studies had described significant improvement in HOAs after CXL. Vinciguerra et al. [13] reported a significant decrease in all corneal aberrations, particularly coma aberration which was the dominant HOAs in KC after CXL. (13) Similarly, Caporossi et al. [16] found a significant continuous reduction in both total HOAs and coma aberration up to 2 years after CXL. [16].

Similar to our study, Naderan et al. [23] stated that CXL is effective in improving HOA parameters in eyes with progressive KC and reported a significant correlation between preoperative measurements of HOAs parameters and best-corrected visual acuity; but they used optical path difference Scan II (OPD-Scan II; Nidek Co., Ltd., Gamagori, Japan) to perform aberrometry and wavefront measurement [23].

On the other hand, Greenstein et al. [20] found insignificant association between the changes in HOAs and improvements in vision, despite the significant improvement in HOA after CXL. However, their study had incomplete data of HOA that limited their analysis [20].

Similar results were obtained by El-Massry et al. [7] who reported in their study significant reduction in total HOA and total coma but in their

study, no significant change was observed in trefoil [24].

6. CONCLUSION

The findings of our study demonstrated an improvement in HOA using the Zywave aberrometer after CXL in keratoconic eyes. Multivariable analysis found changes in total, vertical coma and vertical trefoil aberrations that were significantly correlated with postoperative improvement in BSCVA. Thus, improvement in HOA profile after CXL is one of the explanations of improvement in visual function after CXL in keratoconic eyes.

CONSENT AND ETHICAL APPROVAL

All procedures performed in this study and involving human participants were in accordance with the ethical standards of 1964 Helsinki declaration and its later amendments and were approved by the research ethics committee at Tanta Faculty of Medicine, Egypt and an informed consent was obtained from all individuals who had participated in this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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