

# International Journal of Medical Ophthalmology



E-ISSN: 2663-8274  
P-ISSN: 2663-8266  
[www.ophthalmoljournal.com](http://www.ophthalmoljournal.com)  
IJMO 2025; 7(2): 25-28  
Received: 26-05-2025  
Accepted: 28-06-2025

Dr. Sanjana Garg  
3<sup>rd</sup> Year Resident (M.S  
Ophthalmology), Government  
Medical College Surat, Veer  
Narmad South Gujarat  
University, Surat, Gujarat,  
India

## To assess the long term outcomes of corneal collagen cross linking (c3r) for progressive keratoconus patients

**Sanjana Garg**

**DOI:** <https://www.doi.org/10.33545/26638266.2025.v7.i2a.244>

### Abstract

Keratoconus is a progressive condition characterized by thinning and protrusion of the cornea, leading to visual impairment due to irregular curvature. Corneal collagen cross-linking has emerged as a promising therapeutic intervention aimed at stabilizing the cornea and halting disease progression. This study was conducted to evaluate the long-term clinical outcomes of corneal collagen cross-linking in patients with progressive keratoconus over a period of eighteen months.

A prospective and retrospective observational study was undertaken involving patients diagnosed with progressive keratoconus. All patients underwent corneal collagen cross-linking using riboflavin and ultraviolet light following a standard protocol (Dresden Protocol). Parameters assessed at baseline and at six, twelve, and eighteen months post-procedure included maximum and mean corneal curvature, central and thinnest corneal thickness, manifest and topographic astigmatism, and distance and near visual acuity.

A total of thirty two eyes were studied. At 6 months post-C3R, there was a significant reduction in K-max across all stages of keratoconus, particularly in stages 1 and 2, indicating early corneal stabilization. Manifest astigmatism also showed notable improvement in stage 1 during this period. By 12 months, the reduction in K-max remained stable in stages 1 and 2 but was not sustained in stage 3, and further improvement in astigmatism was observed. At 18 months, over half of the eyes demonstrated regression in K-max, with a smaller proportion showing progression or stability. BCVA remained stable or improved in the majority of eyes, and near visual acuity was largely preserved.

This study concludes that corneal collagen cross-linking is effective in halting the progression of keratoconus while offering improvement or stabilization in corneal shape and visual outcomes with the most pronounced benefits occurring within the first 6 to 12 months and largely sustained through 18 months. Early-stage patients tend to benefit the most, highlighting the importance of timely diagnosis and intervention. The procedure is safe, minimally invasive, and has the potential to reduce the need for corneal surgery in advanced cases.

**Keywords:** Keratoconus, corneal collagen cross-linking, visual acuity, corneal curvature, astigmatism, corneal thickness

### Introduction

Keratoconus is a progressive, bilateral, non-inflammatory ectatic disorder of the cornea characterized by stromal thinning and anterior protrusion, leading to irregular astigmatism, myopia, and gradual visual deterioration. It typically manifests during puberty and progresses at varying rates, often stabilizing by the fourth decade of life. The prevalence of keratoconus has been reported between 50 to 230 per 100,000 individuals globally, with higher incidence observed in Asian populations, including India, where it is estimated at approximately 1 in 2000 individuals <sup>[1, 2]</sup>.

Conventional management options such as spectacles and rigid gas-permeable contact lenses primarily focus on optical correction without addressing disease progression. In advanced cases, penetrating keratoplasty or deep anterior lamellar keratoplasty may be required, but these involve considerable surgical risks and long-term rehabilitation <sup>[3]</sup>.

The introduction of corneal collagen cross-linking has revolutionized the management of progressive keratoconus. This technique strengthens corneal biomechanics by inducing covalent bonds between stromal collagen fibrils through the photochemical interaction of ultraviolet-A light and riboflavin, thereby halting or slowing the ectatic process <sup>[4]</sup>. The standard Dresden protocol has shown promising results, particularly in early and moderate disease stages, with studies demonstrating significant flattening of corneal curvature and stabilization of visual acuity <sup>[5]</sup>.

**Corresponding Author:**  
**Dr. Sanjana Garg**  
3<sup>rd</sup> Year Resident (M.S  
Ophthalmology), Government  
Medical College Surat, Veer  
Narmad South Gujarat  
University, Surat, Gujarat,  
India

Despite these advancements, variations in long-term efficacy, especially across different stages of keratoconus, remain a subject of clinical concern. Moreover, limited stage-wise data from the Indian subcontinent highlight the need for region-specific research that reflects the unique demographic, genetic, and environmental factors influencing keratoconus progression.

