Review Article

Collagen cross-linking for pediatric refractive correction

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Abstract: Corneal collagen-crosslinking (CXL) has been widely investigated in the adult population. There is still little available in the literature, however, on the effects of CXL in children. A review of the literature on CXL in the pediatric population is presented here, with a particular emphasis on the refractive effects. Although several studies demonstrate promising results, most studies have small sample sizes with relatively short follow-up periods. Further investigation on the effects of CXL in the pediatric population is required to better understand long-term effects.

Keywords: Corneal collagen-crosslinking (CXL); pediatric refractive correction; keratoconus

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Introduction

Corneal collagen-crosslinking (CXL) was first described as a treatment for keratoconus by Wollensak *et al.* in 2003 (1). Later that same year, Wollensak and his group described the refractive effects of CXL, in particular an average reduction in refractive error by 1.14 diopters (D) (2). Since then, CXL has garnered significant attention as a treatment modality for progressive keratoconus and was approved by the United States Food and Drug Administration (FDA) in 2016 for this particular use in patients older than 14 years. CXL was initially reported as treatment for progressive keratoconus in the pediatric population in 2011; the patients in this series ranged in age from 10 to 14 years (3). The youngest reported patient to have undergone CXL as treatment for progressive keratoconus was 4 years old at the time of treatment (4). A review of the literature on the use of CXL in the pediatric population is presented here, primarily focusing on the refractive effects, efficacy, and safety.

CXL protocols

The mechanism by which CXL works involves strengthening corneal stromal collagen bonds with riboflavin activated by ultraviolet A (UVA). The standard Dresden protocol was the first CXL protocol proposed by Wollensak *et al.*, and is currently the only protocol with FDA approval in the United States (2,5). There have been multiple other proposed CXL protocols, including accelerated CXL, transepithelial CXL, and iontophoresis (6).

Standard Dresden protocol

The corneal epithelium acts as a barrier to full penetration of riboflavin into the corneal stroma. As such, the standard Dresden protocol requires mechanical debridement of the corneal epithelium under topical anesthesia in the central 9 mm of the cornea. Following debridement, one drop of riboflavin 0.1% solution is administered every 2 minutes for a total of 30 minutes, followed by ultraviolet-A light (370±5 nm wavelength, 5.4 J/cm^2 irradiance) exposure with instillation of the riboflavin solution every 2 minutes for an additional 30-minute period (2). The standard Dresden protocol remains the most widely used CXL protocol in both the adult and pediatric populations to date.

Accelerated CXL protocols

Accelerated protocols were originally derived from the Bunsen-Roscoe Law of Reciprocity of Photochemistry. This law states that the photochemical effect of ultraviolet

light is directly proportional to the total amount of energy delivered and should be equivalent for equivalent total doses regardless of the relative irradiation time and intensity for each protocol (7).

Accelerated CXL in the pediatric population was first reported by Shetty *et al.* in 2014 (8). Since then, accelerated CXL protocols have been applied and investigated by several other groups, resulting in 8 total publications from 2014 through 2018 (9-15). The pediatric patients reported in these studies underwent one of the following accelerated CXL protocols: UVA irradiation of 30 mW/cm^2 for 3 minutes, 10 mW/cm^2 for 9 minutes, or 9 mW/cm^2 for 10 minutes.

Transepithelial CXL protocols

Transepithelial CXL has emerged as an attractive option given the associated improved safety profile and reduction in postoperative discomfort. Modified riboflavin was developed for transepithelial delivery (Ricrolin TE, riboflavin 0.1%, SOOFT Italia SpA, Italy) with the addition of two agents—trometamol and sodium ethylenediaminetetraacetic acid—to enhance penetration through the intact corneal epithelium (6). There have only been three reported studies investigating transepithelial CXL in children, by Buzzonetti *et al.* in 2012, Salman *et al.* in 2016, and Eraslan *et al.* in 2017 (16-18). The only major differences between the transepithelial CXL and standard Dresden protocols are the state of the corneal epithelium and constitution of the riboflavin solution.

Henriquez *et al.* investigated the effects of an accelerated transepithelial CXL protocol on progressive keratoconus in children (19). In this particular protocol, the transepithelial riboflavin solution consisted of 0.25% riboflavin, 1.0% phosphate hydroxypropyl methylcellulose, and 0.007% benzalkonium chloride. This solution was administered every 5 minutes for 30 minutes followed by a balanced salt solution rinse. UVA irradiation of 18 mW/cm^2 was then performed for 5 minutes.

