Keratoconus (KC) is a degenerative disorder of the eye in which cornea becomes progressively thinner and bows outward into a more conical shape than its normal gradual curve. KC affects approximately 0.05% of the global population. Patients with KC often experience eye irritation, headaches, light halos, light sensitivity, worsening myopia, and impaired quality of life. KC is usually diagnosed in the adolescent period. The most frequently used methods to assess KC progression include visual acuity, refractive error, corneal topography and pachymetry. Corneal topography often consists of three measurements: minimum keratometry (Kmin), average keratometry (Kave) and maximum keratometry (Kmax). Pachymetry is a method of measuring corneal thickness. Visual acuity is often measured in best corrected visual acuity (BCVA) or uncorrected visual acuity (UCVA). A Snellen chart is usually used to measure visual acuity. UCVA and BCVA are commonly represented as a number under a numerator of 20 (e.g. 20/18 vision). Visual acuity of 20/20 indicates a normal vision. A patient is considered to have low vision when their BCVA is 20/70 or worse, and is considered to be legally blind with BCVA of 20/200 or worse. Clinically, BCVA and UCVA are presented as a logarithm of the minimal angle of resolution (logMAR) rather than as a fraction. On this scale, normal vision is 0 logMAR. Low vision on the logMAR scale is 0.544, and those considered legally blind have a logMAR of 1. KC progression is usually defined as fulfilling 1 or more of the following criteria:

(1) an increase in central corneal astigmatism of 1.00 diopter (D) or more,
(2) an increase in mean central keratometry of 1.50 D or more, or
(3) a reduction in tomographic central corneal thickness (CCT) of 2% or more at 2 consecutive evaluations.

Various treatment options for KC include simple correction with glasses, soft or rigid gas permeable contact lenses, surgical implantation of intrastromal corneal ring segments (Intacs), and corneal transplant. In addition, corneal-crosslinking with riboflavin and ultraviolet A (CXL) is increasingly considered as a method for managing KC. The treatment objective for CXL is to stabilize the underlying disease process by strengthening the stromal collagen network in order to delay or defer the need for corneal transplant. In the process of CXL, riboflavin (vitamin B2) works as a photo-
mediator to increase the absorption of ultraviolet A light into the corneal stroma. The ultraviolet A (UVA: 370 nm) light increases the degree of molecular bonds of the extracellular matrix of the cornea. Therefore, CXL slows or even stops the progression of KC by increasing the strength and rigidity of the cornea.\(^1\) CXL can be performed with or without removing corneal epithelium.\(^2\) Common reported side-effects of CXL are blurry vision, lacrimation and the sensation of a foreign body for approximately 24 to 48 hours. Serious side effects include corneal haze and keratitis.\(^1\) CXL is only indicated for patients with corneas greater than 400 mcm thick.

Corneal cross-linking with riboflavin – UVA for keratoconus has been increasingly used in some Canadian jurisdictions.\(^1\) However it is currently not covered by any Canadian jurisdiction.\(^1\) In 2012, the reported total cost of CXL was $1167.44 for one eye and $1937.75 for two eyes in Calgary, Canada.\(^1\) The cost of CXL (reported in 2011) was $1,036.12 for one eye and $1,750.55 for two eye in Ontario, Canada.\(^3\) Demand for CXL as the standard of care for keratoconus is increasing in some Canadian jurisdictions, although the long-term effectiveness and CXL's impact on the need for corneal transplant is unknown.\(^1\) The objective of this report is to review the clinical effectiveness (such as improved vision and corneal strength/stabilization) and cost-effectiveness on CXL in the treatment of keratoconus.

**RESEARCH QUESTIONS**

1. What is the clinical effectiveness of corneal cross-linking with riboflavin for keratoconus?
2. What is the cost-effectiveness of corneal cross-linking with riboflavin for keratoconus?

**KEY FINDINGS**

Findings suggest that the corneal cross-linking procedure improve visual acuity and prevents progression of the keratoconus. However, better designed clinical trials and cost-effective analyses in a Canadian setting are needed to determine the long term clinical effectiveness and cost-effectiveness of CXL in the treatment of patients with keratoconus.

