Advances in Ophthalmology Practice and Research 3 (2023) 55–62

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research

Review

Paediatric cornea crosslinking current strategies: A review

Pawan Prasher [a], Ashok Sharma [b,*], Rajan Sharma [b], Vipan K. Vig [c], Verinder S. Nirankari [d]

[a] Department of Ophthalmology, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India
[b] Cornea Centre, SCO 2463 - 2464, Sector 22 C, 160022, Chandigarh, India
[c] Amritsar Eye Hospital, GNDU Shopping Complex, Amritsar, Punjab, India
[d] Department of Ophthalmology, University of Maryland, USA

ARTICLE INFO

Keywords:
Keratoconus
Corneal collagen cross-linking
Corneal transplant
Pediatric keratoconus

ABSTRACT

Background: In the general population, 1 in 2000 people has keratoconus. Indians and other people from Southeast Asia have a higher incidence of keratoconus. Children with keratoconus typically present earlier in life and with a more severe disease. Rubbing the eyes has been identified as a risk factor. Children have a higher incidence and a faster rate of keratoconus progression. Visual rehabilitation in children with keratoconus is challenging. They have a low compliance with contact lens use. Many of these children require penetrating keratoplasty at an early age. Therefore, stopping the progression of keratoconus in children is of paramount importance.

Main text: Compared to treatment, keratoconus progression prophylaxis is not only preferable, but also easier. Corneal collagen cross-linking has been shown to be safe and effective in stopping its progression in children. The Dresden protocol, which involves central corneal deepithelization (7–9 mm), saturation of the stroma with riboflavin (0.25%), and 30 min UV-A exposure, has proven to be the most successful. Two significant disadvantages of the typical Dresden regimen are the prolonged operating time and the significant post-operative pain. Accelerated-CXL (9 mW/cm^2 x 10 min) has been studied to reduce operative time and has been shown to be equally effective in some studies. Compared to accelerated CXL or traditional CXL, epi-off procedures, transepithelial treatment without the need for de-epithelialization and without postoperative discomfort, have been shown to be safer but less effective. Corneal crosslinking should only be performed after treating children with active vernal keratoconjunctivitis. Corneal opacity, chronic corneal edema, sterile infiltrates, and microbial keratitis have been reported after cross-linking of corneal collagen.

Conclusions: The "Dresden protocol", also known as the conventional corneal cross-linking approach, should be used to halt the progression of keratoconus in young patients. However, if the procedure needs to be completed more rapidly, accelerated corneal crosslinking may be considered. Transepithelial corneal cross-linking has been proven to be less effective at stabilizing keratoconus, although being more safer.

1. Introduction

The term "keratoconus" refers to a gradual non-inflammatory thinning and ectasia of the cornea. Myopia, astigmatism, and higher-order aberrations are traits of keratoconus. As the condition worsens, an irregular astigmatism develops, which can seriously impair vision.[1–3] Typically, it is thought to be an adolescent-only illness that worsens by the third or fourth decade of life. Historically, the early stages of keratoconus were commonly treated with spectacles and contact lenses, and the later stages with a corneal transplant.[4–6] Corneal cross-linking, which delays the advancement of illness, has grown in prominence in recent years as a way to obviate the necessity for penetrating keratoplasty. In the past, penetrating keratoplasty was needed for 11%–27% of kids with advanced keratoconus who were not candidates for optical correction.[7,8] Despite extensive research on corneal cross-linking in adults, its use in the treatment of pediatric keratoconus is still under investigation. These concern the effectiveness, the necessity of follow-up, repeat therapies, the management of co-occurring allergy disorders, and the management of behavioral issues such eye rubbing. The pediatric population is particularly sensitive in terms of psychological factors, where the illness and the surgical procedure have a major impact on attendance at school and learning, emphasising the significance of special considerations in this demographic.

* Corresponding author. Cornea Centre, 2463-2464, Sector 22c, Chandigarh, 160022, India.
E-mail address: asharmapgius@yahoo.com (A. Sharma).

https://doi.org/10.1016/j.aopr.2022.11.002
Received 8 July 2022; Received in revised form 13 November 2022; Accepted 16 November 2022
Available online 25 November 2022
2667-3762/© 2022 Published by Elsevier Inc. on behalf of Zhejiang University Press. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2. Main text

2.1. Epidemiology

Keratoconus is more common than previously thought, with incidence rates ranging from 0.9% to 3.3% in various populations worldwide. Recent improvements in early detection could contribute to this increasing occurrence. One in 2000 people globally are thought to have keratoconus.[9–17] The prevalence of keratoconus seems to be higher in hot, arid nations like India and the Middle East than in colder nations like the Netherlands and the UK.[9–11]

The precise pathophysiology of keratoconus is unknown. However, it is thought that various ethnic, genetic, environmental, and regional factors may have an impact on how it develops in certain demographic groups. There have been numerous reports of ocular and systemic correlations in juvenile patients, including allergic keratoconjunctivitis, vernal keratoconjunctivitis, atopy, eye rubbing, and atopic dermatitis.[18–21] Contrary to the widespread perception that keratoconus is a non-inflammatory illness, recent research have revealed that inflammatory mediators may play a role in the development of the condition.[22,23]

According to reports, keratoconus prevalence in many nations is significantly influenced by ethnicity. Patients with South Asian ancestry in the UK showed a higher frequency (4.4 to 7.5-fold) than Caucasians.[24,25] Genetic factors may play a role in the aetiology of keratoconus due to its association with systemic disorders such Down syndrome, Marfan syndrome, retinitis pigmentosa, Leber congenital amourosis, mitral valve prolapse, and collagen vascular diseases.[26,27] Further evidence for the significance of genetic variables comes from the observed higher occurrence in patients of consanguineous descent and higher probability (15%–67%) of developing ectasia in first-degree relatives.[28]

Prevalence data for pediatric keratoconus (onset before age 18) have not been widely reported in the literature. The median age of keratoconus in the pediatric population is 15 years,[29,30] with the youngest reported case being a 4-year-old girl with Down syndrome.[31] Keratoconus behaves differently in children than in adults, and children are more likely to present with advanced disease. Leoni-Mesplie et al.[32] reported that 27.8% of children had stage 4 disease compared to 7.8% of adults. These children are more likely to be males with a history of associated allergic diseases and a habit of rubbing their eyes. It has been suggested that eye rubbing, in addition to its mechanical effect on the cornea, is associated with an increase in ocular surface inflammation, as evidenced by higher levels of MMP-13, IL-6, TNF-alpha in the tear film, which may play a role plays a key role in the pathogenesis of keratoconus.[33] Younger age may be associated with rapid progression and the eventual need for corneal transplant surgery.[34,35] Chatzis and Hafezi reported progression of keratoconus in 88% of children after a follow-up of one year.[36] Compared to adults, children with keratoconus face unique challenges due to additional factors such as underdiagnosis, poor compliance, need for treatment of associated vernal keratoconjunctivitis, schooling, behavioral problems, and amblyopia.