Iontophoretic CXL protocols

Iontophoresis facilitates penetration of a molecule through intact tissue in the presence of a low-intensity electric field. Iontophoresis-assisted transepithelial CXL in the pediatric population has been reported by Buzzonetti *et al.* and Magli *et al.* (20,21). The riboflavin solution designed for iontophoretic CXL consists of riboflavin 0.1% without dextran or sodium chloride and with the addition of two enhancers—tromethamine and ethylenediaminetetraacetic acid (Ricrolin +, SOOFT, Montegiorgio, Italy). Both published studies employed the same iontophoresis system (I-ON CXL; SOOFT Italia SpA, Italy), consisting of a power supply, two electrodes, and a connection cable. In this protocol, iontophoresis is performed for 5 minutes, followed by UVA irradiation of 10 mW/cm^2 for 9 minutes.

Refractive effects of CXL in children

To date, application of CXL in the pediatric population has only been reported in the treatment of progressive keratoconus. Keratoconus is defined as a bilateral, often asymmetric, noninflammatory progressive degeneration of the cornea (22). Progressive corneal thinning results in biomechanical weakening that manifests as corneal thinning and protrusion. This progressive corneal thinning and protrusion leads to moderate to severe visual impairment from irregular astigmatism. Furthermore, there can be fragmentation of Bowman's membrane and breaks in Descemet's membrane causing variable corneal scarring (6). Although typical onset is at puberty, keratoconus does affect younger children. Léoni-Mesplié *et al.* conducted a large retrospective study, evaluating 216 keratoconic patients separated into various age groups and found that keratoconus in children was significantly more severe at diagnosis and progressed faster than in adults (22). Given the more severe and aggressive disease process in pediatric keratoconus, numerous studies have been conducted to date evaluating the effects of CXL on halting progression of keratoconus as well as the subsequent refractive effects.

Padmanabhan *et al.* has published the largest report to date on the effects of CXL in children with progressive keratoconus (23). In this study, 377 eyes of 336 pediatric patients with progressive keratoconus underwent the standard Dresden CXL protocol and had follow-up ranging from 2 years to 6.7 years post-treatment. They observed an increase of 1 full Snellen line for best spectacle-corrected distance visual acuity 2 years post-CXL.

Mazzotta *et al.* has published the longest follow-up, with 10 years of post-CXL data in children with progressive keratoconus (24). They found that at 10 years post-CXL, there was an improvement of 0.21 Snellen lines in uncorrected distance visual acuity and 0.03 Snellen lines in corrected distance visual acuity.

The length of follow-up ranges from 12 months to 10 years in pediatric patients who underwent standard

Table 1 Refractive changes after standard Dresden CXL protocol in pediatric patients

Authors	No. eyes	Age group (years)	Follow-up time (months)	Change in UCDVA (Snellen lines)	Change in CDVA (Snellen lines)	Change in SE (D)	Change in cylinder (D)
Chatzis *et al.* (27)	59	9–19	36	N/A	1	N/A	N/A
Caporossi *et al.* (26)	77	10–18	36	0.18*; 0.16†	0.16*; 0.15†	N/A	N/A
Soeters *et al.* (25)	29	<18	12	N/A	2	N/A	N/A
McAnena *et al.* (28)	25	13–18	36	1	2	–0.19	+0.11
Uçakhan *et al.* (31)	40	10–18	48	3	2	+0.80	–1.0
Godefrooij *et al.* (29)	54	11–17	60	0	1	N/A	N/A
Toprak *et al.* (33)	29	10–17	24	N/A	1	N/A	N/A
Wise *et al.* (32)	39	11–18	12	1	0	–0.24	N/A
Sarac *et al.* (30)	72	9–17	24	1	0	N/A	+0.08
Padmanabhan *et al.* (23)	194	8–18	72	N/A	1	–0.17	N/A
Zotta *et al.* (34)	20	10–17	108	N/A	1	+0.41	N/A
Mazzotta *et al.* (24)	62	8–18	120	2	1	N/A	+0.17
Henriquez *et al.* (35)	26	10–17	36	3	2	N/A	+0.28
Or *et al.* (37)	44	11–18	60	1	1	N/A	–1.50
Knutsson *et al.* (36)	52	12–17	36	1	0	+0.02	–0.38

*, corneas thicker than 450 μm; †, corneas thinner than 450 μm. CXL, corneal collagen-crosslinking; UCDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; SE, spherical equivalent; D, diopters; N/A, not available.