**METHODS**

**Literature Search Strategy**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and August 19, 2013.

**Selection Criteria and Methods**

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.
Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with keratoconus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Corneal cross linking with riboflavin and ultraviolet-A radiation</td>
</tr>
<tr>
<td>Comparator</td>
<td>None specified (may include contact lenses, corneal implants, or other surgical interventions)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Improved vision, improved corneal strength/stabilization, side effects cost, cost-effectiveness</td>
</tr>
<tr>
<td>Study Designs</td>
<td>HTA/ Systematic review/Meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>Non-randomized controlled trials Economic evaluations</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, duplicate publications of the same study, or the study included in a selected systematic review or meta-analysis. The Ontario HTA report by Pron et al. and the HTA report by Stenevi et al. were excluded because the studies were included in the more recent HTA report by Leggett et al. Case series, as well as uncontrolled before and after studies were excluded because these types of studies provided limited information given the absence of a control group, and a meta-analysis of the observational studies was provided in the included HTA report; six case-control or cohort studies were included in this review.

Critical Appraisal of Individual Studies

The methodological quality of the included SR/MA were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. RCTs were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist (SIGN 50 checklist 3 and check list 4). A numeric score was not calculated for each study. Instead, the strengths and weakness of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 354 citations. Upon screening titles and abstracts, 51 potentially relevant articles were retrieved for full-text review. In addition, two potentially relevant reports retrieved from other sources (such as grey literature). Of the 53 potentially relevant articles, forty-six did not meet the inclusion criteria, and thus seven reports (One Health technology assessment report, five cohort studies and one case control study) evaluating the efficacy and safety of CXL for keratoconus were included. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

1. What is the clinical effectiveness of corneal cross-linking with riboflavin for keratoconus?

A summary of the study characteristics can be found in Appendix 2. The characteristics of these studies are briefly summarized below:
Health Technology Assessment

The Health Technology Assessment (HTA) by Leggett et al. was conducted in Canada in 2012. The objective of this HTA report was to evaluate the clinical effectiveness, safety, social impact and economic value of CXL for the management of keratoconus and other corneal thinning disorders. Two RCTs and nineteen cohort studies were identified for CXL in progressive keratoconus. In the RCTs, the outcomes of CXL-treated eyes were compared with untreated control eyes. The results of the two RCTs were summarized narratively in the included HTA report. Wittig-Silva et al. randomly assigned forty-nine patients and had follow-up over 12 months. Hersh et al. randomly assigned forty nine eyes (from KC subgroup) to the CXL treatment group, 28 contralateral eyes underwent sham procedures, and 21 fellow eyes served as a control group. Follow-up took place over twelve months. The results from non-randomized cohort studies (follow-up duration: from 6 to 48 months) were pooled for outcomes such as visual acuity, keratometry and pachymetry.

Non-randomized controlled trials

Five of the six studies were conducted prospectively (cohort study) and one was retrospective (case control). The study duration ranged from 6 months to 2 years. Epithelium-removed CXL procedure was performed in all studies except one study by Salman et al. where the transepithelial CXL was performed. All studies were conducted in adult patients except one conducted in children and one conducted in both adults and children. The studies were conducted in USA, Australia, Italy, Egypt, Turkey and Hungary. The individual trial characteristics are described below.

Viswanathan et al. evaluated epithelium-removed CXL for keratoconus in a prospective cohort study where 51 eyes were selected to undergo the CXL procedure and 25 fellow eyes in control group were left untreated. Follow-up occurred over a mean of 14 months and at each assessment visual acuity was tested. The keratometric and pachymetric measurements were also obtained upon follow-up.

Rechichi et al. evaluated epithelial-disruption CXL in a prospective cohort study in 28 consecutive patients with progressive keratoconus as determined by pachymetry which corneal thickness measurements of less than 400 mcm. The worst eye at baseline was selected for the CXL procedure and the contralateral eye was left untreated and served as a control. Follow-up occurred over 12 months and at each assessment visual acuity was tested by corrected and uncorrected measurements, and keratometric and pachymetric measurements were obtained.

Salman et al. evaluated transepithelial CXL in a prospective cohort study in twenty-two patients (< 18 years old) with progressive keratoconus as determined by keratometry measurements of greater than 45 D and a deteriorating corrected distance visual acuity. Each right eye was assigned to undergo CXL and the left eye was left untreated and served as a control. Follow-up occurred over 12 months and at each assessment visual acuity was tested with corrected and uncorrected measurements, and keratometric and pachymetric measurements were obtained.

