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REVIEW

Pediatric keratoconus: a review of the literature

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Abstract
Purpose To describe the epidemiology and prevalence, rates of progression, difference between adult and pediatric populations, and therapeutic approaches to pediatric keratoconus from documented literature.
Methods A literature search was done on PubMed using key words including pediatric keratoconus, children with keratoconus, adult keratoconus, penetrating keratoplasty, corneal cross-linking and intracorneal ring segments. The literature was reviewed and reported to explore the key epidemiological differences between the pediatric and adult population with regards to presentation and treatment options.
Results Pediatric keratoconus is more aggressive than adult keratoconus, which has been explained by structural differences in the cornea between both populations. High rates of progression were documented in pediatric populations. While corneal collagen cross-linking, intracorneal ring segments and penetrating keratoplasties have been used as therapies in the pediatric population, the literature overwhelmingly shows higher rates of failure and progression despite these measures as compared to adults.
Conclusion Pediatric keratoconus is more aggressive than adult keratoconus, and current therapies used in adults may not be sufficient for the pediatric population.

Keywords Cornea · Keratoconus · Pediatric · Cross-linking · Intacs

Introduction

Keratoconus is a progressive disorder associated with structural changes in corneal collagen organization. Patients with the disease tend to develop corneal thinning that can lead to visual impairment and corneal ectasia if untreated. While keratoconus in adults has been studied extensively, the disease in the pediatric population has not. Pediatric keratoconus is more aggressive than adult keratoconus [1, 2], and therapeutic approaches differ because of the structural and behavioral differences between children and adults. Current therapies for adults include visual rehabilitation through glasses, contact lenses, corneal cross-linking, intracorneal rings segments, penetrating keratoplasty and deep anterior lamellar keratoplasty (DALK), which have also been attempted in pediatric populations. In order to better understand pediatric

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keratoconus separate from adult keratoconus, it is important to describe the epidemiology, rate of progression and approaches to therapy in this population.

Epidemiology and prevalence

Keratoconus is described as a progressive and asymmetric disorder that is associated with structural changes in corneal collagen organization [1]. Classically, the disease manifests in the second decade of life when the cornea assumes a more conical shape, leading to irregular astigmatism, progressive myopia, corneal thinning and subsequently poor visual acuity [3–5]. The majority of the literature describes the disease starting at puberty, but a case report documents the youngest case at age 4 [6].

The prevalence of keratoconus varies among populations with an estimate of the disease occurring in 1/2000 individuals [4]. More recent studies since 2009 in the Middle East and Asia use videokeratography to estimate the prevalence of keratoconus ranging from 0.9 to 3.3% [7–14].

Ethnic differences have also been reported to suggest that genetic influences play an important role in the disease pathogenesis. Pearson et al. [15] found that Asian, including Indians, Pakistani and Bangladeshi, living in the English Midlands had 4.4 times the incidence of keratoconus than their Caucasian counterparts. These findings were confirmed by two other studies conducted in the Midlands where the differences in incidence were reported as 7.5/11 [16] and 9.2/1 [17]. Hashemi et al. [11] further reported that in Iran, non-Persian populations (Arabs, Turks and Kurds) had three times the prevalence than Persian ethnic populations. According to Pan et al. [18], steeper corneas were found in Indians compared to Malays or Chinese in Singapore.

Visual impairment in pediatric patients may affect social and educational development, thus negatively impacting their quality of life. Initially, pediatric keratoconus is unilateral; however, the majority of patients develop bilateral disease. Li et al. showed that 50% of the non-affected fellow eyes developed keratoconus within 16 years [19, 20].

Previously, it has been documented that a non-inflammatory process is involved in the pathogenesis of the disease [4]; however, recent studies found evidence of inflammatory markers, and cytokines including interleukins (IL-1, IL-6, IL-8), TNF-α in the tears of patients with keratoconus [21–23]. Proposed mechanisms include increased kinetics of cyclooxygenase with a tenfold increase in maximal reaction rate and 10 times greater PGE2 production. PGE2 inhibits biologic functions of fibroblasts including collagen synthesis, proliferation and differentiation of myofibroblasts [24, 25]. Additionally, lower levels of cystatin, inhibitors of cysteine proteases, have been found in the tears of patients with keratoconus, suggesting lower protein content in keratoconic eyes [26, 27]. It is the inadequate balance between pro- and anti-inflammatory cytokines that lead to altered corneal structure and function triggering metalloproteinases and keratocyte apoptosis [28–30].