Dresden CXL for treatment of progressive keratoconus, with several studies reporting average improvements of 1 to 2 Snellen lines in uncorrected distance visual acuity and 2 to 3 Snellen lines in corrected distance visual acuity, albeit at various follow-up time points (23-37) (*Table 1*).

Refractive changes are not as clinically significant after accelerated CXL compared to those observed following the standard Dresden protocol, although longer UVA exposure (9 to 10 minutes) seems to have a greater effect (*Table 2*) (8-15). Changes in visual acuity following transepithelial CXL—both with iontophoresis and without—are also less clinically significant when compared to the changes observed following the standard Dresden CXL protocol (*Table 3*) (16-21).

Although CXL has predominantly been used to treat progressive keratoconus in both adults and children, there may be a role for CXL in pediatric refractive correction for a small subset of patients who fail traditional treatment methods, such as glasses, contact lenses, or patching. Current modalities of pediatric refractive surgery include excimer laser therapies, such as photorefractive keratectomy (PRK) and laser-assisted *in situ* keratomileusis (LASIK), phakic intraocular lens (pIOL), lensectomy, and refractive lens exchange (38). With the corneal flattening effect achieved by CXL, there is potentially a role for correcting astigmatism and myopia in children. CXL also offers an improved safety profile over several of the presently employed refractive surgery techniques in children.

Safety profile

Microbial keratitis, although infrequent, has been reported after both standard and accelerated CXL protocols in the pediatric population (39,40). There have been no reported cases of microbial keratitis after transepithelial CXL in the pediatric population. Transient mild haze has also been reported in several children following various CXL protocols (8,10-12,14,19,24,33,35-37). Godefrooij *et al.* reported one case of persistent haze that resulted in deterioration of corrected distance visual acuity at 1 year and 2 years post-CXL (29). Eissa *et al.* found a reduction in endothelial cell count following accelerated CXL in children, but the change was not statistically significant (12). Overall, CXL in children has a good safety profile with low

Table 2 Refractive changes after accelerated CXL in pediatric patients

Authors	No. eyes	Age group (years)	Follow-up time (months)	Change in UCDVA (Snellen lines)	Change in CDVA (Snellen lines)	Change in SE (D)	Change in cylinder (D)
Shetty *et al.* (8)	30	11–14	24	1	1	+0.66	+0.83
Ozgurhan *et al.* (9)	44	9–18	24	1	1	+0.18	+0.13
Badawi *et al.* (10)	33	8–15	12	2	2	N/A	−0.39
Baenninger *et al.* (11)	39	13–17	12	1	1	N/A	N/A
Eissa *et al.* (12)	47	9–14	12	1	0	N/A	N/A
Ulusoy *et al.* (13)	28	<18	12	1*; 2†	1*; 2†	0*; 0†	+0.90*; +0.02†
Sarac *et al.* (14)	49	10–17	24	2	0	+0.46	+0.62
Tian *et al.* (15)	18	10–17	12	N/A	0	−0.36	+0.36

*, corneas thicker than 450 μm; †, corneas thinner than 450 μm. CXL, corneal collagen-crosslinking; UCDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; SE, spherical equivalent; D, diopters; N/A, not available.

Table 3 Refractive changes after transepithelial CXL in pediatric patients

Authors	No. eyes	Age group (years)	Follow-up time (months)	Change in UCDVA (Snellen lines)	Change in CDVA (Snellen lines)	Change in SE (D)	Change in cylinder (D)
Transepithelial CXL with Ricrolin TE							
Salman (16)	22	13–18	12	1	3	+0.30	+0.05
Eraslan *et al.* (17)	18	12–18	24	N/A	0	N/A	N/A
Buzzonetti *et al.* (18)	13	8–18	18	N/A	1	−0.40	+0.70
Transepithelial CXL with iontophoresis							
Buzonetti *et al.* (20)	14	10–18	15	N/A	1	+0.70	+0.70
Magli *et al.* (21)	13	11–18	18	0	1	N/A	N/A
Accelerated transepithelial CXL							
Henriquez *et al.* (19)	36	8–16	12	1	0	+0.05	+0.07

CXL, corneal collagen-crosslinking; UCDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; SE, spherical equivalent; D, diopters; N/A, not available.

incidence of vision-threatening complications.