Toprak et al. evaluated epithelium-removed CXL in a retrospective case-control study in forty-seven patients with keratoconus who underwent the procedure and twenty-six patients with keratoconus that did not undergo CXL that served as age and sex-matched controls. Follow-up occurred over 6 months and at each assessment visual acuity in corrected distance measurements and keratometric and pachymetric measurements were obtained.
Lamy et al. evaluated epithelium-removed CXL in a prospective cohort study in thirty-four patients with keratoconus. The worse eye at baseline was selected for the procedure and the contralateral eye was left untreated and served as a control. Follow-up occurred over 2 years and at each assessment a best-spectacled visual acuity and keratometric measurements were obtained.

Kranitz et al. evaluated epithelium-removed CXL in a prospective cohort study in twenty-two patients with progressive keratoconus. Twenty-five eyes were selected for the procedure and the untreated eyes served as a control. Follow-up occurred over 12 months with visual acuity by uncorrected and corrected distance measurements, keratometric and pachymetric measurements obtained.

2. What is the cost-effectiveness of corneal cross-linking with riboflavin for keratoconus?

No cost-effectiveness evidence was identified.

Summary of Critical Appraisal

The strengths and limitations of the included studies are summarized in Appendix 3.

The methodological quality of the included HTA report was considered good per AMSTAR criteria. The research questions and selection criteria were defined and well presented. Comprehensive literature searches were performed. Quality assessment of the included primary studies was described. Methods used to combine the findings were clearly reported. Conflicts of interest were declared. Unmet AMSTAR criteria included that the publication bias was not assessed.

The methodological quality of the six included non-RCTs reports was compromised by the nature of non-randomized design. The research question, intervention and control were well reported and the outcome measurement was valid. No drop-out was reported in all studies except the study by Lamy et al. The overall methodological quality was considered poor because of a number of factors. The demographics of each group were not reported; the source population baseline characteristics were not compared between treatment and control group; the patient selection process was not clearly reported; the outcome assessment was not blinded; the confounding factors were not controlled although all studies performed statistical analyses. There was no formal statistical analysis to compare the effectiveness of the CXL treatment with control group although the control group was included in these trials. External validity might also be limited as whether study patients were representative of all eligible patients was uncertain. Some studies treated the worse of the two eyes while the contralateral eye served as control, which could be another source of bias. None of the included primary studies and the studies presented in the included HTA report were conducted in a Canadian setting.

Summary of Findings

1. What is the clinical effectiveness of corneal cross-linking with riboflavin for keratoconus?

The key findings of the included studies is summarized in Appendix 4.

Health Technology Assessment

In the Health Technology Assessment report, results from the two RCTs showed that the treatment groups experienced an improvement in visual acuity (BCVA and UCVA) compared to the control.
group, as well as a flattening of maximal keratometry measured at 12-months in one study and 6 months in the other. A pooled analysis of eleven cohort studies reporting on visual acuity demonstrated a statistically significant improvement in visual acuity compared to baseline. A pooled analysis of nineteen cohort studies reporting on keratometry showed a statistically significant decrease in Kmax compared to baseline. Finally, a pooled analysis of fourteen cohort studies reporting on pachymetry revealed a statistically significant decrease in corneal thickness. The author concluded that CXL for the treatment of keratoconus is effective. However, the long-term effectiveness and CXL’s impact on the need for corneal transplant in patients with keratoconus is unknown.

Non-randomized controlled trial

In the study by Viswanathan et al. after a mean follow-up of 14 months, it was found that the CXL treatment group had a significant improvement in visual acuity (-0.05 logMAR; P = 0.04, negative logMAR value indicates visual acuity improved) and Kmax (-0.96 D; P = 0.005, negative Kmax indicates corneal curvature flattened or reduced) while the control group had no significant change in either outcomes. The between group difference of improvement of the BCVA from baseline was not reported. The author concluded that CXL is effective in cases of progressive keratoconus by reducing the corneal curvature (Kmax) and by improving the visual acuity in patients with KC (see Appendix 4).

