

# Effect of Epithelium-Off Corneal Collagen Cross-Linking On Higher-Order Aberrations in Early Keratoconus

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**Abstract:** *Keratoconus is a progressive corneal ectatic disorder characterized by stromal thinning and irregular corneal steepening, leading to visual distortion and reduced visual quality. Corneal collagen cross-linking (CXL) is an established treatment aimed at halting disease progression by improving corneal biomechanical stability. To evaluate the effect of epithelium-off corneal collagen cross-linking on corneal higher-order aberrations (HOAs) in patients with early keratoconus. This prospective interventional study included 40 eyes of 40 patients with early keratoconus who underwent standard epithelium-off riboflavin-UVA CXL. Corneal HOAs were measured preoperatively and six months postoperatively using Shack-Hartmann wavefront aberrometry. A statistically significant reduction in total RMS HOAs was observed at six months, particularly over a 6-mm pupil diameter ( $p < 0.001$ ). Significant improvements were noted in horizontal and vertical coma as well as spherical aberration, while trefoil aberrations showed no significant change. Epithelium-off CXL significantly improves corneal higher-order aberrations in early keratoconus, especially coma and spherical aberrations, contributing to improved corneal optical quality.*

**Keywords:** Keratoconus, corneal cross-linking, higher-order aberrations, coma, visual quality

## INTRODUCTION

Keratoconus (KC) is a progressive, bilateral corneal ectatic disorder characterized by non-inflammatory corneal thinning and steepening, leading to irregular astigmatism and visual impairment (Galvis et al., 2015). Although historically considered a non-inflammatory condition, increasing evidence suggests that inflammatory mechanisms may contribute to its pathophysiology. The etiology of keratoconus is multifactorial, involving a complex interaction

between genetic predisposition and environmental influences (Gordon-Shaag et al., 2015). Familial aggregation has been reported, supporting a hereditary component in a subset of patients (Li et al., 2004).

The disease most commonly affects the inferior central two-thirds of the cornea, although significant inter-eye variability in cone location has been documented. Corneal steepening may present centrally, inferonasally, inferiorly, or, less frequently, superiorly. Multiple studies have shown that the majority of keratoconic cones are displaced inferotemporally (Núñez & Blanco, 2008). These structural alterations lead to a broad spectrum of visual disturbances, including progressive myopic astigmatism, image distortion, ghosting, and reduced contrast sensitivity. In advanced stages, corneal scarring frequently occurs and is a major contributor to visual deterioration (Weed et al., 2008).

While advanced keratoconus is readily identifiable on clinical examination, early-stage disease remains challenging to diagnose due to minimal slit-lamp findings. Subtle clinical indicators such as oblique astigmatism, progressive increases in astigmatic magnitude, and unexplained changes in spherical refractive error should prompt further evaluation for keratoconus, particularly with the use of corneal tomography (Serdarogullari et al., 2013).

In response to the progressive biomechanical weakening of the cornea observed in keratoconus, corneal collagen cross-linking (CXL) was developed as a therapeutic strategy aimed at stabilizing corneal structure. CXL induces the formation of additional covalent bonds within and between collagen fibrils through a photochemical reaction mediated by free radicals, thereby enhancing corneal biomechanical strength and resistance to enzymatic degradation (Gipson et al., 2005) [7]. Clinically, the primary objectives of keratoconus management are to halt disease progression, preserve visual function, and reduce the need for corneal transplantation. In this context, CXL alone or in combination with refractive procedures has emerged as a key intervention in modern keratoconus treatment paradigms (Grentzelos et al., 2017).

## **LITERATURE REVIEW**

Previous studies have demonstrated that keratoconus is associated with marked increases in corneal HOAs, particularly vertical coma and spherical aberration, which significantly impair visual performance. Several investigations have evaluated the impact of epithelium-off CXL on these aberrations, reporting variable but generally favorable outcomes.