Traditional therapies like eyeglasses, contact lenses, corneal transplantation, and intracorneal ring segments have been used for treating keratoconus in both adults and children for a number of years. But there is a highrisk of rejection due to their hperactive immune system. Infections following keratoplasty, glaucoma, and poor compliance are additional risk factors.[37] The development of minimally invasive corneal cross-linking has changed the way keratoconus is treated in recent years. To arrest the progression of ectasia and avois corneal transplant surgery, corneal cross-linking is used.[38,39]

2.2. Crosslinking

Crosslinking is the process by which one polymer chain is joined to another by bonds, which can be covalent or ionic, resulting in a change in physical properties.[39] Crosslinking is commonly used in dentistry to strengthen restorative materials.[40] The three main types of corneal cross-linking responses are as follows: 1) physiological cross-linking mediated by lysyl oxidase, which stabilizes collagen fibril structure and may help reduce the risk of ectasia with age; 2) cross-linking mediated by advanced corneal glycation endproduct in diabetics thought to be responsible for protection against the development of keratoconus; and 3) riboflavin-mediated photooxidative crosslinking used as a treatment option for various types of corneal ectasia.[41]

Corneal cross-linking was first described in 2003 as a new therapeutic option for patients with progressive keratoconus.[42] This technique utilizes a photochemical reaction induced by riboflavin in the corneal stroma upon exposure to ultraviolet light. Corneal crosslinking strengthens the corneal stroma by forming chemical bonds between collagen fibrils.[39,43] Corneal crosslinking has been extensively evaluated in adult keratoconus and its efficacy and safety in adults has been demonstrated. However, the procedure in children is still being evaluated, and evidence of its safety and effectiveness has been accumulating in recent years.

2.3. Corneal crosslinking in children

Rapid decision-making is advisable in adolescents with keratoconus because the disease is advanced at the time of presentation and it progresses more quickly. According to Leoni-Mesplie et al.,[44] a greater proportion (27.8%) of patients younger than 15 years had stage IV Amsler-Krumeich disease at presentation compared to those 27 years and older (7.8%). According to Soeters et al.,[30] the keratoconus increased by 2.6 D in 7 weeks and by about 5.0 D in one year. Chatzis and Hafezi[36] reported progression in 88% of patients after one year of follow-up. Therefore, it is important that children are treated at the time of diagnosis without waiting for signs of progression.[45]

2.4. Protocols for corneal crosslinking in children

Corneal cross-linking procedures in children are not significantly different from those in adults. However, with children, there may be certain additional considerations that need to be made. In this vulnerable demographic it may be prudent to stick with the traditional Dresdon protocol, which has been shown to have the maximum effectiveness, but various protocols aimed at reducing the treatment duration, shortening the recovery period and reducing discomfort are also being explored.[46]

2.5. Standard dresden protocol

The standard Dresden protocol is the most commonly used technique to date for corneal cross-linking in adults and children. It was first reported by Wollensak et al.[42,47] To facilitate riboflavin penetration into the stroma, the central 7–9 mm of the corneal epithelium is removed. Riboflavin drops are administered every 2 min for a total of 30 min after epithelial excision. This is followed by another 30-min exposure to ultraviolet-A light (370.5 nm wavelength, 5.4 J/cm2 irradiance) for another 30 min along with instillation of the riboflavin solution every 5 min. Finally, a bandage contact lens is fitted. The patient is prescribed oral analgesics and antibiotic eye drops. Ucakhan et al.[48] comparred 88 pediatric eyes (54 patients) and 104 adult eyes (68 patients), and found that traditional crosslinking was equally effective in slowing the progression of keratoconus in both groups. The treatment produced comparable visual, refractive, aberrometry, and tomographic results at 3 years follow-up. Numerous long-term studies have documented the effectiveness of the Dresdon protocol in stopping the progression of keratoconus in children.[36,49–54]

Godefrooiz et al.[49] reported results of standard crosslinking in 54 eyes of 36 pediatric patients. They found an improvement in maximal keratometry, the best corrected visual acuity at any follow-up visit. Despite crosslinking, however, 12 eyes (22%) showed a progression of 1.0 D or more up to the last follow-up.

In the largest study to date by Padmanabhan et al.,[50] 194 eyes of 153 children aged 8–18 years with documented progressive keratoconus were followed for up to 6.7 years after corneal crosslinking (142 with standard and 52 with hypoosmolar riboflavin). The authors observed a significant improvement in mean best-corrected visual acuity, a reduction in topographical astigmatism, and a mean flattening of maximal keratometry. However, after 4 years of follow-up, there were features in some eyes that indicated that the cross-linking effect had reversed.

Zotta et al.[51] reported stabilization of keratoconus using the standard crosslinking Dresden protocol in 20 eyes of 10 patients during a mean follow-up of 7.6 years. They reported that stabilization of keratoconus was evident from topographic indices and improvement in mean corrected distance visual acuity during follow-up.

In their prospective analysis, Uakhan et al.[52] recruited 40 eyes from 40 consecutive patients with progressive keratoconus aged 10–18 years. During the four-year follow-up, they documented improvements in topographic indices, reductions in maximal keratometry, and improvements in both uncorrected and best-corrected television acuity. There was no progression or complication that compromised vision.

In a prospective study by Mazotta et al.[53] 62 eyes of 47 keratoconus patients underwent epithelium-off-CXL. It was found that the majority of patients had improved uncorrected and corrected teleacuity and keratoconus stability after 10 years of follow-up. Final follow-up revealed an overall progression rate of 24%. Two of the subjects required a corneal transplant due to progressive disease.

2.6. Accelerated CXL protocols

One focus was on reducing treatment time, as the traditional method requires patient cooperation over a significant period of time, which can be quite challenging in children. The possibility that accelerated cross-linking has the potential to be as effective in children as it is in adults needs to be evaluated. The concept of an accelerated protocol originates from the Bunsen-Roscoe rule of reciprocity, which stipulates that a combination of higher intensity and shorter exposure time should theoretically result in a total dosage to tissue that is equivalent to that applied with standard treatment. In recent years, numerous surgeons have investigated accelerated cross-linking for the pediatric population using a variety of therapies, including UVA irradiation at 30 mW/cm^2 for 3 min, 10 mW/cm^2 for 9 min, or 9 mW/cm^2 for 10 min.[55–59]

Nicula et al.[55] compared the results of accelerated CXL performed on 27 eyes (A-CXL group) with the conventional CXL Epi-Off procedure performed on 37 eyes (S-CXL group) over a follow-up period of 4 years. They noted an improvement in visual acuity and a statistically significant decrease in keratometry measurements in all patients; however, there was no difference in improvements between the two groups. They concluded that both traditional and accelerated procedures are effective and viable treatments for pediatric patients with progressive keratoconus with comparable outcomes.

Eissa et al.[58] recruited 68 eyes (34 patients), randomly assigned them to groups A and B. Group A had standard cross-linking while Group B received rapid cross-linking. They did not discover any statistically significant difference between the two groups in terms of simulated keratometry, corneal densitometry, endothelial density or wavefront aberrations during three years follow-up. There was no progression over the 36-month follow-up period.

Sarac et al.[59] reported the results of their comparative study in which 38 eyes received standard cross-linking (3 MW/cm^2, 30 min) while 49 eyes received accelerated cross-linking (9 mW/cm^2, 10 min) for pediatric keratoconus received over a follow-up period of two years. There was no difference between the two groups in terms of keratometry, higher-order aberration, or uncorrected and best-corrected visual acuity. They concluded that efficacy and safety were similar for both protocols; accelerated cross-linking appeared to be more beneficial for pediatric patients because it is a shorter procedure.