In their 12 month follow-up study, Rechichi et al. reported that both corrected distance vision acuity (CDVA) and uncorrected distance vision acuity (UDVA) were statistically significantly improved in the CXL treatment eye compared to baseline (CDVA logMAR: 0.25 vs. 0.30 at 12 months and baseline respectively, P < 0.05). CDVA and UCVA were not statistically significantly changed in the control eye compared to baseline (CDVA logMAR: 0.37 vs. 0.29). Simulated keratometry also improved in the treatment eye compared to baseline (50.50 D vs. 51.39 D; P < 0.05) and worsened in the control group (52.43 D vs. 51.29 D; P value: not statistically significant [NS]). The change of corneal thickness from baseline (pachymetry) was not statistically significant both groups. The author concluded that corneal epithelial-disruption CXL was safe and effective in medium-term stabilization of keratoconus with an improvement in topographic and refractive parameters.

In the transepithelial CXL trial by Salman et al., it was reported that visual acuity (UDVA) significantly improved at 12-month follow-up in the treated eye in children (0.68 ± 0.45 logMAR) compared with that at baseline (0.95 ± 0.34 logMAR) P = 0.023). But the CDVA was not statistically significant changed in the control eye at 12 months compared with baseline. Keratometry (Kmax) decreased in the treated eye (58.10 D ± 4.20 vs. 60.30 D ± 5.26; P = 0.027) and increased in the control eye (64.20 ± 4.25 D vs. 61.30 ± 6.29 D, P = 0.044). The change from baseline of corneal thickness was not statistically significant in either group. The author concluded that their preliminary 12-month follow-up results of transepithelial CXL in children with keratoconus were encouraging.

In the study by Toprak et al., the results showed that the CXL treatment group had an improvement in visual acuity (CDVA Change: -0.12 ± 0.25 logMAR) at 6 months follow-up compared with baseline. The control group had a decrease in visual acuity (CDVA change: 0.01 ± 0.04 logMAR (P < 0.001). Keratometry (Kmax) was significantly decreased in the treatment group (-0.89 D ± 1.61 D, p<0.001), and pachymetry was also decreased in the treatment group (419.49 mc m ± 59.45 vs. 460.53 mc m ± 46.28 at 6 months and baseline respectively, P < 0.001) but was not statistically significantly changed in the control group (469.35 µm ± 49.63 vs. 474.12 µm ± 47.40, P = 0.360). It was concluded by the author that CXL treatment is effective in improving visual acuity and maximum keratometry in patients with progressive keratoconus, although the treatment might cause corneal thinning and volume loss.
In the study by Lamy et al.,\textsuperscript{4} the CXL treated eyes had an improvement in visual acuity (BCVA) from 0.28 ± 0.17 logMAR before the treatment to 0.12 ± 0.12 logMAR (P < 0.001) at 2 years follow-up. In the control group, however, BCVA worsened from 0.11 ± 0.23 logMAR to 0.14 ± 0.23 logMAR (P = 0.034). Central Kmax at 2 year follow-up improved by -1.11 D in the treated group and had worsened by +0.89 D in the control group. The author concluded that CXL improved contrast sensitivity and inhibited the progression of keratoconus.

After one year follow-up, Kranitz et al.\textsuperscript{5} reported that, compared with baseline, the visual acuity (both UDVA and CDVA) improved significantly in the CXL treated eyes (P > 0.001 and P = 0.019, respectively) whereas these visual acuity change in the control group was not statistically significant (P > 0.05). No statistically significant change in keratometry was reported one year after CXL procedure in patients with keratoconus. The author concluded that corneal CXL showed augmented effect on corneal protrusion in eyes with thinner corneas.

2. What is the cost-effectiveness of corneal cross-linking with riboflavin for keratoconus?

No cost-effective analysis on corneal CXL with riboflavin for keratoconus was identified in this review.