Often keratoconus is an isolated disease; however, ocular associations such as vernal keratoconjunctivitis, atopy, Down syndrome, retinitis pigmentosa, Leber congenital amaurosis, mitral valve prolapse and connective tissue disorders, such as Marfan and Ehlers–Danlos syndromes, have been reported [3, 19, 31]. Léoni-Mesplié et al. [32] conducted a retrospective study to assess the severity of keratoconus at diagnosis and found that affected children were more likely male, diagnosed with allergies, more frequently rubbed eyes, and had a strong family history of keratoconus. Eye rubbing increases the level of tear metalloproteinase-13, IL-6 and TNF-α in normal and keratoconic eyes, and it is the release of inflammatory mediators that contributes to the development of keratoconus [33]. Additionally, it has been documented that 10% of pediatric patients diagnosed with keratoconus have a positive family history [4, 19, 34, 35]. When accounting for subclinical forms, there is estimated 15–67 times higher prevalence of keratoconus in first-degree relatives than the general population [4, 35]. However, recent studies reported lower incidences of keratoconus with vernal keratoconjunctivitis in the pediatric population of 0.61%, as compared to previously documented [36]. Furthermore, Adachi et al. [37] described HLA-A26, B40 and DR9 antigens to be more frequent in pediatric keratoconus populations compared to adults in a Japanese cohort. The HLA haplotype could serve as a familial marker for keratoconus and provide genetic inheritance explanations for the disease. Additionally, investigations of hormonal differences note that the

disease develops earlier and involves more rapid progression in males than females suggesting androgenic dependence [5, 19, 34].

Rate of progression

Pediatric keratoconus tends to be more aggressive than adult keratoconus [3] because of the dynamic environment in the young cornea. Higher rates of corneal collagen remodeling were observed in pediatric corneas when compared to adults. It is thought that the weak ectatic lamellae may exceed the capacity of the cross-linking process [4, 38] leading to more rapid ectasia progression [39] and a sevenfold higher risk of needing corneal transplantation [40] in keratoconus patients. Biochemically, Kotecha et al. [41] suggested stiffening of the cornea with age as they report a negative correlation between corneal viscoelastic properties with advancing age. Furthermore, frequent coexistence of ocular pathology such as atopy and vernal keratoconjunctivitis has been associated with faster progression and long-term complications of pediatric keratoconus [42].

Younger patients are found to have more debilitating progression [1] with increased likelihood of corneal opacities [35, 36] and subsequent keratoplasty [43]. Amsler [44] defined stages of keratoconus in 1961 when he first documented progression of keratoconus with increasing age, noting that young patients with steep keratometry were more likely to progress to surgical stages than young patients with minimal corneal distortion. Chatzis and Hafezi [45] demonstrated that out of 59 keratoconic eyes in participants, ages 9–19, 88% of these patients progressed from initial visit. Furthermore, Tuft et al. [2] retrospectively examined 2723 patients with keratoconus over an 8-year period to identify risk factors that would lead to penetrating keratoplasty. Younger age ($p < 0.0006$) was an independent risk factor. In this report, patients younger than 18 years of age at time of diagnosis progressed to transplantation faster than patients older than 18. In the CLEK study population, progression was measured by corneal curvature, which occurred in 24% of cases and was maximal in patients <20 years old and minimal after age 30. During the 8-year follow-up period, the corneal curvature measured by the first definite clearance lens (FDACL) was predicted to increase by 1.68 D more in younger patients compared with older patients [46]. Similarly, the rate of slope change in Flat K was found to be substantially greater in patients younger than 20 years old than at any other time period [46].