2.7. Transepithelial crosslinking

Epithelial debridement is a critical part of the traditional technique to allow the riboflavin solution to penetrate into the stroma. This maneuver has been reported to be associated with great pain, discomfort, and risk of infection.[4] Transepithelial, or epithelial-on-crosslinking, is a newly developed modification to improve the safety profile and reduce post-operative discomfort. It does not require epithelial debridement. A number of delivery techniques have been explored to promote the diffusion of riboflavin across the intact epithelium. These include chemical enhancers, epithelial disruption devices, intrastromal channels, microneedling, iontophoresis, ultrasound, and vacuum.[39,46] In pediatrics, where more patients are prone to infection, haze, surgical pain, and transient visual impairment, epithelium-on-crosslinking appears even more tempting.

Henriquez et al.[60] reported a comparison of the results of epi-on crosslinking involving 36 eyes with a 30-min impregnation (0.25% riboflavin, 1.0% phosphate hydroxypropyl methylcellulose and 0.007% benzalkonium chloride) and one 5 min irradiation (18 mW/cm), with epi-off crosslinking involving 25 eyes, using 30 min impregnation (riboflavin 0.1% solution plus 20% dextran 500) and 30 min irradiation (3rd mW/cm^2). After one year of follow-up, they found no significant difference between the two groups in terms of changes in pachymetry and posterior height scores. The progression in the epi-on and epi-off groups was 5.6% and 12%, respectively.

In their comparative study of epi-on versus epi-off (18 patients in each group), Erlasan et al.[61] reported that all keratometry readings in the epi-off group improved but remained unchanged or deteriorated in epi-on group during the 24-month follow-up. While there were no complications in the epi-on group, slight corneal opacities occurred in the epi-off group 5(28%). Keratoconus stabilized or improved in 94.4% of patients in the epi-off group compared to 66.6% in the epi-on group. Nath et al.[62] reviewed twelve studies (966 eyes) and found statistically significant difference between transepithelial and epithelium-off cross--linking groups in K max change at 12 months (MD, 0.75; 95% CI, 0.23–1.28; $P = 0.004$; primary outcome) and at longest follow-up (MD, 1.20; 95% CI, 0.62–1.77; $P < 0.001$; secondary outcome) after treatment. The effectiveness of transepithelial cross-linking is lower compared to the epithelium-off method, although it is significantly safer.

2.8. Iontophoretic crosslinking protocols

The process of iontophoresis uses a small electrical current to help chemicals penetrate tissue. Iontophoresis increases the penetration of riboflavin, a negatively charged, water-soluble molecule with a molecular weight of 376.40 g/mol.[63] In a study evaluating the effects of iontophoretic cross-linking in 20 eyes (15 patients) and using the standard epi-off cross-linking in 20 patients (13 eyes), Buzonetti et al.[64] reported that iontophoresis CXL halted progression in only 50% of the eyes, but epi-off-crosslinking in 75% of the eyes.

Thirteen children (13 eyes) with progressive keratoconus treated with corneal iontophoretic transepithelial crosslinking were followed up for 18 months by Magli et al.[65] They noted a stabilization of keratometry measurements as well as a stabilization of uncorrected and best-corrected visual acuity. They concluded that this technique was successful in halting the progression of keratoconus over the course of the study. Table 1 summarizes the results of numerous studies of pediatric keratoconus using different procedures and treatment settings.[66–90]

2.9. Novel cross-linking protocols

Crosslinking of corneal collagen is a photoactive process using riboflavin and exposure to UV light that increases the biomechanical strength of the cornea. The underlying biochemical changes are similar to photodynamic therapy. Both of these treatments produce highly reactive oxygen species that lead to the formation of new cross-links in the

Table 1
Pediatric corneal crosslinking: Outcome of various protocols.

Study	Design	Age (years)	No. of eyes	Protocol	Vehicle	UVA irradiation (mW/cm^2) x period (min)	Outcome	Follow-up (months)
Arora et al. 2012 [70]	P	10–15	15	C	Dx	3 × 30	Stabilization Safe & Effective	12
Vinciguerra et al.2012 [71]	P	9–18	40	C	Dx	3 × 30	Stabilization Improved UCVA, BSCVA	24
Caporossi et al.2012 [72]	P	10–18	56	C	Dx	3 × 30	Stabilization. No stat sig diff b/w < 450, >450 μm.	36
Viswanathan et al.2014 [73]	P	8–17	25	C	Dx	3 × 30	Stabilization + Effective	20
Kodavoor et al. 2014 [74]	R	9–16	35	C	Dx	3 × 30	Stabilization (86%)	12
Soeters et al.2014 [30]	R	12–17	31	C	–	3 × 30	Improvement, Pediatric & Adults equally safe	12
Godefrooij et al.2016 [49]	P	11–17	54	C	Dx	3 × 30	Safe & Effective Progression in 22% eyes (Paracentral Cone)	60
Sarac et al.2016 [75]	R	9–17	72	C	Dx	3 × 30	In Paracentral cone, Thin CCT<450 μm; -Kmax more likely to progress	24
Ucakhan et al.2016 [52]	P	10–18	40	C	Dx	3 × 30	Kmax decreased from 58.4 ± 5.5D to 57 ± 5.3D	48
Wise et al.2016 [76]	R	11–18	39	C	–	3 × 30	Safe, Halts Progression	12
Zotta et al.2017 [51]	P	10–17	20	C	Dx	3 × 30	Safe, Halts Progression	96
Padmanabhan et al.2017 [50]	R	8–18	194	C	–	3 × 30	Kmax decreased at 4 yrs in 76%, CDVA stabilization/ improve in 69.1%	80
Henriquez et al.2018. [77]	P	10–17	26	C	Dx	3 × 30	Safe, Halts Progression. Progress in 23.07%	36
Mazzotta et al.2018 [53]	P	8–18	62	C	Dx	3 × 30	KC stabilization in 80%	120
Barbisan et al. 2020 [79]	R	10–16	105	C	–	3 × 30	No diff pediatric & elder group.	12
Shetty et al. 2014 [81]	P	11–14	30	A	Dx	9 × 10	ACXL safe & effective. Careful management of VKC for progression.	24
Badawi 2017[82]	P	8–15	33	A	HP	10 × 9	ACXL safe & effective. Improvement in UCVA, BCVA, K reading.	12
Agca et al. [83]	R	12–17	30/ 113	A	Dx	30 × 4/18 × 5	ACXL safe & effective Increased Irradiation, Decreased Time > Decreased Effect on Topography	60
McAnena & O'Keefe 2015 [84]	R	13–18	25	C / A	Dx/HP	3 × 30/30 × 4	Stable UCVA, K values, Refractive indices Improved BCVA	36
Henriquez et al.2017 [60]	P	8–16	25/36	C / A	Dx/HP	3 × 30/18 × 5	Both Epi-On & Epi-Off Safe & Effective for stopping progression	12
Sarac et al.2018 [59]	R	10–17	38/49	C / A	Dx/Dx	3 × 30/9 × 10	ACXL more beneficial than Standard CXL	24
Eissa et al.2019 [58]	P	9–16	68/68	C / A	Dx/Dx	3 × 30/18 × 5	Both ACXL, Std. CXL beneficial, No progression seen	36
Amer et al.2020 [85]	P	12–18	34/34	C / A	HPMC	3 × 30/9 × 10	Std. CXL > Better than ACXL in K reading, post Op. thinnest CT	36
Buzzonetti & Petrocelli 2012. [86]	P	8–18	13	TE	Trom	3 × 30	TE-CXL Safe. Not as effective as Std. CXL	18
Tian et al. 2018[87]	R	12–17	18	TE	HP	45 × 5/45 × 3	ATE-CXL safe & effective.	12
Magli et al.2013 [88]	P	12–17	23/16	C / TE	Dx	3 × 30/3 × 30	TE-CXL safer, similar effectiveness, less painful, less complications than Std. CXL.	12
Eraslan et al. 2017 [61]	P	12–18	18/18	C / TE	Dx/Dx	3 × 30/3 × 30	Efficacy of Epi-on 0.70 of the efficacy of epi-off CXL	24
Henriquez et al.2020 [89]	P	8–17	46/32	C / TE	Dx/HP	3 × 30/18 × 5	Epi-off CXL safer and more effective compared to A-*epi*-on CXL	60
Buzzonetti 2019 [64]	R	9–18	20/20	C / I-ON TE	Dx/ Trom	3 × 30/10 × 9	Epi-off CXL halted KC progression in 75% eyes, whereas I-ON CXL in 50% of eyes,	36
Iqbal et al.2020 [90]	P	9–17	91/ 92/88	C / TE	Dx/HP/ HP	3 × 30/30 × 4/45 × 2	SCXL was more effective for pediatric KC and achieved greater stability than ACXL or TE-CXL, and ACXL was superior to TE-CXL	24