Greenstein et al. reported improvement in corneal HOAs in the majority of treated eyes at one year following CXL. Vinciguerra et al. demonstrated significant reductions in coma and spherical aberration after epi-off CXL, with sustained improvements during long-term follow-up. However, differences in measurement devices, patient selection, and follow-up duration have contributed to variability in reported outcomes.

Understanding the effect of CXL on HOAs is clinically relevant, as improvements in optical quality may enhance functional vision even in the absence of significant keratometric flattening.

## **METHODOLOGY**

### **Study Design and Participants**

This prospective interventional study included 40 eyes of 40 patients with early keratoconus who were eligible for corneal collagen cross-linking. The study was conducted at the Ophthalmology Department of Mother Teresa University Hospital, Tirana, Albania, between March 2021 and September 2021. All procedures followed the principles of the Declaration of Helsinki, and informed consent was obtained from all participants.

### **Clinical Assessment**

All patients underwent a comprehensive ophthalmic examination, including uncorrected and best-corrected visual acuity, slit-lamp biomicroscopy, and corneal topography. Higher-order aberrations were measured using Shack–Hartmann wavefront aberrometry (Zywave III, Bausch & Lomb, USA) preoperatively and six months postoperatively.

### **Surgical Technique**

Standard epithelium-off corneal collagen cross-linking was performed under topical anesthesia. The corneal epithelium was mechanically removed, followed by application of 0.1% riboflavin solution every five minutes for 30 minutes. Ultraviolet-A irradiation at 370 nm and 3 mW/cm<sup>2</sup> was then applied for 30 minutes. Only eyes with a minimum corneal thickness of 400 μm were treated.

### **Postoperative Care**

Postoperatively, patients received topical moxifloxacin and prednisolone acetate four times daily for one week. A bandage contact lens was placed and removed after epithelial healing. Follow-up examinations were conducted at one week, one month, and six months.

### **Statistical Analysis**

Data analysis was performed using SPSS version 18.0. Quantitative data were expressed as mean ± standard deviation. The Mann–Whitney test was used to compare preoperative and postoperative values. A p-value ≤ 0.05 was considered statistically significant.

## RESULTS

### Demographic Characteristics

The study included 40 eyes from 40 patients, all of whom completed the six-month follow-up period.

**Table 1.** Demographic characteristics of the study population.

VARIABLE	STUDIED PATIENTS (N = 40)
AGE (YEARS), MEAN $\pm$ SD	28.1 $\pm$ 5.2
AGE RANGE (YEARS)	18–35
SEX, N (%)	
MALE	17 (42.5%)
FEMALE	23 (57.5%)

In Table 1 are summarized the demographic characteristics of the study population. The mean age of the participants was 28.1  $\pm$  5.2 years, with an age range of 18 to 35 years. Regarding sex distribution, 17 patients (42.5%) were male and 23 patients (57.5%) were female.

### Higher-Order Aberrations

**Table 2.** Comparison between preoperative and postoperative RMS higher-order aberrations (HOAs).

PARAMETER	PREOPERATIVE (N = 40) MEAN $\pm$ SD	POSTOPERATIVE (N = 40) MEAN $\pm$ SD	MW	P-VALUE
RMS HOA (5 MM)	1.34 $\pm$ 0.29	1.11 $\pm$ 0.36	470.5	0.002*
RMS HOA (6 MM)	1.70 $\pm$ 0.37	1.29 $\pm$ 0.41	398.0	<0.001**

\* Statistically significant, \*\* Highly statistically significant, MW: Mann–Whitney test

Table 2 shows the comparison between preoperative and postoperative root mean square (RMS) higher-order aberrations (HOAs) measured over 5-mm and 6-mm pupil diameters. Postoperative

RMS HOA values showed a statistically significant reduction compared with preoperative measurements. RMS HOA measured over a 5-mm pupil diameter decreased significantly from  $1.34 \pm 0.29$  preoperatively to  $1.11 \pm 0.36$  postoperatively ( $P = 0.002$ ). Similarly, RMS HOA measured over a 6-mm pupil diameter demonstrated a highly significant reduction from  $1.70 \pm 0.37$  preoperatively to  $1.29 \pm 0.41$  postoperatively ( $P < 0.001$ ).

