Keratoconus in Children

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8.1 Introduction

Keratoconus (KC) in children or pediatric keratoconus is the manifestation of the disease in children or adolescents <18 years of age. It needs to be discussed separately as the disease tends to be aggressive in nature and progression to advanced stages can happen in early years affecting quality of vision and quality of life. Early diagnosis and intervention are key to maintaining good vision and quality of life in children.

8.2 Epidemiology

Keratoconus is not only more aggressive in pediatric age group but also more severe at the time of diagnosis [1]. The younger the child at the time of diagnosis, the more is the risk of rapid progression [2, 3]. This warrants the need of early diagnosis to prevent severe visual damage. Though literature commonly documents puberty as the age at which keratoconus starts, youngest patient of 4 years of age with Down syndrome has been reported by Sabti et al. [4]. The average age of diagnosis is 15 years [5] with male predominance. Greatest incidence has been noted in Middle-Eastern population and India with incidence of 1/2000 cases a year [6]. The Arabs, Indians, and Polynesians are 4.4 times more likely to get affected by KC. This is likely due to higher rate of consanguinity in their population, especially among Muslim community [7]. Greatest severity and incidence of pediatric KC has been reported from Riyadh (prevalence 1.1%) and Saudi Arabia (prevalence 4.4%) [8]. Pearson et al. [9] reported that compared with White patients, Asians have a fourfold increase in incidence, are younger at presentation, and require corneal grafting at an earlier age. KC in children is known to be bilateral but asymmetrical. In unilateral cases, 50% of the uninvolved fellow eye developed the disease within 16 years [10]. Studies used videokeratography in the Middle East and Asia and estimated a prevalence of 0.9–3.3% [11–17]. Children with male predisposition, associated allergies, habitual eye rubbing, and strong family history of keratoconus were more frequently affected with keratoconus [18].

Earlier, KC was documented as a noninflammatory process [6]. However, recent studies have shown increased levels of inflammatory markers like IL-1, IL-6, IL-8, and TNF-α in the tears of patients of keratoconus [19, 20]. There is increased activity of cyclooxygenase activity with ten times increase in PGE2 production, inhibiting fibroblasts from synthesis of collagen, and proliferation and differentiation of myofibroblasts. Also, inhibitors of cysteine proteases were found to be low in the tears of these patients. It

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was the imbalance between activation and inhibition of these cytokines that lead to activation of metalloproteinases and apoptosis of keratocytes [20, 21].

In our experience, we analyzed first visit records of 3316 patients diagnosed with keratoconus based on clinical signs and topography at a tertiary eye center in India, out of which 17.2% were children less than or equal to 16 years. Male-to-female ratio was higher (1.9) compared to individuals more than 16 years of age (1.54). Incidence of allergy and eye rubbing was highest in less than 16 years age group (27.8%) compared to 16–30 years (25%) and more than 30 years age group (17.2%) of patients.

8.3 Genetics

Most of the cases of keratoconus is sporadic, but Kaya et al. has reported incidence of 11% in first-degree relatives of patients with keratoconus [22]. The role of genetics in the disease pathogenesis has been well reflected by ethnic variations [9, 23–25]. Autosomal dominance with incomplete penetrance and autosomal recessive inheritance has also been documented by various studies. Several genetic loci and variants within these genes have been identified to occur in patients with KC. Multiple genome-based studies have been reviewed which mentions at least 19 genes which are associated with development of KC. Of these, LOX at 5q23.2 encoding LOX, lysyl oxidase needs special mention and is implicated in the cross-linking process of elastin and collagen [26]. Authors have also reported association of IL-1 processing and collagen fibril assembly with development of KC [26]. IL1β is implicated in corneal collagen degradation, conversion of plasminogen to plasmin, metalloproteinase 1–3 (MMP-1 and MMP-3), and activation and degradation of collagen in corneal fibroblasts. This further supports an inflammatory etiology for development of KC. Other two loci, Forkhead box protein O1 (FOXO1), and fibronectin type 3 domain containing 3B (FNDC3B) have also been known to increase the risk for KC development [27]. Zinc finger 469 (ZNF469) involved in brittle cornea syndrome type 1, functionally, is known to play a role in the synthesis and/or organization of corneal collagen fibers in conjunction with *PRMD5* [28]. ZNDC3B alleles have been involved in 12.5% European population with KC [29]. Other studies reported contrary results [30]. Thus, the role of ZNDC3B in pathogenesis of KC is controversial. It has been well documented to occur in association with other conditions like Down syndrome, vernal keratoconjunctivitis, Leber congenital amaurosis (LCA), retinitis pigmentosa, Marfan syndrome, and Ehlers-Danlos syndrome.