### Materials and Methodology

This observational longitudinal study was conducted at the tertiary care centre of New Civil Hospital, Surat, to evaluate changes in visual acuity, keratometry, and corneal thickness at 6, 12, and 18 months following Corneal Collagen Cross-Linking (C3R) in keratoconus patients. Ethical clearance was obtained from the Institutional Ethics Committee, and informed consent was secured from all participants.

### Sample Size

A total of 32 eyes from 21 patients were included.

### Inclusion Criteria

- Patients who underwent C3R using the standard Dresden protocol.
- Complete and documented pre-operative data.
- All age groups and both genders.

### Exclusion Criteria

- Presence of any anterior/posterior segment ocular morbidity.
- History of ocular surgery other than C3R.

### Study Procedure

Patients returning for follow-up visits after C3R were recruited. Pre-operative data included visual acuity (distance and near), BCVA, slit-lamp and fundus examination, cycloplegic retinoscopy, and Pentacam-based corneal tomography (Oculus GmbH, Germany). The following Pentacam parameters were analyzed:

- K-max (maximum keratometry)
- K-mean (mean keratometry)
- Pachymetry at the thinnest point
- Topographic astigmatism

Keratoconus severity was graded using the Amsler-Krumeich classification based on refractive error, keratometry, corneal transparency, and central thickness:

- **Stage 1:** 13 eyes.
- **Stage 2:** 15 eyes.
- **Stage 3:** 4 eyes.
- **Stage 4:** 0 eyes.

Clinical and imaging data were collected retrospectively and prospectively at 6, 12, and 18 months post-C3R. Outcomes were classified as:

- **Regression:** K-max reduced  $>0.5$  D from baseline.
- **Stabilization:** K-max within  $\pm 0.5$  D of baseline.
- **Progression:** K-max increased  $>0.5$  D.

### Statistical Analysis

Data were analyzed using Microsoft Excel. Continuous variables were expressed as mean  $\pm$  SD.

- **Paired t-test:** Comparison of pre- and post-operative values
- **Repeated Measures ANOVA:** Evaluation across follow-ups
- **Chi-square test:** For categorical variables like BCVA  
A p-value  $< 0.05$  was considered statistically significant.

### Results and Discussion

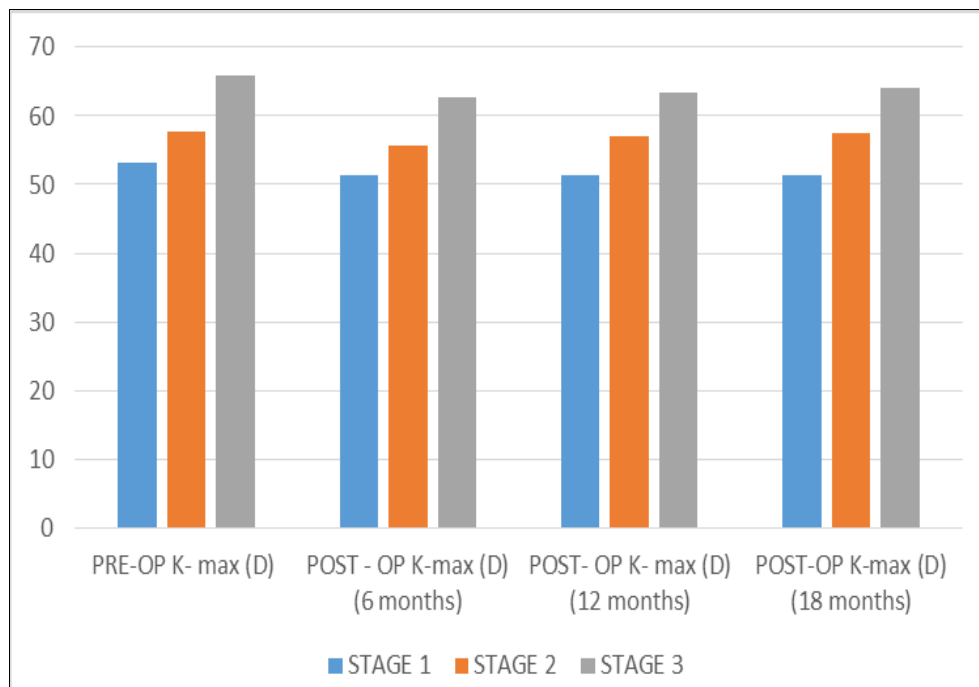
1. The study involved 32 eyes from 21 patients, with an equal distribution of participants in the 12-20 years (50%) and 21-29 years (50%) age groups.
2. A male predominance was observed, with 66.25% male participants and 34.37% female participants.
3. All patients (100%) demonstrated bilateral keratoconus involvement, aligning with its recognized bilateral yet asymmetrical nature.