(Study design: Prospective = P, Retrospective = R, Not described '-'; Vehicles: Dx = dextran, HP= HPMC, Trom = Trometamol. Protocols: Conventional = C, Accelerated CXL = A, Trans-Epithelial CXL = TE, Accelerated Trans-Epithelial CXL = ATE, Iontophoretic transepithelial corneal cross-linking = I-ON).

extracellular matrix. The increased number of cross-links improves the mechanical strength and stability of the corneal tissue.[91] Supplemental oxygen increases oxygen availability during the corneal cross-linking process. At higher irradiance levels, supplemental oxygen is beneficial and eliminates relative oxygen starvation, allowing for potentially more efficient crosslinking.[92] The higher oxygen availability in thin corneas may increase the overall efficacy of riboflavin UV-A CXL compared to standard thickness corneas. Clinical protocols for thin corneas should be revised to implement these results.[93]

Partial de-epithelialization method in which central 3.0 mm of corneal epithelium was kept intact and paracentral corneal epithelium was removed. The authors found that keeping the central corneal epithelium intact was not beneficial for reducing corneal opacity, but this method resulted in better improvement in corrected vision. The total epithelium off technique resulted in better improvement in K-max and Q-value.[94]

Accelerated CXL was developed to achieve shorter treatment times by increasing the intensity of the U V light accordingly. Another way to

compensate for the relative lack of oxygen at high irradiance is to use pulsed light.[95] The authors found that the pulsed light accelerated CXL protocol was less harmful and more effective in inducing changes than the continuous light accelerated CXL protocol in rabbit corneas.[96]

SimLC is an acronym for Simultaneous Laser Cross-linking, introduced to distinguish it from Topography-Guided Photorefractive Keratectomy plus CXL (CXL Extra). The main difference is that in SimLC, the topography-guided element is always the only treatment given with no intention of correcting refractive errors. It is made very clear to the patient that the treatment is not aimed at eliminating their need to wear glasses or improving their uncorrected vision. The treatment aims to improve the corneal shape before it is stabilized with CXL and thus improve best corrected visual acuity (BCVA) and quality of vision.[97]

The newer protocols using hypoosmolar riboflavin and accelerated CXL can be used reliably with reasonable results and are on par with the conventional technique.[98]

Contact lens-assisted corneal cross-linking (CACXL) has been introduced to treat thin keratoconic corneas with riboflavin-impregnated soft contact lenses to artificially increase functional corneal thickness. It is advantageous over other thin corneal cross-linking protocols because it works independently of corneal swelling. Because it is an epi-off technique, no additional time, expensive equipment, or special riboflavin solutions are required.[99]

Intraoperative increase in corneal thickness using a lenticle obtained from the SMILE procedure allows for safe and effective CXL. This procedure has been successfully performed in combination with intracorneal ring segments in ultrathin corneas. This allows the corneal surgeon to avoid, or at least postpone, more invasive surgical procedures, lamellar keratoplasty for visual rehabilitation in such eyes.[100]

2.10. Crosslinking combined with refractive surgery

Crosslinking is used in conjunction with refractive surgery to halt the progression of keratoconus and improve visual and refractive outcomes. Kanellopoulos et al.[66] reported 4-year follow-up results of topography-guided photorefractive keratectomy combined with cross-linking (Athens Protocol) in 39 eyes of 21 pediatric patients. Uncorrected and corrected distance vision improved significantly while keratometer readings decreased. They concluded that the Athens regimen is a safe and effective long-term treatment option for children with keratoconus.

In a study, 67 eyes of 37 children with pediatric keratoconus, were treated with combined crosslinking with intracorneal ring segments using a femtosecond laser. They reported a significant improvement in uncorrected and best-corrected visual acuity and mean spherical equivalent refraction. There were 4 cases (6.4%) of keratoconus progression. They advocated epi-off as the preferred treatment for the future.[67]

2.11. Status of Re-corneal collagen crosslinking in children

Repeated collagen cross-linking has been reported to be successful for progression of keratoconus after primary collagen crosslinking. Wu et al.[101] evaluated the safety and efficacy of repeat corneal collagen cross-linking assisted by double-cycle transepithelial iontophoresis (DI-CXL) in the treatment of keratoconus progression after primary CXL. They excluded patients with a thinnest pachmeter reading of less than 380 μm. They found DI-CXL to be a safe and effective alternative for stabilizing keratoconus progression after primary CXL.[101]

2.12. Complications

Cross-linking collagen seems to have a favourable safety profile, and there have not been many reports of problems in children with keratoconus. Microbial keratitis, one of the more devastating complications, has been reported in epi-off crosslinking, transepithelial and accelerated protocols. Steinwender et al.[68] reported a comparable complication rate for keratoconus in adults (103 eyes) versus children (30 eyes) over a 6-year period. They reported complications in 2 eyes, both in pediatric groups: severe bacterial keratitis 3 days postoperatively in a 15-year-old and infectious crystalline keratopathy 3 weeks postoperatively in a 16-year-old patient. None of the adult patients developed infectious keratitis. Therefore, it is important to emphasize this issue to parents or caregivers as they are believed to be linked to compliance-related concerns in this demographic. The parents should be shown the exact method of drop instillation. Parents need to be warned that they should ensure that the child does not touch or rub the eyes. After various therapies, it has been observed that children may experience a transient moderate opacity that resolves with topical steroid treatment in most cases, while it may persist in 3% of patients.[49]

In 532 eyes subjected to rapid crosslinking, Maharana et al.[69] reported 7 (0.01%) subjects with a mean age of 11 years (range 8–17) who developed microbial keratitis. Vernal keratoconjunctivitis was also present in 3 of the cases, and the median time to onset of infection was three days after surgery. First, they were treated empirically using a tailor-made approach and later treatment was modified based on the microbiological findings. However, one of the patients required therapeutic penetrating keratoplasty due to a corneal perforation.