8.4 Ocular Allergy

Recent studies reported an incidence of 0.61% in children with vernal keratoconjunctivitis [31]. Allergic keratoconjunctivitis and eye rubbing also contribute in increased incidence of corneal hydrops in children with KC [5]. Pediatric patients of KC with VKC undergo more severe and rapid change in corneal topography when compared to children with KC alone suggesting the role of allergic eye condition and eye rubbing with KC progression in children [32]. Eye rubbing and poking have also been postulated to be a cause of KC in children with LCA. Franceschetti's oculodigital sign seen in these children acts as a constant source of corneal trauma and predisposes them to development of KC. Incidence of KC in children with LCA has been reported to be 30% [33]. Habitual eye rubbing has also been blamed to be the cause of KC in children with Down syndrome, with incidence reaching to up to 15% in these patients [34, 35]. When considering atopy, majority of authors have not found significant association of development of KC with atopy, but with eye rubbing [36, 37]. Also, HLA antigen association, particularly HLA-A26, B40, and DR9, has also been found in children with keratoconus as compared to adults [38]. These markers strongly support the genetic association and occurrence of keratoconus in pediatric age group [38]. The effect of androgen in early development and rapid progression of keratoconus has also been described supporting male preponderance in pediatric age group [5].

8.5 Syndromes

Connective tissue disorders with abnormal collagen elasticity like Ehlers-Danlos syndrome and osteogenesis imperfecta and many others show association with KC (Table 8.1). Beckh et al. described three generations of a family with osteogenesis imperfecta to have associated with KC [39]. Various authors have reported the presence of mitral valve prolapse in patients diagnosed with severe KC [40, 41]. Various loci on chromosomes 2, 3, 5, 6, 9, 13, 15, 16, 17, and 20 have been reported to have association with KC [42, 43].

Table 8.1 Keratoconus and syndromic associations

Abnormal collagen elasticity and connective tissue	
Brittle cornea syndrome	Nail patella syndrome
Congenital hip dysplasia	Osteogenesis imperfecta
Joint hypermobility	Ehlers-Danlos syndrome
False chordae tendineae of the left ventricle	Marfan syndrome
Mitral valve prolapse	Pseudoxanthoma elasticum
Oculodigital stimulation with abnormal retinal function	
Albinism	Congenital rubella
Bardet-Biedl syndrome	Leber congenital amaurosis
Neurofibromatosis	Retinitis pigmentosa
Laurence-Moon-Bardet-Biedl syndrome	Cone dystrophy
Tapetoretinal degeneration	Kurz syndrome
Oculodigital stimulation with low mental function	
Apert syndrome	Crouzon syndrome
Angelman syndrome	Hyperornithinemia
Noonan syndrome	
Syndromes associated with eczema and atopy	
Down syndrome	Hyper-IgE syndrome
Ichthyosis	Oculodentodigital syndrome
Turner syndrome	Autographism
Mulvihill-Smith syndrome	

8.6 Risk Factors

In patients with abnormal retinal function, oculodigital stimulation has been reported to be the attributable cause toward development of KC (Table 8.2). This repeated stimulation acts as a source of damage to the corneal epithelium. Expression of lysyl oxidase (LOX) plays a major role in the biogenesis of corneal connective tissue. Its altered activity weakens covalent bonds between collagen and elastin fibrils, causing biomechanical deterioration of the cornea. Abnormal structures were detected within the keratoconic cone, which were reported to be the result of folding or break in the anterior stromal lamellae and eventually led to compromised biomechanical strength of the cornea [44]. On histology, loss of corneal stromal thickness has been reported along with distortion of the cornea due to marked reduction in amount and distribution of collagen fibrils [45]. Takahashi et al. studied quantitative analysis of collagen fibrils and concluded that though these fibrils appeared normal morphologically, the epithelial basement membrane showed fragmentation, Bowman's membrane showed disintegration and fibrillation, and basal epithelial cells showed degenerative changes on electron microscopy [46]. DM ruptures are also seen, and the endothelium, though normal, may have pleomorphism, intracellular dark structures, and elongation of cells in few cases [47].