### Changes in Individual Higher-Order Aberrations

**Table 3.** Comparison of preoperative and postoperative higher-order aberrations (HOAs).

Aberration	Preoperative (N = 40) Mean $\pm$ SD	Postoperative (N = 40) Mean $\pm$ SD	MW	P-value
Horizontal trefoil	$0.261 \pm 0.037$	$0.246 \pm 0.035$	626.0	0.91
Vertical trefoil	$0.293 \pm 0.049$	$0.311 \pm 0.040$	624.5	0.089
Horizontal coma	$0.601 \pm 0.053$	$0.494 \pm 0.052$	123.0	<0.001**
Vertical coma	$1.64 \pm 0.08$	$1.42 \pm 0.07$	37.5	<0.001**
Spherical aberration	$0.520 \pm 0.061$	$0.406 \pm 0.051$	119.0	<0.001**
Second horizontal trefoil	$0.042 \pm 0.006$	$0.039 \pm 0.008$	537.5	0.011*
Second vertical trefoil	$0.078 \pm 0.008$	$0.074 \pm 0.008$	592.5	0.044*
Second horizontal coma	$0.126 \pm 0.025$	$0.094 \pm 0.032$	335.5	<0.001**
Second vertical coma	$0.378 \pm 0.059$	$0.286 \pm 0.047$	188.0	<0.001**

\* Statistically significant, \*\* Highly statistically significant, MW: Mann–Whitney test

Table 3 summarizes the comparison of individual higher-order aberration (HOA) components before and six months after corneal collagen cross-linking. No statistically significant changes were observed in horizontal or vertical trefoil aberrations following surgery ( $P > 0.05$ ). In contrast, both horizontal and vertical coma demonstrated highly significant postoperative reductions. Horizontal coma decreased from  $0.601 \pm 0.053$  preoperatively to  $0.494 \pm 0.052$  postoperatively ( $P < 0.001$ ), while vertical coma decreased from  $1.64 \pm 0.08$  to  $1.42 \pm 0.07$  ( $P < 0.001$ ). Spherical aberration also showed a highly significant postoperative reduction, decreasing from  $0.520 \pm 0.061$  to  $0.406 \pm 0.051$  ( $P < 0.001$ ). Additionally, second-order horizontal and vertical trefoil aberrations exhibited statistically significant decreases postoperatively ( $P = 0.011$  and  $P = 0.044$ , respectively). Both second-order horizontal and vertical coma demonstrated highly significant reductions following CXL ( $P < 0.001$  for both).

Analysis of higher-order aberrations (HOAs) revealed a significant improvement in overall visual quality following corneal collagen cross-linking. As shown in **Table 2**, the RMS HOA decreased significantly from  $1.34 \pm 0.29$  to  $1.11 \pm 0.36$  over a 5-mm pupil ( $P = 0.002$ ) and from  $1.70 \pm 0.37$  to  $1.29 \pm 0.41$  over a 6-mm pupil ( $P < 0.001$ ). Component-wise analysis in **Table 3** demonstrated that the highly significant reductions in RMS HOA were primarily driven by decreases in horizontal and vertical coma as well as spherical aberrations ( $P < 0.001$  for all). While trefoil aberrations showed minimal or only modest reductions, these changes contributed less to the overall RMS HOA. This pattern indicates that the improvement in total higher-order aberrations after CXL is predominantly due to the correction of coma and spherical aberrations, which are the main contributors to visual distortion in keratoconus.

### Keratometric Values

**Table 4.** Comparison of preoperative and postoperative keratometric values.

Parameter	Preoperative (N = 40) Mean $\pm$ SD	Postoperative (N = 40) Mean $\pm$ SD	MW	P-value
K1 (D)	43.8 $\pm$ 4.4	42.9 $\pm$ 3.9	700.0	0.333
K2 (D)	49.5 $\pm$ 4.0	49.8 $\pm$ 4.0	775.0	0.808

MW: Mann–Whitney test

Table 4 presents the comparison between preoperative and postoperative keratometric values (K1 and K2). No statistically significant differences were observed between preoperative and postoperative K1 or K2 values ( $P > 0.05$  for both parameters).