However, some literature argues against the hypothesis that younger age is linked to more rapid progression of keratocoonus to stages III and IV requiring keratoplasty. Dana et al. [47] examined 99 eyes that underwent penetrating keratoplasty and found that adults over age 40 were at higher risk to undergo keratoplasty within 12 months of presentation, while younger patients had longer duration of follow-up before keratoplasty was recommended. Additionally, Pouliquen et al. [48] associates reviewed 187 case reports from the same surgeon to find that the course of keratoconus is in fact independent of the age at which it is detected, with the average period before operation being constant at approximately 10 years. Lass et al. [49] studied 756 keratoconus eyes and did not find an association with the age of the patient or the duration of the disease with risk of transplantation. Similarly, Kennedy and Dyer [50] and Woodward et al. [51] did not find a correlation between age and the risk of keratoplasty. In fact, Lass et al. [49] found that previous contact lens history, BCVA of 20/50 or worse and average keratometry of 55 D or greater at baseline were risk factors for penetrating keratoplasty. Hamilton et al. [52] suggested that eyes with the thinnest corneal thickness <450 μm, higher average central keratometry above 50 D and maximum center posterior elevation above 50 μm at presentation seemed to be risk factors for faster rates of corneal thinning and can be used as tomographic indices for progression. L'eoni-Mespli'e et al. [53] reported in a retrospective study that keratoconus was more severe in children at diagnosis compared to adults (27.8% at stage four vs. 7.8%, respectively), and after diagnosis the disease did not evolve more quickly in children.

Difference between adult and pediatric keratoconus

Keratoconus in children is more severe than in adults and involves rapid deterioration requiring more frequent follow-up. Pediatric and adult corneas are structurally different as there is natural cross-linking that may occur with aging of corneal tissues leading to possible spontaneous stabilization of keratoconus with

advanced age [4]. At the time of diagnosis, the disease stage of keratoconus is more advanced in younger patients. L'eoni-Mespli'e et al. documented that 27.8% of patients younger than age 15 presented with Amsler–Krumeich stage IV disease compared to 7.8% of patients 27 years or older [53]. Furthermore, Chatzis and Hafezi [45] found that 88% of pediatric keratoconus patients progressed from initial visit. Soeters et al. [54] reported keratoconic patients progressing 2.6 D in 7 weeks to 5.0 D over a year. The rapidity in which pediatric corneas evolve suggests that it may be inappropriate to wait for signs of progression as commonly done in adults to offer treatment, but in fact should be offered at diagnosis [1].

Similar treatment algorithms are available for both pediatric and adult keratoconus, including glasses, contact lenses, corneal cross-linking and keratoplasty depending on the stage of the disease. In the past 10 years, corneal cross-linking treatment has gained popularity. Adult patients who have undergone the procedure have less relapse [4], better functional and morphological results [55] and more sustainable effect over longer follow-up periods [56]. However, Soeters et al. [54] did report more corneal flattening and more visual acuity improvement in children compared to adults after cross-linking, while Vinciguerra et al. [57] reported better outcomes in adults ages 18–39. Vinciguerra et al. [55] also reported that pediatric corneas had faster recovery of central corneal thickness compared to adults suggesting a faster healing process in young eyes. Pediatric patients had keratometry stabilization 4 years after treatment with standard epithelium-off cross-linking, while adults with keratoconus had improvement in keratometry 4 years after treatment [57]. Results indicated better functional and morphologic outcomes in adults after cross-linking compared to the pediatric population, who continued to have increasing cylinder at 6 and 12 months after treatment [2, 57, 58].

However, Chatzis and Hafezi [45] did report progression of pediatric keratoconus at 36-month follow-up after standard cross-linking, which was not reported in adults. This could be attributed to the natural cross-linking that occurs with advanced age, and thus it is difficult to ascertain whether long-term stability of corneal cross-linking protocol in adults is due to the surgery or the natural history of the disease [4].

Adults who did relapse after cross-linking procedures were found to have neurodermatitis associated with skin and eye rubbing [5], female sex and preoperative maximum K readings greater than 58 D [59]. Accelerated pediatric keratoconus progression is linked with eye rubbing [1] and vernal keratoconjunctivitis [3].

There are differing results between pediatrics and adults with regards to penetrating keratoplasties, with children having poorer outcomes, including higher graft failure rates and poorer visual prognosis [60–65].