Gender predilection has been unclear. However, few studies from India concluded male predominance in northern and western part of the country and female prevalence in Central India

Table 8.2 Risk factors in pediatric keratoconus

• Lower thinnest corneal thickness
• Higher average central corneal keratometry
• Increased posterior elevation
• Frequent eye rubbing
• Allergic eye disorders

[11, 48, 49]. The higher prevalence of KC among Indian population has also been attributed to geographical factors like hot weather and sunshine [50]. Also, KC in Indian population tends to present at a younger age, progress rapidly, and are associated with higher need of surgery which can be contributed to rapid progression [48, 50].

Literature also describes factors which reduce the risk of KC. These include smoking and diabetic hyperglycemia [51, 52]. Both of these conditions may increase corneal collagen cross-linking and thus protect the cornea from ectatic changes.

8.7 Clinical Features and Diagnosis

Pediatric KC usually presents as a chronic bilateral progressive corneal ectasia with asymmetric pattern [1]. The clinical features of the disease in children are like that in adults. It is characterized by central or inferior paracentral corneal thinning, loss of biomechanical strength, steepening of the cornea, and irregular corneal astigmatism [53]. Externally, the cone can be visualized as distortion of the lower lid in inferior gaze (Munson's sign) and sharp conical reflection of light on the nasal cornea when light is shone from temporal side (Rizzuti's sign) [54].

On slit lamp, one can identify advanced keratoconus, the margins of the cone with a cobalt blue filter, and the presence of Vogt striae and Fleischer's ring [54, 55]. On retinoscopy, the scissors reflex is a characteristic sign demonstrated due to the irregular astigmatism. Retro illumination can also delineate the size and location of the cone, many times seen as an oil droplet sign (Charleux sign) [54, 55]. There can be associated signs of allergic disease, papillae, giant cobblestone papillae, VKC, conjunctival pigment deposition, Horner-Trantas spots, etc.

Diagnosis can be confirmed by photokeratoscopy or video keratoscopy, showing compression of inferior and central mires, increase in surface corneal keratometry, inferior superior asymmetry, and skewing of steepest radial axes above and below the horizontal meridian [53]. Children with central cones and higher irregular astigmatism leading to blurring of vision tend to present early [56]. They can also present with advanced disease with acute hydrops, which leads to corneal scarring [1, 57]. The cornea tends to flatten after scarring; however, due to the predominant irregular astigmatism, the quality of vision may remain poor despite of the contact lens use. Keratoplasty is the treatment of choice in such cases [58, 59]. It is equally important to differentiate other forms of corneal ectasia or similar clinical features presenting in this age group, for example, keratoglobus which is usually congenital (Table 8.3) [60–65].

According to the Intelligent Sight registry AAO, the prevalence of KC in pediatric population worldwide is 0.16% [66]. The guidelines of AAO Practice Patterns for Pediatric Eye Evaluations and the Corneal Ectasia suggest screening of children for diagnosing keratoconus early [66, 67]. These include children with allergic eye diseases, children with high myopia or myopic astigmatism, children with Down syndrome, children with family history of keratoconus, or children from regions exposed to high UV exposure. A retinoscopy, corneal tomographer, aberrometer, and anterior segment OCT are useful tools that can be used for screening in school children.

In our experience of 3316 patients diagnosed with keratoconus, children in the age group of less than 16 years had an advanced presentation with steeper mean keratometry (50.2 D), thinnest pachymetry (450 μm), and pachymetry at apex (461 μm) compared to other age groups. About 77% of children had asymmetric pattern of presentation at the first visit. The inter-eye asymmetry showed a difference of one to two stages of keratoconus (Amsler-Krumeich classification) at the time of presentation. Overall progression rate of keratoconus in children less than 16 years of age was higher (38.6%) compared to others 16–30 years (22.4%).

