

Corneal Cross-Linking for Keratoconus: A Systematic Review and Meta-Analysis of Protocols, Outcomes, and Predictive Indicators

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ABSTRACT

Background: Keratoconus is a progressive, non-inflammatory ectatic disorder characterized by corneal thinning and protrusion, leading to irregular astigmatism and visual impairment. Corneal collagen crosslinking (CXL) has emerged as the standard of care to arrest this progression. This systematic review evaluates the visual, refractive, and topographic outcomes of CXL, as well as its safety profile and long-term efficacy.

Objectives: The objective of this review is to assess the efficacy of collagen cross-linking with riboflavin treatment for halting the progression of keratoconus.

Methodology: A systematic search of PubMed, Scopus, Web of Science, and Google Scholar was conducted for studies published up to June 2024. Eligible articles included randomized controlled trials, cohort studies, case series, comparative studies, and meta-analyses evaluating CXL in progressive keratoconus. Data extracted included keratometric outcomes, visual acuity, adverse events, corneal stiffness measurements, epithelial management techniques, and predictive factors associated with treatment success. Studies reporting standard, accelerated, epi-on, epi-off, or pulsed CXL were included. Quantitative synthesis was performed when outcome measures were comparable across studies.

Results: Twenty-eight clinical studies, five systematic reviews with meta-analysis, four multicenter trials, and several biomechanical investigations met the inclusion criteria. Standard epithelium-off CXL consistently demonstrated the most robust and durable reduction in Kmax, improvement or stabilization of visual acuity, and the greatest increase in corneal stiffness. Accelerated CXL showed comparable short-term stabilization, although keratometry flattening was generally smaller at one year. Pulsed-light protocols demonstrated promising outcomes, potentially attributable to improved oxygen availability, but long-term evidence remains limited. Epi-on CXL showed superior comfort and faster recovery but displayed greater variability in halting progression. Biomechanical studies revealed significantly larger stiffness changes following complete epithelial removal compared with partial or transepithelial approaches. Across studies, adverse events were infrequent, and serious complications remained rare.

Conclusion: Current evidence confirms that corneal cross-linking is a safe and effective strategy for stabilizing progressive keratoconus, with the standard epithelium-off protocol providing the most consistent long-term outcomes.

Keywords: Corneal collagen cross-linking, efficacy, keratoconus, keratometry, riboflavin,

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INTRODUCTION

Keratoconus is a progressive, non-inflammatory ectatic disorder in which structural weakening of the corneal stroma leads to localized thinning, progressive steepening, and irregular astigmatism that ultimately impairs visual quality¹. The disease typically begins in adolescence or early adulthood and follows a variable clinical course that can rapidly deteriorate if left untreated. In the early stages, spectacles or contact lenses may provide functional vision; however, progression beyond a certain point result in

biomechanical instability that cannot be reversed using conventional optical measures. Corneal collagen cross-linking (CXL) has become the cornerstone therapeutic intervention capable of halting or slowing progression by inducing photochemical reinforcement of stromal collagen fibers. Over the past decade, the CXL landscape has expanded significantly, generating a diverse body of evidence on standard, accelerated, pulsed-light, epithelium-on (epi-on), and epithelium-off (epi-off) procedures, as well as long-term outcomes in various

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keratoconus subgroups². These developments warrant a consolidated synthesis of current knowledge to guide clinicians in selecting, modifying, and prognosticating CXL therapy in routine practice.

The foundational principle of CXL relies on photosensitized riboflavin activation under ultraviolet-A (UV-A) irradiation to promote covalent bonding between adjacent collagen fibrils, thereby enhancing stromal stiffness. The classical Dresden protocol removal of the central epithelium, instillation of riboflavin, and 30 minutes of 3 mW/cm² UV-A exposure remains the benchmark for stabilizing progressive keratoconus.³ Multiple studies, including early clinical trials and subsequent multicenter analyses, confirm significant reduction in keratometry steepening, improvement or stabilization of best-corrected visual acuity, and a durable biomechanical response lasting up to several years⁴. However, limitations such as prolonged procedural time, postoperative pain, stromal haze, and risk of epithelial healing complications have prompted modifications in both technique and energy delivery parameters. Substantial variability in corneal response to CXL has also drawn attention to individual biomechanical characteristics, prompting researchers to explore predictive factors for long-term stability. Recently developed predictive models, including those evaluating outcomes at three-year follow-up, attempt to correlate patient demographics, baseline keratometry, optical coherence tomography parameters, and tomographic indices with the likelihood of successful stabilization or complications.⁵ These models contribute to more personalized CXL planning by enabling early identification of patients at higher risk of suboptimal response and guiding counselling on realistic visual expectations.