The potential effects of cross-linking treatment on the limbus (limbal stem cells and limbal niche) are not fully understood. It is important to study the effect of UV exposure on the limbal niche, particularly since UV is known to be mutagenic to cellular DNA and ocular surface tumors can develop in the limbus.[102] Protection of the limbus from UV rays during CXL surgery has been a concern.[103] The use of a PMMA shield to protect the limbal stem cells has not been included as a standard of care in the corneal collagen cross-linking procedure.

Sharma et al.[104] reported persistent corneal edema in 10 patients requiring penetrating keratoplasty. Other findings were: deep vascularization (2 eyes; 20%), iris atrophy (6 eyes; 60%), pigment dispersion (5 eyes; 50%), persistent epithelial defect (3 eyes; 30%), and infectious keratitis (1 eye; 10%). Penetrating keratoplasty was offered to 5 patients when improvement plateaued at 3 months, but only 2 patients underwent penetrating keratoplasty. CXL is a safe and effective procedure with few known side effects. This case series reports the possibility of damage to the corneal endothelium with visually significant corneal edema after CXL treatment.

3. Conclusions

In children with keratoconus, progression is more likely and progression occurs more quickly. Due to the aggressive nature of the disease in pediatric patients, early and efficient therapy is required to halt its progression. Therefore, CXL should be considered immediately. The usual CXL "Dresden Protocol" should be applied with the epithelium off. For kids who are less cooperative, accelerated CXL may be recommended. Even though it is less effective, *trans*-epithelial CXL is safer and may be performed on patients who require repeated corneal collagen crosslinking. Parents of children with aggressive keratoconus should get counselling regarding side effects, temporary challenges, and the need for repeat therapy.

4. Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients or animals was conducted with

the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: AS, RS, VSN; Data collection: RS, PP, VKV; Analysis and interpretation of results: RS, PP, AS, VKV; Drafting the manuscript: AS, PP, VSN; All authors reviewed the results and approved the final version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Thanks to all the peer reviewers for their opinions and suggestions.

