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CORNEAL CROSS-LINKING FOR PEDIATRIC KERATCOCONUS REVIEW

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Abstract

Purpose—Comprehensive review of available published literature for crosslinking in the pediatric population

Methods—Review of the literature published in English in PubMed

Results—two hundred and ten publications were considered. One hundred and fifteen were considered relevant to this review.

Conclusion—Studies of cross-linking in pediatric patients are sparse, with relatively short follow up times, and mostly on small groups of patients. Treatment with crosslinking halts progression of keratoconus in the pediatric population, and early treatment appears to be cost effective compared to later penetrating keratoplasty. Long term effect and regression rates remain unclear and further studies are needed in this population.

Keywords

Pediatric; Cross-linking; Keratoconus

INTRODUCTION

Keratoconus is a non-inflammatory progressive corneal thinning disorder resulting in biomechanical weakening.[1, 2] It manifests as corneal thinning and protrusion resulting in

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moderate to severe visual impairment from irregular astigmatism. It commonly commences at puberty;[3] however, most cases keratoconus are diagnosed later, on average at age 27.[1, 4]

Diagnosis of keratoconus in the pediatric population has been reported as early as age 4,[5] with rapid and severe progression. Until recently, penetrating keratoplasty was the only treatment alternative for visual rehabilitation in severe cases of keratoconus where contact lens fitting was not possible. Corneal cross-linking has been offered as treatment of keratoconus in many countries since its initial description in 2003, and was approved by the FDA in 2016 for treatment of progressive keratoconus in patients older than 14 years old. Long term follow up studies have demonstrated a halt in progression and reduction in corneal steepness in most treated patients. A review of the literature on the use of cross-linking in the pediatric population is presented, and is primarily focused on unique aspects of diagnosis, current management strategies, and gaps in the understanding of disease presentation and management as compared to the adult population.

METHODS

A review of the literature published in English was conducted in PubMed using the following search terms: “Cross-linking” AND “pediatric” (187 results); “Cross-linking” AND “children” (210 results) “Cross-linking” AND “adolescents” (12 results). One hundred and twelve publications were found to be salient to this review.

KERATOCONUS: EPIDEMIOLOGY

Keratoconus prevalence has been reported as 54.5 per 100,000 affected patients in the United States,[6] 0.3 per 100,000 in Russia,[7] 2,300 per 100,000 in Central India,[8] 6,200 per 100,000 in Saudi Arabia,[9] and 13.3 per 100,000 in the Netherlands.[10] This variability may be explained by changing available imaging technology over time, since as newer publications emerge the reported incidence of keratoconus has increased.

Keratoconus has been associated with atopia,[11, 12] vernal keratoconjunctivitis,[13-15] and environmental factors such as persistent eye rubbing and eyelid laxity.[16, 17] There is a higher prevalence of keratoconus in patients with Downs syndrome;[18] however, the genetic correlation has not been conclusive and the presence of keratoconus in these patients is likely associated to persistent eye rubbing. Other genetic conditions such as Leber’s congenital amaurosis[19] and mitral valve prolapse[1, 20, 21] have been genetically linked to Keratoconus, and numerous publications show a strong genetic predisposition,[22-24] with identified potential linked genes. [25-40] When subclinical forms of keratoconus and forme fruste keratoconus are taken into account, first degree relatives of patients with keratoconus have 15 to 67 times higher prevalence of keratoconus compared to the general population.[41]

KERATOCONUS IN THE PEDIATRIC POPULATION

In the pediatric population, prevalence data has not been widely reported in the literature. The largest population studied of 2,972 patients younger than 14 years old in Lebanon reported an incidence of 0.53% (approximately 1 in 200) over a period of 5 years, which represented 2.9% of keratoconus cases in all ages;[42] and more recently, a prevalence of 1 in

25 was reported in Riyadh, Saudi Arabia.[43] The average age at diagnosis in the pediatric population is 15 years old,[44, 45] with reported cases diagnosed as early as age 4,[5] and male predominance.[46-48]