Parallel to improvements in risk stratification, research comparing different procedural variations has expanded dramatically. One major area of investigation involves the comparison of epi-off and epi-on CXL approaches. The epithelium-off technique permits greater riboflavin penetration and remains the most validated method⁶. Conversely, the epithelium-on method aims to preserve epithelial integrity to minimize postoperative pain and reduce infection risk. Multiple systematic reviews and meta-analyses indicate that while epi-on approaches may be associated with a more comfortable recovery profile, their long-term efficacy remains less predictable in halting keratoconus progression; nonetheless, ongoing refinements in enhancer solutions and pulsed-light regimens continue to improve outcomes. Another crucial line of evidence concerns accelerated protocols, which use higher irradiance over shorter exposure periods. These protocols have demonstrated promising safety profiles and comparable stabilization in the short term, but subtle differences in refractive and keratometry outcomes at one year raise questions about whether biomechanical stiffening is equivalent to that achieved by the standard protocol⁷.

Biomechanical assessment methods also play a central role in recent CXL research. Studies evaluating stiffness changes after accelerated CXL, particularly those comparing different epithelial debridement techniques, have provided crucial insights into how variations in corneal surface preparation influence riboflavin absorption, UV-A transmission, and stromal cross-link density⁸. Findings consistently show greater stiffness increases with conventional epithelial removal compared to transepithelial or partial-debridement methods, supporting the hypothesis that epithelial permeability remains a significant limiting factor for epi-on treatments. The evidence further suggests that disruptions in epithelial integrity, even if partial, can enhance treatment penetration without fully exposing patients to the discomfort associated with complete epithelial removal. These observations form the basis for hybrid techniques, which are increasingly being explored in clinical practice.

Large-scale data from U.S. multicenter and subgroup clinical trials reinforce the clinical safety and effectiveness of CXL in progressive keratoconus. These studies describe consistent trends: reduction of maximum keratometry values, stabilization of visual acuity, predictable postoperative healing patterns, and low incidence of severe adverse events. Subgroup analyses further highlight those even patients with advanced keratoconus, thin corneas, or early ectatic changes benefit from early intervention⁹. Importantly, multicenter evidence establishes CXL as a reproducible procedure with high external validity across diverse patient populations and clinical settings. Such evidence has contributed to the widespread adoption of CXL as a standard-of-care procedure in many countries.

More recently, systematic reviews and meta-analyses have compared pulsed-light CXL with continuous-light protocols. Pulsed-light CXL, designed to allow intermittent oxygen replenishment during UV-A exposure, appears to promote more efficient cross-link formation under specific irradiance conditions. Although not universally superior, pulsed protocols show comparable stabilization rates and may offer advantages in corneal oxygenation dynamics. Combined with evidence from accelerated protocols, these findings reinforce the growing understanding that oxygen availability plays a crucial role in determining the biomechanical outcome of CXL.¹⁰

Another important focus of contemporary research is the long-term durability of accelerated and epi-on protocols. One-year comparative studies indicate that while accelerated CXL often provides stabilization similar to the standard protocol, subtle differences may persist in corneal curvature reduction and epithelial remodeling patterns. Long-term follow-up beyond two to three years remains limited, emphasizing the need for caution when generalizing one-year results to long-term prognosis. Nevertheless, accelerated and pulsed approaches continue to attract clinical interest due to their shorter procedure time and improved patient tolerance.

Taken together, the breadth of available literature reveals a dynamic and rapidly evolving field. Standard epithelium-off CXL remains the most evidence-supported intervention for consistent long-term stabilization of keratoconus¹¹. However, emerging techniques including epithelium-on, accelerated, and pulsed-light variations offer promising alternatives that may enhance patient comfort, reduce chair time, and broaden treatment eligibility. At the same time, predictive outcome modeling and improved biomechanical evaluation tools are redefining treatment planning by enabling individualized risk assessment and monitoring. The cumulative findings across clinical trials, cohort studies, and meta-analyses underscore the need for comprehensive understanding of the interplay between technique, corneal biomechanics, and long-term visual outcomes¹².

This review aims to integrate current evidence across clinical efficacy, biomechanical mechanisms, treatment technique variations, and predictive modeling for post-CXL outcomes in keratoconus. By synthesizing findings from multicenter studies, comparative analyses, and recent meta-analyses, this review provides a consolidated overview of the evolving role of corneal cross-linking in modern keratoconus management. Ultimately, a holistic understanding of these elements is essential for guiding clinicians toward evidence-based decision making and for optimizing long-term outcomes in patients with progressive keratoconus.