Abbreviations

CXL	Cornea Croos-Linking
UV-A	Ultraviolet A rays
Epi-Off	Epithelium off

References

1. Rabinowitz YS. *Keratoconus. Surv Ophthalmol.* 1998;42(4):297–319. https://doi.org/10.1016/S0039-6257(97)00119-7.
2. Beckman KA, Gupta PK, Farid M, et al. Corneal crosslinking: current protocols and clinical approach. *J Cataract Refract Surg.* 2019;45(11):1670–1679. https://doi.org/10.1016/j.jcrs.2019.06.027.
3. Davis LJ, Schechtman KB, Wilson BS, et al. Longitudinal changes in visual acuity in keratoconus. *Invest Ophthalmol Vis Sci.* 2006;47(2):489–500. https://doi.org/10.1167/iovs.05-0381.
4. Subasinghe SK, Ogbuehi KC, Dias GJ. Current perspectives on corneal collagen crosslinking (CXL). *Graefes Arch Clin Exp Ophthalmol.* 2018;256(8):1363–1384. https://doi.org/10.1007/s00417-018-3966-0.
5. Diakonis VF, Shehadeh M. Corneal cross linking in pediatric keratoconus. In: Barbara A, ed. *Controversies in the Management of Keratoconus*. Cham: Springer; 2018:159–165. https://doi.org/10.1007/978-3-319-98032-4_13.
6. McAnena L, Doyle F, O'Keefe M. Cross-linking in children with keratoconus: a systematic review and meta-analysis. *Acta Ophthalmol.* 2017;95(3):229–239. https://doi.org/10.1111/aos.13224.
7. Javadi MA, Motlagh BF, Jafarinasab MR, et al. Outcomes of penetrating keratoplasty in keratoconus. *Cornea.* 2005;24:941–946. https://doi.org/10.1097/01.ico.0000159730.45177.cd.
8. Mamalis N, Anderson CW, Kreisler KR, et al. Changing trends in the indications for penetrating keratoplasty. *Arch Ophthalmol.* 1992;110:1409–1411. https://doi.org/10.1001/archopht.1992.01080220071023.
9. Shehadeh MM, Diakonis VF, Jalil SA, et al. Prevalence of keratoconus among a palestinian tertiary student population. *Open Ophthalmol J.* 2015;9:172–176. https://doi.org/10.2174/1874364101509010172.
10. Hashemi H, Beiranvand A, Khabazkhoob M, et al. Prevalence of keratoconus in a population-based study in Shahroud. *Cornea.* 2013;32:1441–1445. https://doi.org/10.1097/ICO.0b013e3182a0d014.
11. Godefrooij DA, de Wit GA, Uiterwaal CS, et al. Age-specific incidence and prevalence of keratoconus: a nationwide registration study. *Am J Ophthalmol.* 2017;175:169–172. https://doi.org/10.1016/j.ajo.2016.12.015.
12. Jonas JB, Nangia V, Matin A, et al. Prevalence and associations of keratoconus in rural Maharashtra in central India: the Central India eye and medical study. *Am J Ophthalmol.* 2009;148(5):760–765. https://doi.org/10.1016/j.ajo.2009.06.024.
13. Millodot M, Shneor E, Albou S, et al. Prevalence and associated factors of keratoconus in Jerusalem: a cross-sectional study. *Ophthalmic Epidemiol.* 2011;18(2):91–97. https://doi.org/10.3109/09286586.2011.560747.
14. Wakend N, Fayad AM, Fadlallah A, et al. Keratoconus screening in Lebanese students' population. *J Fr Ophthalmol.* 2012;35(1):23–29. https://doi.org/10.1016/j.jfo.2011.03.016.
15. Xu L, Wang YX, Guo Y, et al. Prevalence and associations of steep cornea/keratoconus in greater Beijing. The Beijing Eye Study. *PLoS One.* 2012;7(7), e39313. https://doi.org/10.1371/journal.pone.0039313.
16. Hashemi H, Khabazkhoob M, Fotouhi A. Topographic keratoconus is not rare in an Iranian population: the Tehran eye study. *Ophthalmic Epidemiol.* 2013;20(6):385–391. https://doi.org/10.3109/09286586.2013.848458.
17. Shneor E, Millodot M, Gordon-Shaag A, et al. Prevalence of keratoconus among young Arab students in Israel. *Int J KeratoEctatic Corneal Dis.* 2014;3(1):9–14. https://doi.org/10.5005/jp-journals-10025-1070.
18. Kaya V, Karakaya M, Utine CA. Evaluation of the corneal topographic characteristics of keratoconus with orbscan II in patients with and without atopy. *Cornea.* 2007;26(8):945–948. https://doi.org/10.1097/ICO.0b013e3180de1e04.
19. Cingu AK, Cinar Y, Turkcu FM, et al. Effects of vernal and allergic conjunctivitis on severity of keratoconus. *Int J Ophthalmol.* 2013;6(3):370–374. https://doi.org/10.3980/j.issn.2222-3959.2013.03.21.
20. Naderan M, Rajabi MT, Zarrinbakhsh P. Effect of allergic diseases on keratoconus severity. *Ocul Immunol Inflamm.* 2017;25(3):418–423. https://doi.org/10.3109/09273948.2016.1145697.
21. Jafri B, Lichter H, Stulting RD. Asymmetric keratoconus attributed to eye rubbing. *Cornea.* 2004;23(6):560–564. https://doi.org/10.1097/01.ico.0000121711.58571.8d.
22. Wisse RP, Kuiper JJ, Gans R, et al. Cytokine expression in keratoconus and its corneal microenvironment: a systematic review. *Ocul Surf.* 2015;13(4):272–283. https://doi.org/10.1016/j.jtos.2015.04.006.
23. Lema I, Duran JA. Inflammatory molecules in the tears of patients with keratoconus. *Ophthalmology.* 2005;112(4):654–659. https://doi.org/10.1016/j.ophtha.2004.11.050.
24. Pearson AR, Soneji B, Sarvananthan N, et al. Does ethnic origin influence the incidence or severity of keratoconus? *Eye.* 2000;14(Pt 4):625–628. https://doi.org/10.1038/eye.2000.154.
25. Mukhtar S, Ambati BK. Pediatric keratoconus: a review of the literature. *Int Ophthalmol.* 2018;38(5):2257–2266. https://doi.org/10.1007/s10792-017-0699-8.
26. Perez-Straziota C, Gaster RN, Rabinowitz YS. Corneal cross-linking for pediatric keratcoconus review. *Cornea.* 2018;37(6):802–809. https://doi.org/10.1097/ICO.0000000000001579.
27. Olivo-Payne A, Abdala-Figuerola A, Hernandez-Bogantes E, et al. Optimal management of pediatric keratoconus: challenges and solutions. *Clin Ophthalmol.* 2019;13:1183–1191. https://doi.org/10.2147/OPTH.S183347.
28. Wang Y, Rabinowitz YS, Rotter JI, et al. Genetic epidemiological study of keratoconus: evidence for major gene determination. *Am J Med Genet.* 2000;93:403–409. PMID: 10951465.
29. Olivares Jimenez JL, Guerrero Jurado JC, Bermudez Rodriguez FJ, et al. Keratoconus: age of onset and natural history. *Optom Vis Sci.* 1997;74:147–151. https://doi.org/10.1097/00006324-199703000-00025.
30. Soeters N, van der Valk R, Tahzib NG. Corneal cross-linking for treatment of progressive keratoconus in various age groups. *J Refract Surg.* 2014;30:454–460. https://doi.org/10.3928/1081597X-20140527-03.
31. Sabti S, Tappeiner C, Frueh BE. Corneal cross-linking in a 4-year-old child with keratoconus and Down syndrome. *Cornea.* 2015;34:1157–1160. https://doi.org/10.1097/ICO.0000000000000491.
32. Leoni-Mesplie S, Mortemousque B, Mesplie N, et al. Epidemiological aspects of keratoconus in children. *J Fr Ophtalmol.* 2012a;35:776–785. https://doi.org/10.1016/j.jfo.2011.12.012.
33. Balasubramanian SA, Pye DC, Willcox MD. Effects of eye rubbing on the levels of protease, protease activity and cytokines in tears: relevance in keratoconus. *Clin Exp Optom.* 2013;96:214–218. https://doi.org/10.1111/cxo.12038.
34. Tuft SJ, Moodaley LC, Gregory WM, et al. Prognostic factors for the progression of keratoconus. *Ophthalmology.* 1994;101:439–447. https://doi.org/10.1016/s0161-6420(94)31313-3.
35. Reeves SW, Stinnett S, Adelman RA. Risk factors for progression to penetrating keratoplasty in patients with keratoconus. *Am J Ophthalmol.* 2005;140(4):607–611. https://doi.org/10.1016/j.ajo.2005.05.029.
36. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric [corrected] corneal collagen cross-linking in children and adolescents [published correction appears in J Refract Surg. 2013 Jan;29(1):72]. *J Refract Surg.* 2012;28(11):753–758. https://doi.org/10.3928/1081597X-20121011-01.
37. Vanathi M, Panda A, Vengayil S, et al. Pediatric keratoplasty. *Surv Ophthalmol.* 2009;54(2):245–271. https://doi.org/10.1016/j.survophthal.2008.12.011.
38. Subasinghe SK, Ogbuehi KC, Dias GJ. Current perspectives on corneal collagen crosslinking (CXL). *Graefes Arch Clin Exp Ophthalmol.* 2018;256(8):1363–1384. https://doi.org/10.1007/s00417-018-3966-0.
39. Sorkin N, Varssano D. Corneal collagen crosslinking: a systematic review. *Ophthalmologica.* 2014;232(1):10–27. https://doi.org/10.1159/000357979.
40. Sung HW, Chang WH, Ma CY, et al. Crosslinking of biological tissues using genipin and/or carbodiimide. *J Biomed Mater Res.* 2003;64(3):427–438. https://doi.org/10.1002/jbm.a.10346.
41. McKay TB, Priyadarsini S, Karamichos D. Mechanisms of collagen crosslinking in diabetes and keratoconus. *Cells.* 2019;8(10):1239. https://doi.org/10.3390/cells8101239. Published 2019 Oct 11.
42. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135:620–627. https://doi.org/10.1016/s0002-9394(02)02220-1.
43. Suri K, Hammersmith KM, Nagra PK. Corneal collagen cross-linking: ectasia and beyond. *Curr Opin Ophthalmol.* 2012;23(4):280–287. https://doi.org/10.1097/ICU.0b013e328354865e.