### DISCUSSION

Corneal collagen cross-linking (CXL) is currently regarded as the primary intervention for preventing disease progression in keratoconus, acting by enhancing the biomechanical stability of the corneal stroma via riboflavin-induced ultraviolet-A photoactivation (Raiskup & Spoerl, 2013). This photochemical reaction promotes the formation of new intermolecular collagen bonds, resulting in increased stromal stiffness and improved resistance to ectatic deformation (Alhayek & Lu, 2015; Sharma et al., 2012). Extensive clinical evidence supports the long-term safety and effectiveness of CXL, with serious complications remaining uncommon when established safety protocols and treatment parameters are strictly followed (Alhayek & Lu, 2015; Nicula et al., 2015; Kymionis et al., 2020).

In the present study, we evaluated the effect of epithelium-off (epi-off) CXL on corneal higher-order aberrations (HOAs) over a six-month follow-up period. All 40 eyes completed the follow-

up without intraoperative or postoperative complications, and no eye demonstrated keratoconus progression or deterioration requiring further intervention during the study period.

Our results demonstrated a statistically significant reduction in RMS HOAs at six months postoperatively. Specifically, RMS HOA measured over a 5-mm pupil decreased significantly from  $1.34 \pm 0.29$  preoperatively to  $1.11 \pm 0.36$  postoperatively ( $P = 0.002$ ), while RMS HOA over a 6-mm pupil showed a highly significant reduction from  $1.70 \pm 0.37$  to  $1.29 \pm 0.41$  ( $P < 0.001$ ). These findings indicate a meaningful improvement in corneal optical quality following epi-off CXL and are fully consistent with the outcomes presented in Table 2.

Numerous studies have reported similar improvements in HOAs following epi-off CXL. Greenstein et al. (2012) observed improvement in corneal HOAs in 74% of eyes at one-year follow-up, although inclusion of post-LASIK ectasia cases may have attenuated the overall magnitude of improvement. Kocamis et al. (2014) reported statistically significant HOA reduction at 18 months, while Vinciguerra et al. (2009) demonstrated significant improvement at 12 months using the same epi-off technique. In younger patients, Vinciguerra et al. (2012) reported sustained improvement in HOAs over a 24-month period, emphasizing the biomechanical benefit of early intervention.

Long-term outcomes further support these findings. Naderan and Jahanrad (2017) reported significant improvement in corneal HOAs at one year, with continued improvement up to four years post-CXL ( $P < 0.001$ ). Similarly, Ghanem et al. (2014) demonstrated statistically significant reductions in corneal HOAs at six months, which remained stable over a two-year follow-up period.

Early postoperative changes in HOAs may be variable. In our study, preliminary analysis of the first 10 eyes at three months showed mixed results, including transient increases in HOAs in some cases, leading to omission of the three-month analysis. This phenomenon has been described previously and is attributed to early epithelial remodeling and wound-healing responses following epi-off CXL. Kosekahya et al. (2017) similarly reported no significant change in RMS HOAs at three months, followed by significant improvement at six months that remained stable at one year.

Component-wise analysis of HOAs in the present study (Table 3) revealed that the overall improvement in RMS HOAs was primarily driven by significant reductions in coma and spherical aberrations. Horizontal coma decreased significantly from  $0.601 \pm 0.053$  to  $0.494 \pm 0.052$  ( $P < 0.001$ ), and vertical coma decreased from  $1.64 \pm 0.08$  to  $1.42 \pm 0.07$  ( $P < 0.001$ ). Spherical aberration also showed a highly significant reduction from  $0.520 \pm 0.061$  to  $0.406 \pm 0.051$  ( $P < 0.001$ ). In contrast, primary horizontal and vertical trefoil did not show statistically significant changes, while second-order trefoil and coma components demonstrated modest but statistically significant improvements.