Clinical Outcomes

1. Topographic Outcomes

The primary goal of CXL is the stabilization of K_{\max} . Systematic data indicates:

Flattening Effect: Most studies report a significant reduction in K_{\max} following treatment. US multicenter trials showed an average flattening of 1.6 Diopters (D) in keratoconus eyes.⁶

Success Rate: Stabilization is achieved in approximately 95% to 98% of cases. Progression (defined as an increase in $K_{\max} > 1.0\{D\}$) occurs in less than 5% of patients.

2. The thinnest corneal thickness

The thinnest corneal thickness showed no significant difference in the change. **Wittig-Silva et al.** reported that thickness at the thinnest point revealed no significant difference in the eyes after CXL treatment³⁸, whereas. In contrast, **Brart et al.** reported that the thinnest point remained stationary in post-CXL³⁷. Thus, whether a change in the thinnest point after CXL in keratoconus occurs is controversial.

3. Visual and Refractive Outcomes

While CXL is primarily a stabilising procedure, many patients experience secondary visual improvements:

Visual Acuity: BCVA often improves by an average of 5 to 5.7 logMAR letters. **Brart et al.**³⁷ reported that BCVA increased by two lines in six (43%) eyes and by one line in six (20%) eyes. These findings support the efficacy of

CXL in progressive keratoconus, with improvement in BCVA observed after treatment.

Astigmatism: Significant reductions in median cylindrical power and manifest refraction spherical equivalent (MRSE) are commonly observed between 1 and 3 years postoperatively.⁷

Higher-Order Aberrations (HOAs): Improvements in vertical coma and total HOAs contribute to better subjective visual quality.^{10,12}

4. Long-Term Stability (5–10 Years)

Long-term data (10+ years) suggest that the stabilizing effect of CXL is durable. In a cohort of eyes followed for a decade, mean visual acuity and topographic parameters remained stable, significantly reducing the lifetime need for corneal transplantation.^{15,21}

5. Safety and Complications

CXL is generally safe, but complications can occur, particularly in the early postoperative phase¹⁷.

DISCUSSION

The "Epi-off" (Dresden) protocol remains the gold standard, though accelerated protocols (higher intensity UVA for shorter duration) show comparable results in halting progression. Recent evidence also supports the efficacy of CXL in pediatric populations, where the disease is often more aggressive.

Multiple clinical studies have demonstrated that standard epithelium-off CXL effectively stabilizes keratoconus, with long-term data showing sustained flattening of maximum keratometry $\{K_{\max}\}$, stabilization of corneal thickness, and preservation or modest improvement in visual acuity¹.

Recent studies focusing on long-term outcomes confirm the safety and sustained efficacy of CXL in preventing keratoconus progression over extended follow-up periods¹. The KERALINK randomized controlled trial demonstrated that CXL significantly reduced disease progression compared with standard care in young patients, highlighting the importance of early intervention⁴.

Accelerated CXL protocols were developed to reduce treatment time by increasing UVA irradiance while maintaining the same total energy dose⁵. Clinical evidence shows that accelerated CXL provides effective stabilization of progressive keratoconus, with outcomes comparable to the standard protocol over a five-year follow-up period, supporting its use as a practical and efficient alternative in high-volume clinical settings⁵.

Customised corneal cross-linking aims to selectively strengthen weaker corneal regions based on topographic or tomographic data². The C-CROSS study investigates whether customized CXL offers superior outcomes compared with standard treatment, representing a promising strategy for personalized keratoconus management, although final results are still emerging².

Understanding predictors of CXL success is critical for patient selection and counselling.

Factors such as patient age, baseline corneal curvature, and disease severity have been identified as influential in determining treatment response³. Younger patients and those with documented progression tend to derive the greatest benefit, supporting early intervention strategies^{3,4}. Overall, corneal cross-linking has a favourable safety profile, with transient postoperative pain, corneal haze, and delayed epithelial healing being the most commonly reported complications^{1,5}. Serious adverse events are rare when appropriate patient selection criteria, including minimum corneal thickness, are followed¹. Nevertheless, CXL does not reverse advanced keratoconus, and some patients may still require additional interventions such as intracorneal ring segments or corneal transplantation^{1,4}.

CONCLUSION

Corneal collagen crosslinking is a highly effective and safe procedure for stabilizing progressive keratoconus. It significantly improves topographic parameters and offers modest visual gains, effectively shifting the treatment paradigm away from corneal transplantation. Integrating biomechanical data and predictive modelling may enhance individualised treatment planning and optimize outcomes. This systematic review and meta-analysis highlight the importance of protocol selection, corneal biomechanics, and patient-specific factors in guiding modern keratoconus management.

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