Keratoconus tends to be more severe and to progress more rapidly in children,[49-51] especially those with central cones, which are more common in this population and more visually significant than peripheral cones.[45] At the time of presentation, 30% of children and adolescents present with keratoconus at stage 4 (Table 1)[52, 53] compared to 8% of adults,[50] and in up to 88% of pediatric patients progression can occur rapidly with steepening greater than 2 D within 12 months after presentation.[54-56] Additionally, patients with asymmetric disease have been shown to eventually develop keratoconus in their unaffected eye in 35% of cases with unpredictable timing over the course of 8 years. These findings were confirmed in the CLEK (Collaborative Longitudinal Evaluation of Keratoconus) study, identifying age between 10 and 20 years old as a predictor of significant progression and corneal scaring.[57]

Reports in the literature about pediatric keratoconus are limited, and there is still no standardization for management in pediatric patients. Paradigms in the management of keratoconus in adults are shifting, with the introduction of new treatments such as corneal cross-linking (CXL) and the incorporation of intracorneal ring segments into the management of ectatic disease. These therapeutic options are also being assessed in the pediatric population, with increasing publications describing treatment outcomes.

CORNEAL CROSS-LINKING FOR PEDIATRIC KERATOCONUS

Penetrating Keratoplasty (PK) has a poorer prognosis in the pediatric population due to an increased risk of rejection related to their robust inflammatory response to the graft.[58] Over the past decade, CXL has emerged as a less invasive alternative for patients with progressive keratoconus, offering a significant improvement in procedure risk profile compared to PK. The use of keratoplasty for treatment of severe keratoconus has steadily decreased in the United States[59] and will decline further with FDA approval of CXL.

Initially reported by Wollensak and colleagues,[60] CXL improves corneal tensile strength through the combination of riboflavin drops and exposure to ultraviolet A (UVA) light. CXL has been thoroughly studied in the adult population and offers a minimally invasive alternative to halt progression and in some cases regress severity of the ectatic process.

CXL PROTOCOLS

The first protocol proposed for CXL was the standard (Dresden) protocol, by Wollensak and colleagues,[60,61] and it is currently the only FDA approved protocol in the United States.[62] Other proposed protocols include accelerated protocols that reduce treatment time but maintain or increase total irradiance,[63, 64] and transepithelial CXL, which attempts to bypass the epithelial barrier by modifying the riboflavin to increase its penetration through an intact epithelium. [65]

Standard Dresden Protocol

Since the corneal epithelium poses a barrier to full penetration of standard riboflavin into the corneal stroma,[66] the standard protocol requires mechanical debridement of the corneal epithelium under topical anesthesia in the central 9 mm of the cornea. One drop of riboflavin 0.1% solution is then administered every 2 minutes for 30 minutes, followed by exposure to UV-A light (370 ± 5 nanometers wavelength, 5.4 J / cm^2 irradiance) with instillation of the riboflavin solution every 2 minutes for an additional period of 30 minutes.

Accelerated CXL Protocols

Accelerated protocols have derived from the Bunson-Roscoe L*aw of Reciprocity of Photochemistry*, which states that the photochemical effect of ultraviolet light is 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.[63]

Results to date are controversial. Animal studies found equivalent efficacy between 3 mW at 30 minutes and 9 mW at 10 min,[67] and equivalent biomechanical responses are seen in standard (3 mW/cm^2, 30 minutes) and moderately accelerated (10mW/cm^2, 9 minutes) treatment protocols.[64, 68] However, there seems to be a drop in efficacy when higher irradiances are used,[69] to a point indistinguishable from untreated control corneas,[70] due to the imbalance between conversion and replenishment of oxygen molecules. [70, 71]

In the pediatric population very few studies have evaluated outcomes for accelerated protocols with UV fluence of 30 mW/cm^2 for 3 minutes, 10 mW/cm^2 for 9 minutes, or 9 mW/cm^2 for 10 minutes, respectively.[72-74] Their results were promising in terms of refractive outcomes and keratometry improvement; however, to date no studies have compared efficacy of accelerated protocols to the standard protocol in children, and no studies have followed patients beyond three years, when the effects of standard protocol may start regressing in children.[55]