In some of these cases, the fellow eye may have had stable or early-stage disease not meeting the criteria for immediate intervention. However, in other instances, logistical factors such as socioeconomic barriers, patient compliance, or loss to follow-up may have contributed to incomplete bilateral treatment.

4. Among 21 patients, 68.75% underwent bilateral C3R, while 31.25% had unilateral treatment.
5. In terms of keratoconus severity, 41% of the eyes were classified as stage 1, 47% as stage 2, and 12.5% as stage 3. No patients were categorized as stage 4

In stage 1, K-max significantly decreased at 6 months (mean change:  $1.81 \pm 8.09$ ,  $p=0.001$ ) and remained stable thereafter. In stage 2, K-max also decreased significantly at 6 months (mean change:  $2.23 \pm 6.79$ ,  $p=0.001$ ) in stage 3, K-max reduced significantly by 6 months ( $p=0.001$ ), but there was no reduction seen beyond 6 months.

These findings suggest that C3R is more effective in reducing corneal steepening in advanced keratoconus compared to earlier stages.



**Chart 1:** Progression of K-max (D) in different stages of KC Pre and Post- operatively (6months, 12months and 18 months) (Pentacam)

6. At the 18-month follow-up, 56.25% of eyes showed regression in K-Max, 31.25% showed progression, and 12.5% were stable ( $p=0.0098$ ).

linking led to significant regression of K-max in a majority of eyes over an 18-month period, supporting its role in stabilizing keratoconus progression.

The present study concluded that, corneal collagen cross-

**Table 1:** K-max changes at 18 month follow up (Pentacam)

Changes in K- max	Frequency	Percentage
Progression	10	31.25%
Stable	4	12.5%
Regression	18	56.25%

7. Risk factors related to progression after C3R was most commonly observed in patients with Stage 2 keratoconus (90%), K-max >55 D (60%), and corneal thickness <450  $\mu$ m (60%), with 40% aged  $\leq 18$  years.

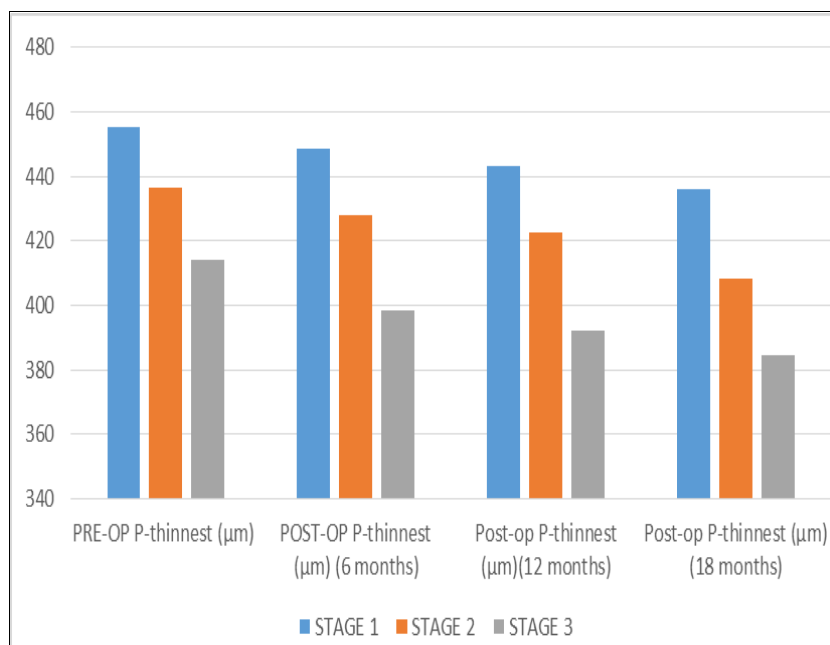
Most common risk triad is Stage 2 with K-max value more than 55D and with thinnest pachymetric values less than 450  $\mu$ m.