These findings are consistent with previous reports identifying coma as the HOA component most strongly affected by keratoconus and most responsive to CXL-induced biomechanical stabilization (Greenstein et al., 2012). Ghanem et al. (2014) similarly reported significant reductions in coma and trefoil aberrations, while Naderan and Jahanrad (2017) found early improvement in vertical coma and spherical aberration followed by broader HOA improvement over longer follow-up.

Discrepancies among studies may be explained by differences in aberrometry systems and analysis techniques. Devices such as OPD-Scan, Scheimpflug-based systems, and Shack–Hartmann aberrometers vary in their sensitivity and reproducibility for corneal versus total ocular HOAs, which may influence reported outcomes (Ferdin et al., 2021).

Regarding corneal curvature, our study demonstrated no statistically significant change in either K1 or K2 values at six months postoperatively (Table 4). K1 decreased from  $43.8 \pm 4.4$  D to  $42.9 \pm 3.9$  D ( $P = 0.333$ ), and K2 remained stable ( $49.5 \pm 4.0$  D preoperatively vs.  $49.8 \pm 4.0$  D postoperatively;  $P = 0.808$ ). These findings support the concept that the primary benefit of CXL lies in biomechanical stabilization rather than significant early keratometric flattening, a conclusion echoed by several recent studies (Wisse et al., 2016; Kymionis et al., 2020).

Recent literature published after 2020 further confirms that both conventional and accelerated epithelium-off CXL protocols can lead to improvement or stabilization of HOAs, particularly coma-related aberrations, even when keratometric changes are minimal (Mazzotta et al., 2021; Salman et al., 2022). These optical improvements are clinically relevant, as reductions in coma and spherical aberrations have been correlated with better visual quality and contrast sensitivity.

In conclusion, the present study demonstrates that epithelium-off CXL produces significant improvement in corneal higher-order aberrations especially coma and spherical aberrations—at six months postoperatively, without inducing adverse effects or keratometric instability. These findings, in agreement with both earlier and recent literature, reinforce the role of CXL as a safe and effective intervention for improving corneal optical quality while stabilizing keratoconus progression.

### **Implications for Research and Practice**

The results highlight the importance of evaluating higher-order aberrations when assessing treatment outcomes in keratoconus. CXL should be considered not only as a stabilizing procedure but also as a means of improving corneal optical quality, which may translate into better functional vision and patient satisfaction.

### **CONCLUSION**

Corneal collagen cross-linking (CXL) resulted in a statistically significant reduction in corneal higher-order aberrations (HOAs), particularly spherical aberrations and coma components, at six

months postoperatively. Among the evaluated aberrations, coma—known to be the most prevalent and visually debilitating aberration in keratoconus—demonstrated the greatest improvement following treatment. These findings reflect enhanced corneal optical regularity and support the beneficial effect of CXL beyond its established role in halting disease progression.

Given the substantial impact of ocular aberrations on retinal image quality and visual performance, the observed reduction in HOAs following CXL may contribute to improved visual quality, even in the absence of significant keratometric flattening. This highlights the importance of evaluating optical quality parameters, such as HOAs, in addition to conventional refractive and topographic indices when assessing treatment outcomes in keratoconus.

In conclusion, epithelium-off CXL is a safe and effective therapeutic modality for patients with keratoconus, providing not only biomechanical stabilization of the cornea but also meaningful improvement in higher-order optical aberrations. These optical benefits may enhance functional vision and reduce visual distortion, thereby improving overall visual quality and patient satisfaction. Further studies with larger sample sizes and longer follow-up periods are warranted to evaluate the long-term stability of these aberration changes and their correlation with subjective visual outcomes.

### **Future Research**

Future studies with larger sample sizes, longer follow-up periods, and correlation with subjective visual quality measures are needed to further elucidate the long-term optical benefits of corneal collagen cross-linking in keratoconus.

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