Conclusions

CXL in the pediatric population is an exciting and relatively new field that has shown promising results to date in the treatment of progressive keratoconus in children. The procedure has also been shown to have a relatively good safety profile. Given the more severe and aggressive nature of pediatric keratoconus, CXL should be considered as a treatment in children once progression is noted. Some even argue that CXL should be offered to parents as a treatment for their child at the time of diagnosis, without waiting to document progression (37). Improvement in uncorrected and corrected distance visual acuity as early as 1 year following CXL also opens the door to considering CXL as a treatment modality to address astigmatism and myopia in children who have or are at risk of anisometropic amblyopia but have failed traditional treatment methods. Further investigation with larger, prospective, randomized controlled trials and longer follow-up periods are needed in order to gain a better understanding of the refractive and keratometric effects, efficacy in halting progression of keratoconus, and safety of CXL in the pediatric population.

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Footnote

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References

1. Wollensak G, Spörl E, Seiler T. Treatment of keratoconus by collagen cross linking. Ophthalmologe 2003;100:44-9.
2. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003;135:620-7.
3. Soeters N, Van der Lelij A, van der Valk R, et al. Corneal crosslinking for progressive keratoconus in four children. J Pediatr Ophthalmol Strabismus 2011;48 Online:e26-9.
4. Sabti S, Tappeiner C, Frueh BE. Corneal Cross-Linking in a 4-Year-Old Child With Keratoconus and Down Syndrome. Cornea 2015;34:1157-60.
5. Hersh PS, Stulting RD, Muller D, et al. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. Ophthalmology 2017;124:1259-70.
6. Perez-Straziota C, Gaster RN, Rabinowitz YS. Corneal Cross-Linking for Pediatric Keratcoconus Review. Cornea 2018;37:802-9.
7. Schumacher S, Oeftiger L, Mrochen M. Equivalence of biomechanical changes induced by rapid and standard corneal cross-linking, using riboflavin and ultraviolet radiation. Invest Ophthalmol Vis Sci 2011;52:9048-52.
8. Shetty R, Nagaraja H, Jayadev C, et al. Accelerated corneal collagen cross-linking in pediatric patients: two-year follow-up results. Biomed Res Int 2014;2014:894095.
9. Ozgurhan EB, Kara N, Cankaya KI, et al. Accelerated corneal cross-linking in pediatric patients with keratoconus: 24-month outcomes. J Refract Surg 2014;30:843-9.
10. Badawi AE. Accelerated corneal collagen cross-linking in pediatric keratoconus: One year study. Saudi J Ophthalmol 2017;31:11-8.
11. Baenninger PB, Bachmann LM, Wienecke L, et al. Pediatric Corneal Cross-linking: Comparison of Visual and Topographic Outcomes Between Conventional and Accelerated Treatment. Am J Ophthalmol 2017;183:11-6.
12. Eissa SA, Badr Eldin N, Nossair AA, et al. Primary Outcomes of Accelerated Epithelium-Off Corneal Cross-Linking in Progressive Keratoconus in Children: A 1-Year Prospective Study. J Ophthalmol 2017;2017:1923161.
13. Ulusoy DM, Goktas E, Duru N, et al. Accelerated corneal crosslinking for treatment of progressive keratoconus in pediatric patients. Eur J Ophthalmol 2017;27:319-25.
14. Sarac O, Caglayan M, Uysal BS, et al. Accelerated versus standard corneal collagen cross-linking in pediatric keratoconus patients: 24 months follow-up results. Cont Lens Anterior Eye 2018;41:442-7.
15. Tian M, Jian W, Sun L, et al. One-year follow-up of accelerated transepithelial corneal collagen cross-linking for progressive pediatric keratoconus. BMC Ophthalmol 2018;18:75.
16. Salman AG. Corneal Biomechanical and Anterior Chamber Parameters Variations after 1-year of Transepithelial Corneal Collagen Cross-linking in Eyes of Children with Keratoconus. Middle East Afr J Ophthalmol 2016;23:129-34.
17. Eraslan M, Toker E, Cerman E, et al. Efficacy of Epithelium-Off and Epithelium-On Corneal Collagen Cross-Linking in Pediatric Keratoconus. Eye Contact Lens 2017;43:155-61.