Table 8.3 Differential diagnosis for keratoconus and other corneal ectasias

Keratoconus (KC)	Keratoglobus (KG)	Brittle cornea syndrome (BCS)	Terrien's marginal degeneration (TMD)	Pellucid marginal corneal degeneration (PMCD)
Asymmetric bilateral	Symmetric bilateral	Symmetric bilateral	Asymmetric bilateral	Bilateral may be symmetric or asymmetric
Acquired forms—may be associated with congenital and hereditary disorders like Down syndrome	Congenital and acquired forms Acquired forms can represent as a severe manifestation of keratoconus or PMCD	Congenital	Acquired	Acquired Can present along with KC 10% and along with KG 13%. Associated with high astigmatism
First half of second decade, puberty, no gender predilection	Since birth, no gender predilection	Since birth, no gender predilection	Third to fourth decade, no gender predilection	Second to fifth decade, no gender predilection
Inferior paracentral or central corneal stromal thinning	Diffuse corneal involvement	Diffuse corneal involvement with typical blue sclerae and high myopia. Has keratoglobus like corneal picture	Superior stromal thinning with intact epithelium along with pannus and a leading edge of lipid deposition	Crescent-shaped band of inferior corneal thinning approaching 20% of normal thickness that is 1–2 mm in height, 6–8 mm in horizontal extent, and 1–2 mm from the limbus
Isolated or sporadic, multiple genes mapped. For example, LOX at 5q23.2, FOXO1, ZNDC3B	Autosomal recessive	Autosomal recessive. ZNF469 (BCS type 1), PRDM5 gene (BCS type 2)	Isolated	Isolated
Progressive	Nonprogressive	Nonprogressive; associated connective tissue disorders involve musculoskeletal (joint hypermobility), deafness, and cardiovascular manifestations	Usually nonprogressive. The thinning tends to be steeper in the center and slopes toward the periphery	Slowly progressive Unlike KC, area of steepening above the area of ectasia and no Fleischer's ring or Vogt striae
Steepening of the cone, corneal thinning, and irregular astigmatism	Diffuse corneal thinning leading to spontaneous corneal rupture or scarring with trivial trauma	Diffuse corneal thinning leading to spontaneous corneal rupture or scarring with trivial trauma. Scleral rupture and high myopia are also associated	Leads to astigmatism but can be associated with thinning and perforation in rare cases	Progresses slowly leading to irregular astigmatism and corneal protrusion causes vision loss in working age group and is difficult to manage because of the location of ectasia

(continued)

Table 8.3 (continued)

Keratoconus (KC)	Keratoglobus (KG)	Brittle cornea syndrome (BCS)	Terrien's marginal degeneration (TMD)	Pellucid marginal corneal degeneration (PMCD)
Spectacles, contact lenses, collagen cross-linking, keratoplasty (PK, DALK)	Protective glasses or tuck-in/ epi-keratoplasty	Protective glasses	Topical steroids or immunomodulatory treatment, spectacles and contact lenses for astigmatism, patch grafting, or keratoplasty to manage perforations	Treatment is difficult depending on the degree of protrusion. Special contact lenses—toric hydrophilic, hybrid, or RGP
		Epi-keratoplasty		CXL can be done to prevent progression. Needs to be decentered over the inferior band. Large graft (9 mm), keratoplasty, C-shaped lamellar grafts, and crescentric or wedge-shaped resection are some options

8.8 **Adult vs.** Pediatric Keratoconus

Keratoconus in children tends to present earlier, usually in the later part of first decade of life; is more advanced at presentation; has a higher chance of progression, higher incidence of eye rubbing, allergy, and VKC; and is associated with various syndromes when compared to adults (Table 8.4). Although keratoconus presents asymmetrically, the incidence of asymmetry is higher in children [1, 68]. This can lead to early deprivation of vision and amblyopia. Ocular aberrations generated by the irregular cornea may be partially compensated by internal ocular structures and the high accommodative power resulting in parents reporting their children later to the clinic [58]. The cohort of keratoconus in the age group 18–35 years and in adult populations tends toward natural stabilization in third to fourth decade unlike children <18 years age group where the progression can be aggressive. Pediatric keratoconus also has a high incidence of acute hydrops during the follow-up or even at the first visit to the clinic and may need descemetopexy. Higher rates of corneal collagen remodeling were observed in pediatric corneas due to the weak ectatic lamellae which may exceed the capacity of the cross-linking process leading to more rapid ectasia progression and a sevenfold higher risk of needing corneal transplantation [69–71].

Table 8.4 Challenges in pediatric kheratoconus

• Late diagnosis
• Faster progression
• Allergic eye disorders and eye rubbing
• Accurate diagnosis (tomography)
• Follow-ups
• Poor outcomes of conservative approach
• Need of early surgical intervention

When it comes to management, the protocols of treatment remain the same in adults and children. However, Vinciguerra et al. in their study in collagen cross-linking identified that children had faster healing process and recovery in central corneal thickness. Adults did tend to have better morphological and functional outcomes than children, and the keratometry continued to improve beyond 4 years [72, 73]. Chatzis and Hafezi have reported progression at 36 month follow-up in children after cross-linking, which

was not seen in adults, and this could be attributed to the natural cross-linking occurring in corneal stroma in adults [3]. Also in keratoplasty outcomes, pediatric grafts are known to have higher graft failure rates and poor visual outcomes compared to adults [74, 75].