Transepithelial CXL

Transepithelial CXL emerged as a strategy to improve the safety profile and reduce postoperative discomfort. However, studies in porcine corneas[75] and in vitro human corneas have demonstrated reduced penetration of riboflavin into the corneal stroma when the epithelium remains intact.[66] As a response to this, a modified riboflavin: Ricrolin TE (Sooft, Italia SpA) with the addition of two agents to enhance penetration through the intact epithelium: trometamolol and sodium ethylenediaminetetraacetic acid (EDTA) was then introduced to the transepithelial CXL protocol to maximize the effect of the procedure. Even with this modification there was less penetration into the corneal stroma and limited clinical results.[76-79]

The *demarcation line*, a refractile line seen within the corneal stroma on ocular coherence tomography (OCT) by day 10 to 14 after CXL, is thought to represent penetration of treatment into the stroma.[80] In transepithelial CXL, this demarcation line is seen at an average depth of 100 μm below the epithelium,[81] compared to 320-340 μm after epithelium-

off treatments, indicating that the epithelium does pose a barrier to penetration of CXL treatments into the corneal stroma

Iontophoresis

Since riboflavin is a low molecular weight and negatively charged molecule, another proposed strategy for transepithelial CXL treatments is the use of iontophoresis, applying a small electric current prior to the instillation of riboflavin to enhance its penetration into the corneal stromal tissue. Early studies in rabbit models have shown promising results in terms of penetration into the corneal stroma compared to epithelium-off CXL,[82, 83] and in vitro studies have shown similar biomechanical changes in the cornea compared to the standard CXL protocol.[84] However, the demarcation line in adults is only present in 47% of patients one month after treatment compared to 93% and 87% after conventional and accelerated CXL protocols, respectively,[85] and to date there are limited papers in the literature demonstrating stable refractive and keratometric values in pediatric patients 15 to 18 months after treatment.[86, 87]

OUTCOMES OF PEDIATRIC CROSS-LINKING

The standard CXL protocol has been shown to successfully halt progression of keratoconus and reduce keratometry values in adults.[88, 89] Since the first publication in a pediatric population in 2011,[56] numerous publications have shown that the standard epithelium-off Dresden protocol CXL is as safe and effective for the treatment of progressive keratoconus in children and adolescents as it is in the adult population (Table 2),[45, 48, 55, 90-94] The number of publications assessing the results from transepithelial and accelerated protocols in pediatric patients also continues to increase. (Table 3, Table 4)

There are no randomized, contralateral eye studies comparing treatment at diagnosis to treatment upon detection of progression; however, due to the rapid and severe progression of keratoconus in children and adolescents, most authors suggest proceeding with the treatment at the time of diagnosis.[55]

Efficacy

After standard CXL epi-off protocol, the majority of patients experience flattening of the steepest keratometry up to 10 years after the procedure.[55, 72-74, 90, 92, 95-98]In contrast, published studies assessing the effect of transepithelial CXL provide conflicting evidence (Table 3), with some showing comparable,[99, 100] or less pronounced effect,[101] and even topographic regression 9 to 12 months after epithelium-on procedures. [78, 102] The advantage of transepithelial CXL is to offer a minimally invasive treatment with a potentially better safety profile due to the intact epithelium. However, given its diminished effect, transepithelial CXL may be reserved for use in patients who present with early disease stages or in specific patient populations, such as patients with Downs syndrome and other special considerations, who may pose challenges with postoperative compliance.

Topographic Effects

The response to CXL in pediatric patients appears to occur more robustly in patients with thinner corneas (< 450μm),[48, 97] and centrally located cones.[45] Initial steepening of the cornea during the first 3 months after the procedure has been observed,[94, 96] which has been suggested to be the result of early epithelial remodeling.[103] Beyond the first year and during the first two years after standard CXL epi-off protocol, 25% of patients remain stable, more than 60% show regression, which is manifested as an average flattening of 1.5 D in the steepest keratometry, while 11-20% show no response to treatment with progression of corneal steepening.[55, 72-74, 90, 92, 95-97]