18. Buzzonetti L, Petrocelli G. Transepithelial corneal cross-linking in pediatric patients: early results. J Refract Surg 2012;28:763-7.
19. Henriquez MA, Rodriguez AM, Izquierdo L Jr. Accelerated Epi-On Versus Standard Epi-Off Corneal Collagen Cross-Linking for Progressive Keratoconus in Pediatric Patients. Cornea 2017;36:1503-8.
20. Buzzonetti L, Petrocelli G, Valente P, et al. Iontophoretic transepithelial corneal cross-linking to halt keratoconus in pediatric cases: 15-month follow-up. Cornea 2015;34:512-5.
21. Magli A, Chiariello Vecchio E, Carelli R, et al. Pediatric keratoconus and iontophoretic corneal crosslinking: refractive and topographic evidence in patients underwent general and topical anesthesia, 18 months of follow-up. Int Ophthalmol 2016;36:585-90.
22. Léoni-Mesplié S, Mortemousque B, Touboul D, et al. Scalability and severity of keratoconus in children. Am J Ophthalmol 2012;154:56-62.e1.
23. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, et al. Corneal Collagen Cross-Linking for Keratoconus in Pediatric Patients-Long-Term Results. Cornea 2017;36:138-43.
24. Mazzotta C, Traversi C, Baiocchi S, et al. Corneal Collagen Cross-Linking With Riboflavin and Ultraviolet A Light for Pediatric Keratoconus: Ten-Year Results. Cornea 2018;37:560-6.
25. Soeters N, van der Valk R, Tahzib NG. Corneal cross-linking for treatment of progressive keratoconus in various age groups. J Refract Surg 2014;30:454-60.
26. Caporossi A, Mazzotta C, Baiocchi S, et al. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. Cornea 2012;31:227-31.
27. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric [corrected] corneal collagen cross-linking in children and adolescents. J Refract Surg 2012;28:753-8. Erratum in: J Refract Surg 2013;29:72.
28. McAnena L, O'Keefe M. Corneal collagen crosslinking in children with keratoconus. J AAPOS 2015;19:228-32.
29. Godefrooij DA, Soeters N, Imhof SM, et al. Corneal Cross-Linking for Pediatric Keratoconus: Long-Term Results. Cornea 2016;35:954-8.
30. Sarac O, Caglayan M, Cakmak HB, et al. Factors Influencing Progression of Keratoconus 2 Years After Corneal Collagen Cross-Linking in Pediatric Patients. Cornea 2016;35:1503-7.
31. Uçakhan ÖÖ, Bayraktutar BN, Saglik A. Pediatric Corneal Collagen Cross-Linking: Long-Term Follow-Up of Visual, Refractive, and Topographic Outcomes. Cornea 2016;35:162-8
32. Wise S, Diaz C, Termote K, et al. Corneal Cross-Linking in Pediatric Patients With Progressive Keratoconus. Cornea 2016;35:1441-3.
33. Toprak I, Yaylali V, Yildirim C. Visual, Topographic, and Pachymetric Effects of Pediatric Corneal Collagen Cross-linking. J Pediatr Ophthalmol Strabismus 2017;54:84-9.
34. Zotta PG, Diakonis VF, Kymionis GD, et al. Long-term outcomes of corneal cross-linking for keratoconus in pediatric patients. J AAPOS 2017;21:397-401.
35. Henriquez MA, Villegas S, Rincon M, et al. Long-term efficacy and safety after corneal collagen crosslinking in pediatric patients: Three-year follow-up. Eur J Ophthalmol 2018;28:415-8.
36. Knutsson KA, Paganoni G, Matuska S, et al. Corneal collagen cross-linking in paediatric patients affected by keratoconus. Br J Ophthalmol 2018;102:248-52.
37. Or L, Rozenberg A, Abulafia A, et al. Corneal Cross-Linking in Pediatric Patients: Evaluating Treated and Untreated Eyes-5-Year Follow-Up Results. Cornea 2018;37:1013-7.
38. Stahl ED. Pediatric refractive surgery. Curr Opin Ophthalmol 2017;28:305-9.
39. Steinwender G, Pertl L, El-Shabrawi Y, et al. Complications From Corneal Cross-linking for Keratoconus in Pediatric Patients. J Refract Surg 2016;32:68-9.
40. Kodavoor SK, Sarwate NJ, Ramamurhy D. Microbial keratitis following accelerated corneal collagen cross-linking. Oman J Ophthalmol 2015;8:111-3.

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