8.9 Treatment

Pediatric KC tends to be advanced and progressive in nature; however, in earlier stages of the disease, spectacles can be prescribed as early as possible to avoid development of amblyopia (if age is <10 years). Due to progression in the irregular astigmatism over time, spectacles fail to deliver the best results, and rigid gas-permeable contact lenses or scleral contact lenses can be tried for visual improvement. However, eye rubbing should be strictly avoided. Eye rubbing, with knuckles, fingertips, sleeping in prone position and side position, dry eyes, screen time, and male sex have been found to be important risk factors in a multivariate analysis study done by Moran et al. and Gatinel et al. [76, 77] VKC and ocular allergy also need to be adequately controlled. Antihistamines (e.g., olopatadine, levocabastine), mast cell stabilizers (e.g., cromolyn sodium, nedocromil), dual-acting agents (e.g., alcaftadine, bepotastine, azelastine, ketotifen), topical immunomodulators (tacrolimus, cyclosporine 0.1% in the USA), and low-dose tapering steroids (loteprednol etabonate, rimexolone, prednisolone) should be given to children, to decrease the severity of allergy and itching [78]. Many physicians prefer to offer early cross-linking as an option in pediatric keratoconus, but ocular allergy should be controlled adequately before planning any surgical intervention or giving a contact lens trial.

8.10 Contact Lens

Various options available for patients with KC include conventional rigid gas-permeable lenses (RGP), piggyback lenses, Rose K lenses, and mini-scleral and scleral lenses. In pediatric KC as the disease tends to be aggressive, one might not be able to achieve correct fit over a long period of time. It is also shown that although it takes additional 15–20 min of sitting time in clinic to train and orient children toward contact lens usage, the complication rate in adults and children associated with CL usage remains the same [79]. Still in the initial stage of disease, soft toric contact lenses (Toric K SiHy) can help improve quality of vision. In the later stages of disease, RGP lenses are preferred [80]. The type of RGP lens to be prescribed depends upon the severity of KC. Mild-to-moderate KC patient can be fitted with monocurve GPs, while more advanced KC does well with bicurve GP lens [81]. In children, RGPs with high oxygen permeability are preferred and need to be replaced frequently.

8.11 Surgical Procedures

8.11.1 Collagen Cross-linking

Collagen cross-linking (CXL) was first described by Wollensak et al. as a technique to arrest the progression of keratoconus in children in 2003. The procedure strengthens collagen fibrils and imparts biomechanical strength by the formation of covalent bonds due to the action of reactive oxygen species like singlet oxygen and superoxide anions released after activation of photosensitive riboflavin with exposure to ultraviolet-A light (UVA) 370 nm. Resultant process leads to photopolymerization of collagen fibrils by increasing bonds between collagen and proteoglycans [82, 83]. Keratoconus tends to progress faster in children, and thus CXL is an important modality in arresting this process. If diagnosed earlier, CXL can halt the disease process in children, save a few lines of best corrected vision, and can also decrease the need of keratoplasty.

8.11.1.1 Indications and Timing of the Procedure in Children vs. Adolescent

Although the strategy in planning CXL in adults/adolescents is to follow up every 6–12 months and wait until progression is documented clini-

cally, when it comes to children, it is better to suspect and diagnose keratoconus earlier, follow up sooner, and better plan CXL earlier as suggested by groups of Chatzis and Hafezi wherein the benefits significantly outweigh the risks. In certain scenarios like severe disease in the other eye, family history of keratoconus, other associated systemic associations like Down syndrome, and family history of keratoplasty, CXL can be considered earlier. The exclusion criteria for CXL in children are similar to adults, thinnest pachymetry of less than 400 μm, corneal opacities, corneal infections, severe dry eyes, severe vernal keratoconjunctivitis, concomitant autoimmune disease, history of previous ocular surgery, and endothelial cell count of less than 1000 cells/mm^2 [3, 6, 56, 73, 84–88].

8.11.2 CXL Standard Dresden Protocol

The standard Dresden protocol described by Wollensak et al. was FDA recognized in 2011. The protocol is still widely used in adults as well as children. This involves epithelial debridement up to 9 mm and application of riboflavin one drop 0.1% solution every 2 min for a total of 30 min, followed by ultraviolet-A light (370 ± 5-nm wavelength, 5.4 J/cm^2 irradiance) exposure with instillation of the riboflavin solution every 2 min for an additional 30-min drop of riboflavin 0.1% solution administered every 2 min for a total of 30 min, followed by ultraviolet-A light (370 ± 5-nm wavelength, 5.4 J/cm^2 irradiance) exposure with instillation of the riboflavin solution every 2 min for an additional 30-min period [82, 83]. This protocol is time tested and has been proven to be safe and efficacious in halting the disease process over several long-term follow-up studies in children. But children are usually uncooperative, and the intraoperative ocular movements occurring in the 1-h-long procedure might affect the radiance and efficacy. Epithelial debridement under topical anesthesia can be cumbersome in children and can lead to postoperative pain; as a result, some novel protocols of delivering the energy and novel techniques of applying riboflavin with no touch technique were explored for better results in children.