Limitations

There are several limitations of the body evidence presented in this review. Firstly, despite the good methodological quality of the included HTA report,\textsuperscript{1} the strength of the synthesized evidence are limited due to the low-quality observational studies, on which the pooled data was based. Secondly, the methodological quality of the included non-randomized cohort studies was considered poor because of the nature of the study design. In addition, no formal statistical analysis was performed in any included non-randomized study to compare the effectiveness of the CXL treatment with control group; therefore, the actual comparative clinical effectiveness of the CXL with control in these trials is unknown. Thirdly, all of the clinical studies have relatively small samples sizes and relatively short term follow-up for a chronic progressive disease such as keratoconus. As of yet, long-term effects of CXL are not known. No safety data was reported in the included studies. Fourthly, there is no data comparing CXL to other standard care of keratoconus (such as intrastromal corneal ring segments [Intacs] or corneal transplant), therefore, whether CXL will replace or delay the need for these procedures is uncertain. None of the primary studies were conducted in Canada. The generalizability of the study results to Canadian patients is uncertain. Finally, there were no cost-effectiveness studies available for CXL as a treatment for keratoconus.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Findings in this review suggest that the CXL procedure improves visual acuity scores and prevents progression of keratoconus over an up to 48-month follow-up period. However, these results need to be interpreted with caution considering some important limitations of the body evidence such as poorly methodological quality, lack of trials conducted in Canadian settings, and no cost-effectiveness analysis available for CXL for keratoconus. Therefore, better designed clinical trials and cost-effectiveness analyses in a Canadian setting is needed to determine the clinical effectiveness and cost-effectiveness of CXL in the treatment of patients with keratoconus in Canada.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca
REFERENCES


APPENDIX 1: Selection of Included Studies

354 citations identified from electronic literature search and screened

303 citations excluded

51 potentially relevant articles retrieved for scrutiny (full text, if available)

2 potentially relevant reports retrieved from other sources (grey literature)

53 potentially relevant reports

46 reports excluded:
- design not of interest (32)
- irrelevant outcomes (2)
- population not of interest (1)
- already included in at least one of the selected HTA report (11)

7 reports included in review
### APPENDIX 2: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention / Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leggett 2012 Canada</td>
<td>HTA</td>
<td>Patients with KC* HTA, SRs RCTs, Non-RCTs and observational cohort studies included</td>
<td>For RCT: CXL / No CXL For pooled data: post CXL /pre CXL</td>
<td>Visual acuity keratometry pachymetry</td>
</tr>
<tr>
<td>Viswanathan 2013 Australia</td>
<td>Prospective case-control cohort study</td>
<td>Patients with KC and the worse eye undergoing CXL procedure N=35</td>
<td>For RCT: CXL / No CXL For pooled data: post CXL /pre CXL</td>
<td>BCVA keratometry pachymetry</td>
</tr>
<tr>
<td>Rechichi 2013 Italy</td>
<td>Prospective case-control cohort study</td>
<td>28 consecutive patients with progression of KC determined by keratometry and pachymetry and minimum corneal thickness of ≥ 400um</td>
<td>28 eyes (worst eye) underwent epithelial-disruption CXL with riboflavin 0.1% and UVA irradiation / 28 fellow eyes served as control</td>
<td>UDVA CDVA keratometry pachymetry</td>
</tr>
<tr>
<td>Salman 2013 Egypt</td>
<td>Prospective case-control cohort study</td>
<td>22 patients younger than 18 y/o with KC determined by keratometry &gt;45 D and deterioration of CDVA</td>
<td>Each right eye underwent transepithelial CXL with riboflavin 0.1% and UVA irradiation / Left was untreated and served as control</td>
<td>UDVA CDVA keratometry pachymetry</td>
</tr>
<tr>
<td>Toprak 2013 Turkey</td>
<td>Retrospective case-control cohort study</td>
<td>47 patients with KC undergoing CXL and 26 age and sex-matched patients with KC untreated</td>
<td>47 eyes undergoing epithelium-removed CXL with riboflavin 0.1% and UVA irradiation / control group left untreated</td>
<td>Changes in CDVA, keratometry and pachymetry</td>
</tr>
<tr>
<td>Lamy 2013 USA</td>
<td>Prospective case-control cohort study</td>
<td>34 patients with KC with one eye undergoing CXL</td>
<td>34 eyes undergoing epithelium-removed CXL with riboflavin 0.1% and UVA irradiation / fellow eyes served as control</td>
<td>BCVA keratometry</td>
</tr>
<tr>
<td>Kranitz 2012 Hungary</td>
<td>Prospective case-control cohort study</td>
<td>22 patients with KC with the worse eye undergoing CXL</td>
<td>25 eyes undergoing epithelium-removed CXL with riboflavin 0.1% and UVA irradiation / 15 fellow eyes served as control</td>
<td>UDVA CDVA keratometry pachymetry</td>
</tr>
</tbody>
</table>

BCVA= best corrected vision acuity; CDVA=corrected distance visual acuity; CXL= corneal Cross-linking using riboflavin and ultraviolet-A radiation; D = diopters; KC=keratoconus; RCT=randomized control trial; UCVA=uncorrected vision acuity; UDVA Z corrected distance visual acuity.