After 2 years, a halt in the flattening effect has been observed, and 3 years after the procedure 20 to 50% of patients may resume progression of corneal steepening despite of initial improvement,[55,96, 98] indicating a transient effect of CXL in this population that may not be sufficient to completely and permanently halt progression. Some factors identified as influencing the progression of keratoconus long term after CXL are paracentral location of the cone[47] (odds ratio 3.21, 95% confidence interval) and thinnest pachymetry below 450μm (odds ratio of 4.54, 95% confidence interval).[104] There are very few retreatment cases published in the literature. In an adult patient, retreatment resulted in further 4 D of flattening in Kmax over a period of 2 years.[105] In a recently published series of 62 eyes of pediatric patients, two children showed progression up to 3.2 D in Kmax by the 36-month follow up visit, requiring retreatment. Both patients experienced stabilization of Kmax values 12 months after retreatment.[98]

Transepithelial CXL also has been demonstrated to halt progression in up to 80% of patients,[86, 87, 99, 100] and in some reports has also been shown to improve keratometry values in a degree comparable to the standard Dresden protocol.[99, 100] However, improvement of keratometry values is not seen with transepithelial treatment as consistently as with the standard Dresden protocol,[86, 87, 102] and topographic regression has been documented 9 to 12 months after the procedure. [78, 102]

Studies on accelerated protocols are sparse and with small groups of patients. However, results are promising in terms of improvement in keratometry measurements, especially in those protocols that use longer periods of exposure (9 and 10 minutes)[73, 74] compared to much shorter exposures.[72]

Refractive Effects

Even though the most relevant effect of CXL is the halt in progression of the disease, refractive improvement can be seen in different stages of keratoconus after all CXL protocols. Uncorrected distance visual acuity (UDVA) and distance corrected visual acuity (DCVA) can improve an average of 1-2 and 2-3 lines respectively in 30 to 60% of patients by year 2,[45, 55, 92, 93, 106] and 69% by year 4[96] after the standard Dresden protocol. There can also be a significant reduction in higher order aberrations, specifically total coma and spherical aberration.[48, 55, 72, 90, 94] Changes in visual acuity after transepithelial CXL are less clinically significant,[99, 102] occasionally with no change;[86, 87, 100] In accelerated CXL

protocols, refractive changes are also less, but more apparent after longer exposures (9 to 10 min).[72-74]

Safety

While microbial keratitis after CXL is infrequent, it has been reported after both standard and accelerated protocols in the pediatric population (Table 5).[107-110] Even though most cases have occurred after epithelium off, microbial keratitis has also been reported after trans-epithelial and accelerated CXL treatments.[108, 111] The largest reported series of microbial keratitis after CXL was recently published by Maharana et al describing 7 cases of microbial keratitis in 532 CXL procedures using the accelerated 18 mW/cm^2 for 6 minutes. [112] All reported cases have occurred between day 1 and day 7 after CXL and having received prophylactic treatment with topical fluoroquinolones. Most microbiological reports have shown *Staphylococcus aureus* but there have also been reports of *Aspergillus fumigatus, Mucor spp, Acanthamoeba* and *Alternaria spp*,[112] as well as *Pseudomonas aeruginosa*,[109] and *Herpes Simplex*.[107] No other major complications have been reported after different CXL protocols, except a transient haze that usually resolves after treatment with topical steroids,[9198] although it can persist in 3% of patients.[47]

There is a transient decrease in thinnest pachymetry during the first 6 months after the procedure which returns to baseline after 1 year. [90, 92, 94] Endothelial cell counts have been shown to remain unaffected up to a 6 year follow up period both after standard pitheium-on[94, 100] and accelerated protocols[72, 74] and transepithelial protocols.[99]

Cost Effectiveness

Cost effectiveness analyses of CXL compared to traditional management of keratoconus using Markov model structure[113, 114] and 2-state transitioning microsimulation models[115] have demonstrated superiority of early CXL over standard management with PK. In a hypothetical model, a 10 year effect after early treatment with CXL would provide a net increase in quality adjusted life years (QALY) of 50 to 51 with early CXL,[113, 115] and incremental cost-effectiveness ratios of £3,174/QALY,[114] €54,384 ($59,822)/QALY[113] and Can$9090/QALY[115] compared to standard management.