8.11.3 Transepithelial CXL (TE CXL)

Epi-On CXL or transepithelial CXL involves administering riboflavin along with 15% dextran supplemented with trometamol + EDTA (Ricrolin TE, Sooft, Montegiorgio, Italy). This enables passage of a heavy riboflavin molecule through the corneal intact epithelium to reach till the stroma, which in normal circumstances acts as a barrier for riboflavin due to its lipophilic nature. The time for riboflavin application and irradiance is similar to the standard protocol [89, 90].

8.11.4 Accelerated Cross-linking Protocol

Accelerated cross-linking protocol involves delivering, a higher irradiance, to reduce exposure time (i.e., 9 mW/cm^2 for 10 min or 30 mW/cm^2 for 4 min instead of 3 mW/cm^2 for 30 min) [56].

8.11.5 Other Methods

CXL has also been tried in other nonstandard methods with the help of cross-hatched grid pattern for epithelial debridement, contact lens-assisted cross-linking, and application of BAK (benzalkonium chloride) and benzoate to improve riboflavin penetration and iontophoresis [91]. There is less literature to prove the efficacy of these methods.

8.11.6 Safety

Overall, CXL has shown to be a safe procedure with long-term follow-up in adults with no significant major complications [92, 93]. In children, not many long-term follow-up studies have been seen. Longest follow-up in one study up to 7.5 years has been observed [85].

8.11.6.1 Epithelial Defect

The epithelium usually heals within 48 h after CXL. A bandage contact lens in place usually aids this. With delayed epithelialization up to 10 days, glare and corneal edema was seen in a few studies [3, 89]. Persistent corneal haze has been reported in two case series in 3.5% patients [56] and in 14.2% patients [94]. More importantly, it is the longer duration of de-epithelialization during the standard protocol procedure that leads to pain and difficult cooperation in children. This can also increase the risk of ulceration, infection, sterile infiltrates, and activation of herpes keratitis [88, 94].

8.11.6.2 Endothelial Cell Loss

The current pachymetry cut-off values of 400 μm primarily prevent endothelial cell damage due to exposure to UVA. Although a few case reports have been noted in adults, there are no significant complications pertaining to endothelial cell loss and corneal decompensation in children; however, more long-term follow-up studies are needed to conclude on this observation [56, 73, 87, 90, 94].

8.11.6.3 Limbal Cell Loss

Recently, few studies have highlighted the aspect of UV-related damage to the limbal stem cells after CXL [95]. De-epithelialization and UV treatment occurs over the central cornea, but being a topical procedure, there is some amount of exposure of riboflavin and UV to the limbal cells. Also, it has shown that de-epithelialized surface ensures better riboflavin concentration even in the peripheral cornea and the limbus which can increase UV exposure. CXL leads to induction of pro-apoptotic genes, inducing oxidative damage to DNA and inhibiting growth of cultured human epithelial stem cells, and cells derived from cadaver eyes have been shown in studies [96–98]. A case of conjunctival intraepithelial neoplasia has been reported [99]. Considering the pediatric age group, these studies do raise a concern of a long-term ocular surface-related complications post-CXL; however, still in majority, the re-epithelialized surface shows normal characteristics, and no long-term ocular surface or limbal stem cell deficiency has been reported so far.