- only data on the patients with KC was extracted.
## APPENDIX 3: Summary of Study Strengths and Limitations

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HTA report assessed with AMSTAR²</strong></td>
<td>![List of Strengths](<a href="https://example.com/">https://example.com/</a> strengths_list)</td>
<td>![List of Limitations](<a href="https://example.com/">https://example.com/</a> limitations_list)</td>
</tr>
</tbody>
</table>
| Leggett et al.¹ | • Research questions and selection criteria were defined and presented  
• Comprehensive literature search based on pre-defined criteria  
• 2 independent investigators performed study selection, data extraction and quality assessment  
• List of included and excluded studies provided  
• Quality assessment of the included primary studies was described (with Jadad Scale)  
• Methods used to combine the findings was clearly reported  
• Conflict of interests declared | • Quality assessment of the included HTA report was not well described  
• Publication bias was not assessed |
| **Non - RCT assessed with SIGN 50 Check list 3 and 4 ⁹,¹⁰** | ![List of Strengths](https://example.com/ strengths_list) | ![List of Limitations](https://example.com/ limitations_list) |
| Viswanathan et al.¹¹ | • Research question (objective) was clearly stated  
• Reporting (intervention, control, outcomes and main findings) was clearly stated  
• Outcome measurement was valid and reliable  
• Confidence interval was reported  
• No drop-out  
• Long-term follow-up  
• Statistical analyses were performed  
• Conflict of interest reported | • Demographics of each group not reported.  
• Source population baseline characteristics was not compared between treatment and control group  
• Patient selection process was not clearly reported  
• Outcome assessment was not blinded  
• Confounding factors were not controlled  
• External validity limited; uncertain as whether study patients were representative of all eligible patients |
| Rechichi et al.⁴⁴ | • Research question (objective) was clearly stated  
• Reporting (intervention, control, outcomes and main findings) was clearly stated  
• Outcome measurement was valid and reliable  
• Confidence interval was reported  
• No drop-out  
• Long-term follow-up  
• Statistical analyses were performed  
• Conflict of interest reported | • Demographics of each group not reported.  
• Source population baseline characteristics was not compared between treatment and control group  
• Patient selection process was not clearly reported  
• Outcome assessment was not blinded  
• Confounding factors were not controlled  
• External validity limited; uncertain as whether study patients were representative of all eligible patients |
| Salman⁵⁵ | • Research question (objective) was clearly stated  
• Reporting (intervention, control, outcomes and main findings) was clearly stated  
• Outcome measurement was valid and reliable  
• Confidence interval was reported  
• No drop-out  
• Long-term follow-up  
• Statistical analyses were performed  
• Conflict of interest reported | • Demographics of each group not reported.  
• Source population baseline characteristics was not compared between treatment and control group  
• Patient selection process was not clearly reported  
• Outcome assessment was not blinded  
• Confounding factors were not controlled  
• External validity limited; uncertain as whether study patients were representative of all eligible patients |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Toprak et al 12               | • Research question (objective) was clearly stated  
• Age and sex matched between treatment groups  
• Reporting (intervention, control, outcomes and main findings) was clearly stated  
• Outcome measurement was valid and reliable  
• Confidence interval was reported  
• No drop-out  
• Long-term follow-up  
• Statistical analyses were performed  
• Conflict of interest reported | • Retrospective design  
• Demographics of each group not reported.  
• Source population baseline characteristics was not compared between treatment and control group  
• Patient selection process was not clearly reported  
• Outcome assessment was not blinded  
• Confounding factors were not controlled  
• External validity limited; uncertain as whether study patients were representative of all eligible patients |
| Lamy et al 4                  | • Research question (objective) was clearly stated  
• Reporting (intervention, control, outcomes and main findings) was clearly stated  
• Outcome measurement was valid and reliable  
• Confidence interval was reported  
• Low drop-out (5% at 6 months, 10% at 2 years)  
• Long-term follow-up  
• Statistical analyses were performed  
• Conflict of interest reported | • Demographics of each group not reported.  
• Source population baseline characteristics was not compared between treatment and control group  
• Patient selection process was not clearly reported  
• Outcome assessment was not blinded  
• Confounding factors were not controlled  
• External validity limited; uncertain as whether study patients were representative of all eligible patients |
| Kranitz et al 5               | • Research question (objective) was clearly stated  
• Reporting (intervention, control, outcomes and main findings) was clearly stated  
• Outcome measurement was valid and reliable  
• Confidence interval was reported  
• No drop-out  
• Long-term follow-up  
• Statistical analyses were performed  
• Conflict of interest reported | • No randomization  
• Demographics of each group not reported.  
• Source population baseline characteristics was not compared between treatment and control group  
• Patient selection process was not clearly reported  
• Outcome assessment was not blinded  
• Confounding factors were not controlled  
• External validity limited; uncertain as whether study patients were representative of all eligible patients |