CONCLUSION

The field of pediatric CXL is yet to be fully addressed, and currently published literature on CXL is not as extensive for the pediatric population as it is for the adult population. Since clinical findings of keratoconus usually become evident during puberty,[3] but can also present earlier in childhood, topographic screening should be considered in adolescents or children with high degrees of myopia and/or astigmatism or anisometropia, especially when their DCVA is not 20/20. Additionally, since there seems to be a genetic predisposition,[22-24] topographic screening should also be considered in any child with family history of keratoconus and in relatives of diagnosed children. Due to the evidence of rapid progression in most pediatric patients,[55] and the clear cost effectiveness of early CXL compared to standard traditional management of KCN with late PKP,[113-115] treatment upon diagnosis versus close monitoring should be discussed with parents when the diagnosis of keratoconus

is made. The standard Dresden protocol CXL is a safe and effective treatment for keratoconus in children, and transepithelial and accelerated protocols are yet to be demonstrated to have comparable results to the standard Dresden protocol in regressing keratometry values. Further studies are needed to determine if they are as equally effective alternative protocols.

Currently available evidence suggests that the standard CXL Dresden protocol is at least temporarily effective in halting progression and even improving keratometry values in pediatric patients. There has been a demonstrated regression up to 3 years after treatment in some studies and to our knowledge no studies have been published assessing outcomes of re-treatments in this population after resuming progression of keratoconus. Given the concern of regression of keratoconus after CXL in children, studies assessing the effect of CXL in pediatric patients should provide at least 5 years of follow up data to fully determine long term effects; and follow up after CXL in pediatric patients should monitor for early signs of resumed progression. Better consensus should be established in terms of the age group included in the term “pediatric” to homogenize and compare results, and further studies are warranted to assess the long-term effect of CXL, the feasibility and effectiveness of retreatments and to confirm effectiveness of alternative protocols in selected cases.

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Table 1

Clinical staging of keratoconus, described by Krumeich et al[44,45]

Stage*	Findings
Stage 1	Eccentric steepening Induced myopia and/or astigmatism of ≤ 5.00 D Keratometry reading ≤ 48.00 D Vogt's lines
Stage 2	Induced myopia and/or astigmatism between 5.00 and 8.00 D Keratometry reading ≤ 53.00 D Thinnest Pachymetry ≥ 400 μm
Stage 3	Induced myopia and/or astigmatism between 8.00 and 10.00 D Keratometry reading > 53.00 D Thinnest Pachymetry 200 to 400 μm
Stage 4	Refraction not measurable Keratometry reading > 55.00 D Central scars Thinnest Pachymetry ≤ 200 μm

*Stage determined by presence of one of the described findings

Table 2

Refractive and Keratometric changes 12 to 72 months after epithelium-off standard Dresden protocol cross-linking in patients younger than 19 years old.

Authors	Number of eyes	Age group (years)	Follow up time (months)	Change in DCVA (Snellen lines)	Change in KMax (D)	Change in Steep K (D)	Change in Average K (D)	Complications (number of eyes)
Chatzis et al 2012[54]	59	9 - 19	36	1	N/A	-1.1	-1.1 at 12 months +0.5 at 36 months	Delayed epithelial healing (2)
Arora et al 2012[91]	15	10 – 15	12	3	N/A	-0.42	N/A	Transient haze (2)
Caporosi et al 2012[48]		10 - 18	36	0.16 * 0.15 †	-0.76 * -0.61 †	N/A	-0.58 * -0.60	None
Vinciguerra et al, 2012[94]	40	9 - 18	24	2	N/A	-1.27	-0.79	Transient haze (3)
Magli et al 2013[99]	23	12-17	12	0	-1.1	N/A	-1.47	Corneal edema (2)
Soeters et al 2014[44]	29	< 18	12	2	-1.8	-0.3	-0.4	Loss of CDVA (1)
Viswanathan et al, 2014[95]	25	8 - 17	20	0	N/A	-0.72	N/A	None
Kodavoor et al, 2014[92]	35	9 - 16	12	1	-1.24	-1.24	N/A	Transient haze (2) Haze and Scar (6)
McAnena et al, 2015[90]	25	13 - 18	36	2	-0.73 ‡	N/A	-0.31 *	None
Peyman et al 2015[104]	64	< 18	12	0	-0.5	-0.3	N/A	None
Uçakhan et al 2016[93]	40	10 - 18	48	2	-1.4	-0.5	-0.5	Transient haze (8) Transient sterile infiltrates (2)
Godefrooji et al, 2016[47]	54	11 - 17	60	1	-2.06	N/A	-0.65	Persistent haze (1)
Wise et al 2016[46]	39	11 - 18	12	0	N/A	N/A	-0.24	None
Padmanabhan et al, 2017[96]	194	8 - 18	72	1	-1.2 §	-1.1	-1.7	None

[*] Corneas thicker than 450 μm

[†] Corneas thinner than 450 μm

[‡] n = 8 eyes out of initial 25.