8.11.6.4 Efficacy of Standard Protocol

Multiple studies have proven the efficacy of the standard epi-off protocol in halting the progression of the disease within 12–36 months in children [100]. There have been some instances of failure of CXL with documented progression, and the reported rate has been 5%, 23%, and 88% in some of the reported studies at different follow-up periods [3, 101, 102]. Chatzis and Hafezi reported progression in the disease despite of cross-linking, while Kumar Kodavoor et al. reported the same in three eyes [3, 94]. All of these patients had frequent eye rubbing and documented allergic symptoms or VKC. Henriquez et al. reported CXL failure and progression in 6 out of 26 eyes and highlighted an importance of preoperative high *K* readings more than 54 D as a possible risk factor [102]. In adults, CXL has also shown to improve the flat and steep keratometry, posterior elevation, BCVA, UCVA, and aberrometry over a long period of time. However, in children, the results are variable across multiple studies with different follow-up periods after CXL [3, 72, 87]. Along with stabilization of the disease, BCVA was shown to improve in most of the studies. In the Siena protocol, Caporossi et al. followed 77 and 152 patients (10–18 years) for a period of 36 and 48 months, respectively, in 2 separate studies and highlighted visual improvement in 80% of patients and 90% stabilization achieved in 4 years [92]. Zotta et al.'s long-term results of 20 eyes of (14.34 ± 2.14 years) followed for a period of 89 months noted that *K*1, *K*2, and the topographic cylinder remained stable at 7.5 years [84]. Soeters et al. also reported more corneal flattening and visual improvement in children [56]; however, Vinciguerra reported better visual and functional outcomes of CXL in the age group of 18–39 years [72, 73]. On the other hand, Chatzis and Hafezi observed improvement in keratometry only up to 24 months, with regression to preoperative values by 36 months follow-up suggesting a decrease in efficacy of CXL over a period of time in children <10 years of age [3]. In adults, stabilization of the disease is seen to be

long-lasting due to an additive factor contributed by the natural cross-linking occurring in the stromal fibers with increasing age.

8.11.6.5 Efficacy of Transepithelial CXL (EPI-ON) and Accelerated Protocol

Transepithelial CXL did show an advantage in decreasing the postoperative pain, corneal edema in children, and in initial studies by Magli et al. and Salman et al., they found to have no significant difference with the standard protocol with respect to the disease stabilization [86, 89]. However, the sample size of these studies was small, and the follow-up period was shorter. Most of the subsequent studies in children and adults showed progression of keratoconus with the Epi-On technique with a transient improvement in keratometry values. Buzzonetti et al. performed a prospective analysis of TE CXL for pediatric keratoconus (8–18 years age) in 13 eyes of 13 patients and demonstrated that *K* readings and HOA aberrations significantly worsened during follow-up [90]. Confocal microscopy demonstrated a demarcation line at depth of only 105 μm in contrast to the demarcation line typically seen at 300 μm in standard CXL treatment. They concluded that TE CXL appears to be safe but does not effectively halt keratoconus progression as compared with standard CXL. Irregular concentration of riboflavin in the stroma, restricted entry for oxygen due to the intact epithelium, and some amount of riboflavin absorbed by the epithelium could be the causes of its decreased efficacy [103].

Accelerated cross-linking protocol did show an overall improvement in visual acuity and flattening of *K* readings in both children and adults; however, in the long-term follow-up in children at 36 months, increase in K_{max} and posterior elevation values was noted [104]. It was found that the demarcation line post-CXL, which helps us to gauge the depth of treatment in the cornea, was in the range of 100–240 μm compared to 300–350 μm in the standard protocol. This also highlights an area of need for further research to find out the optimal time and irradiance for such accelerated protocols [105].

8.11.7 Intracorneal Ring Segments

Intracorneal ring segments (ICRS) are short PMMA arc/ring segments which when implanted in the peripheral cornea exert an arc-flattening effect and alter the geometry of the cornea leading to central flattening. This effect is inversely proportional to the thickness and size of the ICRS, which means the shorter and thicker segment, implanted in the peripheral cornea, exerts a more flattening effect. There are various normograms to calculate the size and length of ICRS based on the keratometry and refraction: [106]

- Contact lens intolerance.
- Corrected distance visual acuity < 0.6 on the decimal scale.
- Corneal pachymetry > 400 μm in the site of the corneal tunnel (depending on the thickness of ICRS to be implanted).
- Absence of central corneal scarring.
- Alignment of refractive axis and the flattest keratometric meridian *K*1 of the cornea should be such to form an angle between 0° and 15° and is considered properly aligned.

Option of ICRS in children is usually avoided due to a very advanced presentation of the disease, eye rubbing due to allergy, and noncompliance. In patients with VKC, there is a high risk of implant extrusion. Option of ICRS can be considered as a lesser invasive alternative than keratoplasty in children. Very few studies have shown efficacy of intracorneal ring segments in children [107]. A case series in children studied the efficacy of intracorneal ring segments along with CXL and did show regularization of surface and improved visual outcomes [108].