RCT= randomized controlled trial; SR= systematic review; AMSTAR = A Measurement Tool to Assess the Methodological Quality of Systematic Reviews.
## APPENDIX 4: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Main Study findings</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leggett ¹ 2012, Canada</td>
<td>Pooled ES difference (95%CI): (post CXL – pre CXL, up to 48 mos ) BCVA (logMAR) * (N=11 studies) -0.09 (-0.12, -0.06) UCVA (logMAR) (N=7) -0.26 (-0.30, -0.22) Kmax (diopters)# (N=19) -1.37 (-1.61,-1.12) Pachymetry (um) (N=14) -3.67 (-7.23,-0.12) Data from 2 RCTs (reported separately, not pooled) - Wittig-Silva et al. ¹³ Difference (CXL- control) at 1 year (n=66 eyes): BCVA (LogMAR) -0.12 (p=0.036) K-max - 1.45 Diopters (P = .002) -Hersh et al. ¹⁴ (mixed data of KC [n=49 eyes] with KE[n=22 eyes]) Difference (CXL – control) at 6 mos UCVA (logMAR) -0.07 (P=0.04) BCVA -0.12 (p=0.001)</td>
<td>The meta-analysis in this report shows that CXL stabilizes the cornea. With keratoconus patients, CXL treatment was shown to produce statistically significant improvements in all outcomes. There are a number of gaps in the literature that limit this report. The long-term effects of CXL are not known. Since this technology is new, there is no outcome or safety data over a long follow-up time. Similarly, there is also no data on whether CXL will replace or delay the need for corneal transplant; this information would likely result from studies with long follow-up periods.</td>
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<td>Viswanathan ¹¹ 2013 Australia</td>
<td>Follow-up: 14.38 +/- 9.36 mos (difference: at the end of the trial – baseline) CXL group: (n=51 eyes) improved visual acuity ( by -0.05 ± 0.13 logMAR, P = 0.04) Kmax flattened by - 0.96 + 2.33 dioptres (P = 0.005) Control group (n=25 eyes) decreased visual acuity (by 0.05 ±0.14 logMAR , P = 0.2) Kmax increased by 0.43 + 0.85 dioptres (P = 0.05) (The between group difference of change from baseline of above outcomes was not reported)</td>
<td>On page 531: &quot;Results indicate that corneal collagen cross-linking using riboflavin and ultraviolet A is effective as a therapeutic option in cases of progressive keratoconus by reducing the corneal curvature and by improving the visual acuity in these patients&quot;</td>
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<td>Rechichi ² 2013 Italy</td>
<td>(At 12 mos vs. baseline) CXL group (N=28 eyes) CDVA (logMAR): 0.25 vs. 0.30 (p&lt;0.05) UDVA (logMAR) : 0.48 vs.0.73 (p&lt;0.05) SimKs (improved) (50.5 D vs. 51.39 D , p&lt;0.05) Control group (n=28 eyes) CDVA (logMAR) (0.37 vs. 0.29 , NS) UDVA (logMAR) improved (0.85 vs. 0.75, NS) SimKs worsened (52.43 D vs. 51.29 D, NS)</td>
<td>On page 1171: “Corneal epithelial-disruption CXL was safe and effective in medium-term stabilization of Keratoconus with an improvement in topographic and refractive parameters and less patient discomfort.&quot;</td>
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<td>First Author, Publication Year, Country</td>
<td>Main Study findings</td>
<td>Author’s Conclusions</td>
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<td>Salman, 2013, Egypt</td>