**Table 2:** Percentage distribution of Risk factors related to progression in C3R operated patients

Risk factors	Criteria	Frequency	Percentage
AGE	$\leq 18$ years	4	40%
	>18 years	6	60%
K-max	>55D	6	60%
	$\leq 55$ D	4	40%
Pachy- thinnest	<450 $\mu$ m	6	60%
	$\geq 450$ $\mu$ m	4	40%
KC Staging	Stage 2	9	90%
	Stage 1	1	10%

8. The pachymetry data indicated a decrease in the central corneal thickness in all stages, with significant changes observed in stage 1 and stage 2 at 18 months ( $p=0.0008$  for stage 1 and  $p=0.01$  for stage 2).

A slight decrease in mean keratometry values across all stages of keratoconus, with significant improvement only in Stage 3 at 6 months postoperatively. However, this reduction was not sustained in the long term.



**Chart 2:** Average Pachy-thinnest Pre Vs Post C3R (6months, 12months and 18 months) (Pentacam)

9. There were no significant changes in the K-mean values across the stages at the 6, 12 and 18-month follow-ups.
10. Astigmatism (both topographic and manifest) showed improvements post-C3R, with significant changes observed in manifest astigmatism at 6 months in stage 1 ( $p=0.000$ ) and continued improvement at 12 months ( $p=0.010$ ).
11. At 18 months post-C3R, 59.37% of patients maintained stable BCVA, 34.37% showed significant visual improvement, and only 3.12% experienced mild deterioration.
12. At 18 months post-C3R, near visual acuity remained stable in 93.75% of eyes, with mild improvement in 6.25% and no deterioration.

### Conclusion

The parent study “To assess the long term outcomes of Corneal Collagen Cross Linking (C3R) for Progressive Keratoconus patients” findings reaffirm the efficacy of C3R in stabilizing or reversing disease progression in a substantial proportion of eyes.

- The 18 months follow up revealed significant reduction in K-max in Stage 1 and 2 KC, indicating effective disease stabilisation in early stages. However, Stage 3 KC patients has limited long term benefits of C3R.
- Significant reduction in manifest astigmatism, especially in Stage 1, indicates improved refraction outcomes and supports the clinical value of C3R beyond structural stability.
- The 18 months follow up revealed patients having typical parameters like Stage 2 disease, K-max  $>55D$ , pachymetry  $<450 \mu m$  and age  $\leq 18$  years had higher risk of post-C3R progression emphasizing the importance of close monitoring and possibly earlier or alternative treatment strategies in these groups.
- A substantial proportion of eyes (59.37%) maintained stable BCVA and (34.37%) improved. However near vision remained stable in the majority (93.75%). This signifies that C3R preserves and improves visual acuity.

This study demonstrates that Corneal Collagen Cross-Linking (C3R) is an effective and safe procedure for halting or stabilizing progressive keratoconus over an 18-month

follow-up.

### Acknowledgement

I greatly appreciate my mentor Dr. Priti Kapadia, for her constant advice. I want to thanks my parents, siblings and my seniors for their support during my studies. There is no financial disclosure and no conflict of interest related to this work.

### References

1. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. *J Cataract Refract Surg.* 1999 Oct;25(10):1327-1335.
2. Krachmer JH, Mannis MJ, Holland EJ, editors. *Cornea*. 3<sup>rd</sup> ed. St. Louis (MO): Mosby/Elsevier; 2011.
3. Tan BU, Purcell TL, Torres LF, Schanzlin DJ. New surgical approaches to the management of keratoconus and post-LASIK ectasia. *Trans Am Ophthalmol Soc.* 2006;104:212-220.
4. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Curr Opin Ophthalmol.* 2006 Aug;17(4):356-360.
5. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R, Balestrazzi A. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. *Cornea.* 2012 Mar;31(3):227-231.

### How to Cite This Article

Garg S. To assess the long term outcomes of corneal collagen cross linking (c3r) for progressive keratoconus patients. *International Journal of Medical Ophthalmology* 2025; 7(2): 25-28.

### Creative Commons (CC) License

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 International (CC BY-NC-SA 4.0) License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.