8.11.8 Keratoplasty

Advanced keratoconus, with scarred corneas, irregular corneas not suitable for contact lens fitting, poor compliance with glasses, and contact lenses are common indications for keratoplasty in children with keratoconus. Keratoconus is the most common acquired nontraumatic indication

for corneal transplantation in children [1]; however, in India, it is the third most common acquired nontraumatic indication for pediatric keratoplasty after infectious keratitis and adherent leukoma [109]. Although keratoplasty in keratoconus is safer compared to other indications, corneal transplantation in children has its own share of difficulties.

In pediatric keratoconus, it is important to consider various preoperative factors like age of the patient, presence of allergy, VKC, other associated connective tissue disorders, postoperative follow-ups, and compliance with medications. Intraoperatively, it is important to tackle low scleral rigidity and high intravitreal pressure which can be achieved by a general anesthesia, ocular massage, and use of Flieringa ring if needed. Centration of the trephine is important, and it should be around the visual axis or the center of the cone so as to include the entire ectatic region [110]. Intraoperatively, the apex of the cone can be identified in retro-illumination. Usually, a same size donor graft or a 0.25-mm increment is preferred. Postoperative examination of sutures, graft host junction, intraocular pressure, optic disc, and refraction need to be performed under anesthesia. We can anticipate early loosening of the sutures in children especially when there is a history of antecedent allergic disease and VKC, which can also lead to graft host junction dehiscence. Repeated incidents of premature loosening of sutures, followed by suture placements, attract blood vessels and in the long run lead to focal thinning of the graft host junction leading to high post-PK/DALK astigmatism. Immunological graft rejection is more common in PK compared to DALK and is more common in children under the age of 5 years compared to those above 5 years or adolescent [74]. Most common cause of immunological rejection is noncompliance to topical steroids; however, on the other hand, steroid-induced glaucoma and cataract are also known side effects of long-term topical steroid medications [111]. This can be prevented by shifting to steroid-sparing immunomodulators like cyclosporine and tacrolimus. Topical tacrolimus ointment formulation has shown to have great compliance and a great alternative to steroids as a posttransplant maintenance therapy [112].

Deep anterior lamellar keratoplasty (DALK) is preferred over penetrating keratoplasty (PK) for its advantages of structural integrity, endothelium integrity, and lesser chances of immunological rejection [113]. Although surgically more challenging than PK, DALK can be attempted as predescemetic DALK with manual dissection or descemetic DALK with the help of a big-bubble technique. Anwar's big-bubble technique is preferable [75]. The likelihood of getting a big bubble to achieve a plane between the Dua's layer and the Descemet membrane is higher in keratoconus corneas, considering weaker ectatic stromal lamellae. Faezi et al. demonstrated successful big-bubble technique in 75% of cases. In the remaining cases, dissection can be completed manually [75]. There is a risk of Descemet's perforation (11.5%) in manual dissection or stromal air injection, which can lead to interface-related complications such as double anterior chamber formation, infection, and vascularization [114, 115].

Visual outcomes of PK for keratoconus in pediatric patients are good as reported by Patel et al. in 65 pediatric patients with logMAR equal to better than 0.3 at the last visit, mean age 10.6 ± 4.3 years [116]. In DALK for keratoconus in children, Ashar et al. noted that more than 75% of patients had best corrected vision better than 20/80 at their last visit, while Karimian et al. compared outcomes of big-bubble DALK vs predescemetic DALK and found that the former had better outcomes but the subgroup analysis did not show any significant difference [113, 114]. Buzonetti et al. studied the advantages of a femtosecond laser-assisted DALK over mechanical trephine and found that although corrected distance visual acuity and manifest astigmatism remained comparable, the spherical equivalent was lower in the femtosecond-assisted group [111].

Multiple graft registries and old studies have shown that long-term graft survival for pediatric keratoconus patients is good. The Australian Graft Registry study for keratoconus for all age groups reported best graft survival of 89% for the first PK for the first 10 years [117]. Gulias-Cañizo et al. in their large retrospective series of 574

pediatric patients reported survival of 85% at 60 months follow-up for keratoconus, which was best compared to other indications [118]. In spite of this, graft rejection is a leading cause of graft failure especially in cases undergoing PK. Buzzonetti et al. did show that DALK grafts had better survival than PK and that children under 5 years of age had higher chances of graft failure compared to the older children (75% vs. 31%) [74, 117, 119].

Compared to earlier days, keratoplasty has become a safer procedure and is capable of delivering good anatomical and visual outcomes in children with DALK having definite long-term advantages in children. Thus, pediatric keratoconus is a disease that needs a keen eye to observe and diagnose early for successful early medical and surgical intervention to save significant lines of vision and quality of life.

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