44. Léoni-Mesplié SMB, Touboul D, et al. Scalability and severity of kertoconus in children. *Am J Ophthalmol*. 2012;154(1):56–62. https://doi.org/10.1016/j.ajo.2012.01.025.
45. Kankariya VP, Kymionis GD, Diaknois VF, et al. Management of pediatric keratoconus—evolving role of corneal collagen cross-linking: an update. *Indian J Ophthalmol*. 2013;61(8):435–440. https://doi.org/10.4103/0301-4738.116070.
46. Hamada S, et al. Corneal cross-linking in children. In: Sinjab M, Cummings A, eds. *Corneal Collagen Cross Linking*. Cham: Springer; 2017:229–268. https://doi.org/10.1007/978-3-319-39775-7_8.
47. Lalgudi VG, Nischal KK. Pediatric corneal collagen cross-linking for keratoconus: not an experimental procedure. *J AAPOS*. 2019;23(2):63–65. https://doi.org/10.1016/j.jaapos.2018.12.001.
48. Öö Uçakhan, Celik Buyuktepe T, Yavuz Z, et al. Pediatric versus adult corneal collagen crosslinking: long-term visual, refractive, tomographic and aberrometric outcomes. *Curr Eye Res*. 2021;46(1):14–22. https://doi.org/10.1080/02713683.2020.1782940.
49. Godefrooij DA, Soeters N, Imhof SM, et al. Corneal cross-linking for pediatric keratoconus: long-term results. *Cornea*. 2016;35(7):954–958. https://doi.org/10.1097/ICO.0000000000000819.
50. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, et al. Corneal collagen cross-linking for keratoconus in pediatric patients-long term results. *Cornea*. 2017;36(2):138–143. https://doi.org/10.1097/ICO.0000000000001102.
51. Zotta PG, Diakonis VF, Kymionis GD, et al. Long-term outcomes of corneal cross-linking for keratoconus in pediatricpatients. *J AAPOS*. 2017;21(5):397–401. https://doi.org/10.1016/j.jaapos.2017.07.205.
52. Öö Uçakhan, Bayraktutar BN, Saglik A. Pediatric corneal collagen cross-linking: long-term follow-up of visual, refractive, and topographic outcomes. *Cornea*. 2016;35(2):162–168. https://doi.org/10.1097/ICO.0000000000000702.
53. Mazzotta C, Traversi C, Baiocchi S, et al. Corneal collagen crosslinking with riboflavin and ultraviolet a light for pediatric keratoconus:ten-year results. *Cornea*. 2018;37(5):560–566. https://doi.org/10.1097/ICO.0000000000001505.
54. Raiskup F, Theuring A, Pillunat LE, et al. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg*. 2015;41(1):41–46. https://doi.org/10.1016/j.jcrs.2014.09.033.
55. Nicula C, Nicula D, Pop RN. Results at 7 years after cross-linking procedure in keratoconic patients. *J Fr Ophtalmol*. 2017;40(7):535–541. https://doi.org/10.1016/j.jfo.2017.03.003.
56. 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;52:9048–9052. https://doi.org/10.1167/iovs.11-7818.
57. Nicula CA, Rednik AM, Bulboacă AE, et al. Comparative results between "Epi-Off" conventional and accelerated corneal collagen crosslinking for progressive keratoconus in pediatric patients. *Therapeut Clin Risk Manag*. 2019;15:1483–1490. https://doi.org/10.2147/TCRM.S224533.
58. Eissa SA, Yassin A. Prospective, randomized contralateral eye study of accelerated and conventional corneal cross-linking in pediatric keratoconus. *Int Ophthalmol*. 2019;39(5):971–979. https://doi.org/10.1007/s10792-018-0898-y.
59. Sarac O, Caglayan M, Uysal BS, et al. Accelerated versus standard corneal collagen cross-linking in pediatric keratoconus patients: 24 months follow-up results. *Contact Lens Anterior Eye*. 2018;41(5):442–447. https://doi.org/10.1016/j.clae.2018.06.001.
60. Henriquez MA, Rodríguez AM, Izquierdo L Jr. Accelerated epi-on versus standard epi-off corneal collagen cross-linking for progressive keratoconus in pediatric patients. *Cornea*. 2017;36(12):1503–1508. https://doi.org/10.1097/ICO.0000000000001366.
61. Eraslan M, Toker E, Cerman E. Efficacy of epithelium-off and epithelium-on corneal collagen cross-linking in pediatric keratoconus. *Eye Contact Lens*. 2017;43(3):155–161. https://doi.org/10.1097/ICL.0000000000000255.
62. Nath S, Shen C, Koziarz A, et al. Transepithelial versus epithelium-off corneal collagen cross-linking for corneal ectasia: a systematic review and meta-analysis. *Ophthalmology*. 2021 Aug;128(8):1150–1160. https://doi.org/10.1016/j.ophtha.2020.12.023. Epub 2020 Dec 28. PMID: 33383093.
63. Vinciguerra P, Rechichi M, Rosetta P, et al. High fluence iontophoretic corneal collagen cross-linking: in vivo OCT imaging of riboflavin penetration. *J Refract Surg*. 2013;29(6):376–377. https://doi.org/10.3928/1081597X-20130509-01.
64. Buzzonetti L, Petrocelli G, Valente P, et al. Iontophoretic transepithelial collagen cross-linking versus epithelium-off collagen cross-linking in pediatric patients: 3-year follow-up. *Cornea*. 2019;38(7):859–863. https://doi.org/10.1097/ICO.0000000000001965.
65. 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(4):585–590. https://doi.org/10.1007/s10792-015-0166-3.
66. Kanellopoulos AJ, Vingopoulos F, Sideri AM. Long-term stability with the Athens protocol (Topography-Guided partial PRK combined with cross-linking) in pediatric patients with keratoconus. *Cornea*. 2019;38(8):1049–1057. https://doi.org/10.1097/ICO.0000000000001996.
67. Iqbal M, Elmassry A, Tawfik A, et al. Analysis of the outcomes of combined cross-linking with intracorneal ring segment implantation for the treatment of pediatric keratoconus. *Curr Eye Res*. 2019;44(2):125–134. https://doi.org/10.1080/02713683.2018.1540706.
68. Steinwender G, Pertl L, El-Shabrawi Y, et al. Complications from corneal cross-linking for keratoconus in pediatric patients. *J Refract Surg*. 2016;32(1):68–69. https://doi.org/10.3928/1081597X-20151210-03.
69. Maharana PK, Sahay P, Sujeeth M, et al. Microbial keratitis after accelerated corneal collagen cross-linking in keratoconus. *Cornea*. 2018;37(2):162–167. https://doi.org/10.1097/ICO.0000000000001439.
70. Arora R, Gupta D, Goyal JL, et al. Results of corneal collagen cross-linking in pediatric patients. *J Refract Surg*. 2012;28:759–762. https://doi.org/10.3928/1081597X-20121011-02.
71. Vinciguerra P, Albé E, Frueh BE, et al. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. *Am J Ophthalmol*. 2012;154:520–526. https://doi.org/10.1016/j.ajo.2012.03.020.
72. Caporossi A, Mazzotta C, Baiocchi S, et al. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. *Cornea*. 2012;31:227–231. https://doi.org/10.1097/ICO.0b013e31822159f6.
73. Viswanathan D, Kumar NL, Males JJ. Outcome of corneal crosslinking for progressive keratoconus in paediatric patients. *BioMed Res Int*. 2014;2014, 140461. https://doi.org/10.1155/2014/140461.
74. Kodavoor KS, Ariswala AZ, Ramamurthy D. One year clinical study of efficacy of corneal cross-linking in Indian children with progressive keratoconus. *Cornea*. 2014;33(9):919–922. https://doi.org/10.1097/ICO.0000000000000197.
75. 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;35:1503–1507. https://doi.org/10.1097/ICO.0000000000001051.
76. Wise S, Diaz C, Termote K, et al. Corneal cross-linking in pediatric patients with progressive keratoconus. *Cornea*. 2016;35:1441–1443. https://doi.org/10.1097/ICO.0000000000000923.
77. Henriquez MA, Villegas S, Rincon M, et al. Long-term efficacy and safety after corneal crosslinking in pediatric patients: three-year follow-up. *Eur J Ophthalmol*. 2018;28:415–418. https://doi.org/10.1177/1120672118760149.
78. 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;37:1013–1017. https://doi.org/10.1097/ICO.0000000000001629.
79. Barbisan PR, Pinto RD, Gusmão CC, et al. Corneal collagen cross-linking in young patients for progressive keratoconus. *Cornea*. 2020;39:186–191. https://doi.org/10.1097/ICO.0000000000002130.
80. Ozgurhan EB, Kara N, Cankaya KI, et al. Accelerated corneal cross-linking in pediatric patients with keratoconus: 24-month outcomes. *J Refract Surg*. 2014;30:843–849. https://doi.org/10.3928/1081597X-20141120-01.
81. 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. https://doi.org/10.1155/2014/894095.
82. Badawi AE. Accelerated corneal collagen cross-linking in pediatric keratoconus: one year study. *Saudi J Ophthalmol*. 2017;31:11–18. https://doi.org/10.1016/j.sjopt.2017.01.002.
83. Agca A, Tulu B, Yasa D, et al. Accelerated corneal crosslinking in children with keratoconus: 5-year results and comparison of 2 protocols. *J Cataract Refract Surg*. 2020;46:517–523. https://doi.org/10.1097/j.jcrs.0000000000000101.
84. McAnena L, O'Keefe M. Corneal crosslinking in children with keratoconus. *J AAPOS*. 2015;19:228–232. https://doi.org/10.1016/j.jaapos.2015.02.010.
85. Amer I, Elaskary A, Mostafa A, et al. Long-term visual, refractive and topographic outcomes of "epi-off" corneal collagen cross-linking in pediatric keratoconus: standard versus accelerated protocol. *Clin Ophthalmol*. 2020;14:3747–3754. https://doi.org/10.2147/OPTH.S275797.
86. Buzzonetti L, Petrocelli G. Transepithelial corneal cross-linking in pediatric patients: early results. *J Refract Surg*. 2012;28:763–767. https://doi.org/10.3928/1081597X-20121011-03.
87. 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. https://doi.org/10.1186/s12886-018-0739-9.
88. Magli A, Forte R, Tortori A, et al. Epithelium-off corneal collagen cross-linking versus transepithelial cross-linking for pediatric keratoconus. *Cornea*. 2013;32:597–601. https://doi.org/10.1097/ICO.0b013e31826cf32d.
89. Henriquez MA, Hernandez-Sahagun G, Camargo J. Accelerated epi-on versus standard epi-off corneal collagen cross-linking for progressive keratoconus in pediatric patients: five years of follow-up. *Cornea*. 2020;39:1493–1498. https://doi.org/10.1097/ICO.0000000000002463.
90. Iqbal M, Elmassry A, Saad H, et al. Standard cross-linking protocol versus accelerated and transepithelial cross-linking protocols for treatment of paediatric keratoconus: a 2-year comparative study. *Acta Ophthalmol*. 2020;98:e352–e362. https://doi.org/10.1111/aos.14275.
91. Choi S, Shin JH, Cheong Y, et al. Structural and biomechanical effects of photooxidative collagen cross-linking with photosensitizer riboflavin and 370 nm UVA light on human corneoscleral tissues. *Microsc Microanal*. 2013;19(5):1334–1340. https://doi.org/10.1017/S1431927613001669.
92. Seiler TG, Komninou MA, Nambiar MH, et al. Oxygen kinetics during corneal cross-linking with and without supplementary oxygen. *Am J Ophthalmol*. 2021 Mar;223:368–376. https://doi.org/10.1016/j.ajo.2020.11.001. Epub 2020 Nov 21. PMID: 33227242.
93. Kling S, Richoz O, Hammer A, et al. Increased biomechanical efficacy of corneal cross-linking in thin corneas due to higher oxygen availability. *J Refract Surg*. 2015 Dec;31(12):840–846. https://doi.org/10.3928/1081597X-20151111-08. PMID: 26653730.
94. Razmjoo H, Rahimi B, Kharraji M, et al. Corneal haze and visual outcome after collagen crosslinking for keratoconus: a comparison between total epithelium off and partial epithelial removal methods. *Adv Biomed Res*. 2014 Nov 29;3:221. https://doi.org/10.4103/2277-9175.145677. PMID: 25538907; PMCID: PMC4260293.