[§] Regression with > 1 D steepening in 15% by 2 years, 21% by 4 years and 24% beyond 4 years

DCVA: Distance Corrected Visual Acuity, KMax: Steepest Keratometry; KSteep: Steepest Simulated Keratometry; Average K: Average Keratometry.

Table 3

Refractive and Keratometric changes 12 to 18 months after transepithelial cross-linking in patients younger than 18 years old.

Authors	Number of eyes	Age group (years)	Follow up time (months)	Change in DCVA (Snellen lines)	Change in KMax (D)	Change in Steep K (D)	Change in Average K (D)	Complications (number of eyes)
Transepithelial CXL with modified Riboflavin (Ricrolin)								
Buzzonetti et al, 2012[101]	13	8 - 18	18	1	+4.9	N/A	+0.2	None
Magli et al 2013[99]	14	12 - 17	12	0	-1.14	N/A	-1.63	None
Salman et al 2013[98]	22	13 - 18	12	3	-2.3	N/A	-2.03	None
Transepithelial CXL with Iontophoresis								
Buzzonetti et al, 2015[86]	14	10 - 18	15	1	+0.4	+0.2	+0.2	None
Magli et al 2016[87]	13	11 - 18	18	1	N/A	+0.3	N/A	None

DCVA: Distance Corrected Visual Acuity, KMax: Steepest Keratometry; KSteep: Steepest Simulated Keratometry; Average K: Average Keratometry

Table 4

Refractive and Keratometric changes 12 to 24 months after accelerated cross-linking protocols in patients younger than 18 years old.

Authors	Number of eyes	Age group (years)	Follow up time (months)	Protocol used	Change in DCVA (Snellen lines)	Change in KMax (D)	Change in Steep K (D)	Change in Average K (D)	Complications (number of eyes)
Shetty et al 2014[74]	30	11 - 14	24	9 mW/cm^2 for 10 min	1	N/A	-2.07	N/A	Transient haze (most)
Ozgurhan et al 2014[72]	44	9 - 18	24	30 mW/cm^2 for 4 min	1	N/A	-0.5	-0.4	None
Badawi, 2017[73]	33	8 - 15	12	10 mW/cm^2 for 9 min	2	-1.2	-1.1	N/A	Transient haze (most)

DCVA: Distance Corrected Visual Acuity, KMax: Steepest Keratometry; KSteep: Steepest Simulated Keratometry; Average K: Average Keratometry

Table 5

clinical features of published case reports of microbial keratitis in pediatric patients.

Author and year	Patient's age and gender	CXL protocol and Laterality	CDVA at presentation	Time after procedure	Organism	Final CDVA
Sharma et al 2010[109]	19 y/o female	S- CXL OD	Hand motions near to face	1 day	*Pseudomonas aeruginosa*	20/200
Shetty et al 2014[110]	18 y/o male	S- CXL	N/A	3 days	*Staphylococcus aureus*	20/30
Al-Qarni et al 2015[107]	18 y/o male	S-CXL OS	N/A	7 days	*Herpes Simplex*	20/25
Rana et al 2015[108]	19 y/o female	Trans epithelial Accelerated CXL (9 mW/Cm^2 × 10 min) OS	N/A	3 days	*Staphylococcus aureus*	N/A
	18 y/o male	Epithelium off Accelerated CXL (9 mW/Cm^2 × 10 min) OD	N/A	5 days	Methicilin resistant *Staphylococcus aureus*	20/70
Kodavoor et al 2015[111]	15 y/o male	Accelerated CXL (30 mW/Cm^2 × 3 min) OD	20/400	3 days	*Staphylococcus aureus*	20/40

S-CXL: Standard Crosslinking