<td>(At 12 mos vs. baseline) CXL group (n=22 eyes) UDVA logMAR: 0.68 ± 0.45 vs. 0.95 ± 0.34 (p = 0.023) CDVA logMAR: 0.49 ± 0.09 vs. 0.51 ± 0.11 (p = 0.189) Kmax (D): 58.10 ± 4.20 vs. 60.30 ± 5.26 (p=0.027) Corneal thickness (mcm): 467.7 ± 21.4 vs. 469.6 ± 19.1 (p = 0.679) Control group (n=22 eyes) UDVA LogMAR 0.84 ± 0.52 vs. 0.94 ± 0.22 (p=0.324) CDVA LogMAR 0.51 ± 0.21 vs. 0.42 ± 0.11 (p=0.543) Kmax (D) 64.20 ±4.25 vs. 61.30 ± 6.29 (p=0.044) Corneal thickness (mcm) 477.7 ± 21.7 vs. 482.6 ± 19.6 (p=0.579)</td>
<td>On page 1164: “Preliminary results of transepithelial CXL in children with keratoconus were encouraging, with no evidence of progression of keratoconus over 12 months.”</td>
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<td>Toprak, 2013, Turkey</td>
<td>CXL group (n=47 eyes) Control group (N=26 eyes) Change from baseline at 6 months: CDVA logMAR: CXL: -12 ± 0.25 (P&lt;0.001) Control: 0.01 ± 0.04 (P=0.001) Kmax: CXL: -0.89 D ± 1.61 D (p&lt;0.001). Control: 0.32 ± 1.43 (P value: NR) Pachymetry At 6 mos vs. at baseline: mcm CXL: 419.49 ± 59.45 vs. 460.53 ± 46.28, p&lt;0.001 Control: 469.35 ± 49.63 vs. 474.12 ± 47.40, p=0.360</td>
<td>On page 1: “In patients with progressive keratoconus, CXL treatment is effective in improving visual acuity and maximum keratometry. Although the treatment might cause corneal thinning and volume loss, anterior chamber parameters seem not to be affected during the postoperative course.”</td>
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<td>Lamy, 2013, USA</td>
<td>(At 2 years vs. baseline) BCVA logMAR (N=78 eyes) 0.12 ± 0.12 vs. 0.28 ± 0.17 (-0.16, p&lt;0.001) Control: (N=78 eyes) 0.14 ± 0.23 vs. 0.11 ± 0.23 (0.3, P = 0.11) Kmax (central) (at 2 years – baseline) CXL: -1.11 D (P&lt;0.001) Control: +0.89 D (P=0.007)</td>
<td>CXL with riboflavin and UV-A improved visual acuity and inhibited the progression of keratoconus.</td>
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<td>Kranitz, 2012, Hungary</td>
<td>(At 1 year vs. baseline) CXL (N=25 eyes) UDVA (decimal) CXL: 0.31±0.25 vs. 0.23±0.25, P&lt;.001, improved) CDVA (decimal) CXL: 0.72 ± 0.19 vs. 0.58±0.28, P=0.019, improved ) Control group (n=15 eyes) UDVA and CDVA did not change in the control group (P&gt;0.05) Keratometry not significantly different between one year and baseline in both CXL and control groups p=0.24 and p=0.86</td>
<td>On page 645: “Posterior elevation is a sensitive parameter to monitor corneal remodeling after CXL. Corneal CXL showed augmented effect on corneal protrusion in eyes with thinner corneas.”</td>
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<tr>
<td>First Author, Publication Year, Country</td>
<td>Main Study findings respectively</td>
<td>Author’s Conclusions</td>
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BCVA = best corrected vision acuity; CDVA = corrected distance visual acuity; CI = confidence interval; CXL = corneal Crosslinking using riboflavin and ultraviolet-A radiation; D = diopters; ES = effect size; KC = keratoconus; KE = Keratectasia; Kmax = Maximum Keratometry; LogMAR = Logarithm of the minimal angle of resolution; mcm = micrometer; MOs = months; NR = not reported; NS = not statistically significant; RCT = randomized control trial; SimKs = simulated keratometry steep axis; UCVA = uncorrected vision acuity; UDVA = uncorrected distance visual acuity.

- Negative LogMAR value indicates an improved vision at post CXL compared with pre-CXL.
- Negative Kmax value indicates an improvement at post CXL compared with pre-CXL.