95. Zhu Y, Reinach PS, Zhu H, et al. Continuous-light versus pulsed-light accelerated corneal crosslinking with ultraviolet-A and riboflavin. *J Cataract Refract Surg*. 2018 Mar;44(3):382–389. https://doi.org/10.1016/j.jcrs.2017.12.028.PMID:29703291.
96. Dervenis N, Dervenis P, Dragoumis N, et al. Accelerated, pulsed collagen cross-linking versus the dresden protocol in keratoconus: a case series. *Med Princ Pract*. 2020;29(4):332–337. https://doi.org/10.1159/000505598. Epub 2020 Feb 4. PMID: 32018247; PMCID: PMC7445675.
97. Cummings AB, Mascharka N. Outcomes after topography-based LASIK and LASEK with the wavelight oculyzer and topolyzer platforms. *J Refract Surg*. 2010;26(7): 478–485. https://doi.org/10.3928/1081597X-20090814-05.
98. Singh T, Taneja M, Murthy S, et al. Evaluation of safety and efficacy of different protocols of collagen cross linking for keratoconus. *Rom J Ophthalmol*. 2020 Apr-Jun;64(2):158–167. PMID: 32685782; PMCID: PMC7339692.
99. Srivatsa S, Jacob S, Agarwal A. Contact lens assisted corneal cross linking in thin ectatic corneas - a review. *Indian J Ophthalmol*. 2020 Dec;68(12):2773–2778. https://doi.org/10.4103/ijo.IJO_2138_20. PMID: 33229652; PMCID: PMC7856986.
100. Sachdev GS, Sachdev R, Sachdev MS. Intra corneal ring segment implantation with lenticule assisted stromal augmentation for crosslinking in thin corneas. *Am J Ophthalmol Case Rep*. 2020 Jun 5;19, 100726. https://doi.org/10.1016/j.ajoc.2020.100726. PMID: 32566797; PMCID: PMC7298359.
101. Wu H, Li L, Luo S, et al. Safety and efficacy of repeated crosslinking assisted by transepithelial double-cycle iontophoresis in keratoconus progression after primary corneal crosslinking. *Eye*. 2021 Nov;35(11):3020–3027. https://doi.org/10.1038/s41433-020-01365-1. Epub 2021 Jan 7. PMID: 33414527; PMCID: PMC8526808.
102. Moore JE, Schiroli D, Moore CB. Potential effects of corneal cross-linking upon the limbus. *BioMed Res Int*. 2016;2016, 5062064. https://doi.org/10.1155/2016/5062064. Epub 2016 Sep 5. PMID: 27689081; PMCID: PMC5027324.
103. Jeyalatha V, Jambulingam M, Gupta N, et al. Study on polymethylmethacrylate ring in protecting limbal stem cells during collagen cross-linking. *Ophthalmic Res*. 2013; 50(2):113–116. https://doi.org/10.1159/000351644. Epub 2013 Jul 17. PMID: 23867297.
104. Sharma A, Nottage JM, Mirchia K, et al. Persistent corneal edema after collagen cross-linking for keratoconus. *Am J Ophthalmol*. 2012 Dec;154(6):922–926. https://doi.org/10.1016/j.ajo.2012.06.005.