Results with cross-linking

Due to its success in adult keratoconus patients, corneal cross-linking has recently been studied as therapy to slow progression in pediatric keratoconus. Most studies in the literature report the standard epithelium-off cross-linking protocol for pediatric keratoconus, but other non-standard techniques used in children include trans-epithelial cross-linking and accelerated cross-linking [4]. There are few reviewed studies reporting data on cross-linking in children, however, of the articles published good safety, efficacy, improvement in uncorrected visual acuity (UCVA), best spectacle corrected visual acuity (BSCVA) and significant flattening in K readings have been reported [53, 55, 66–71].

Standard cross-linking protocol in children stabilized the disease process for up to 5 years of follow-up. Arora et al. and Wise et al. [66, 67] reported that pediatric standard corneal cross-linking was safe and effective at halting progression in the first 12 months with topographic and visual outcomes comparable to adults. At 2 years follow-up, Toprak et al. [69] found that 5 of 7 Scheimpflug topographic indices showed significant improvement between baseline and 2 years follow-up. However, paracentral cone location and corneal thickness at thinnest point <450 μm were found in cases more likely to progress after corneal cross-linking procedures [70]. Caporossi et al. and Zotta et al. [71, 72] reported stable efficacy at 3-year follow-up. More recent studies report stabilization in visual parameters at 4-year follow-up, including improvement in corrected distance vision (CDVA) in 69.1% of treated patients and a decrease in Kmax by 1.4 D ($p = 0.04$) [69, 73, 74]. At 5-year follow-up, Godefrooji et al. [75] showed improvement in

maximum keratometry by mean of −2.06 diopters, $p = 0.01$. However, while Chatzis and Hafezi [45] agree with 3-month outcomes, they reported regression of K readings after 2-year follow-up to preoperative values when patients presented at their 3-year follow-up. Since only 11 patients were measured, the results should be taken with caution. BSCVA trends mirrored K readings but at slower progression and at 3-year follow-up BSCVA were still significantly improved from preoperative values [53]. Higher rate of corneal collagen remodeling in children compared to adults can explain the progression after cross-linking has been performed [1]. Additionally, progression of disease after cross-linking has been linked to persistent eye rubbing and/or vernal keratoconjunctivitis [53, 76] and therefore must be taken into consideration when performing the procedure on the pediatric population.

Risks of standard cross-linking include corneal haze, scars, abrasion-related discomfort, blepharitis and mild photophobia [55, 76]. Because the procedure involves stripping the epithelium; it is associated with severe pain, temporary visual loss, stromal haze and infections [57, 76–80]. However, Vinciguerra et al. [55] did not observe endothelial cell damage or significant intraocular pressure changes at 2-year follow-up. Furthermore, in 62% of the eyes, cross-linking specific golden striae developed and 6.9% of the eyes had corneal haze. The haze regressed after 1 month of steroid treatment [55].

Trans-epithelial cross-linking has been reported as a better technique in children because of significant reduction in length of treatment, "no touch" protocol, and ability to perform the procedure under topical anesthesia [1]. The primary objective behind trans-epithelial cross-linking is to reduce postoperative pain and infection risk. However, the epithelium provides for a significant barrier for riboflavin and UVA light to penetrate [1]. Buzonetti and Petrocelli report that the procedure did not show improvement in topographic indices or higher order aberrations [4, 81]. Furthermore, significant worsening of all keratometric parameters at 18 months post trans-epithelial cross-linking in pediatric keratoconus were observed [75]. When compared to standard cross-linking, Magli et al. [82] reported no statistical difference in efficacy between standard or trans-epithelial approaches with regards to disease stabilization and improvement in children. The sample size was small (23 eyes for trans-epithelial cross-linking and 16 eyes for standard cross-linking group), and follow-up was up to 1 year, but it is worthwhile to note that patients in the trans-epithelial cross-linking group had fewer eyes with corneal edema and less pain reported. Caparossi et al. [83, 84] report that patients treated with trans-epithelial riboflavin cross-linking demonstrated stable keratometry measurements at 12 months that worsened at 24 months, and 1 year results were also supported by more recent studies. Eraslan et al. [85] found that at 24-months follow-up, trans-epithelial cross-linking was 0.7 efficacious at stabilizing corneal progression compared to standard procedures, $p = 0.038$. The data overwhelmingly support that even though trans-epithelial procedures result in fewer complications, standard protocols treat corneal progression better in pediatric keratoconus. However, neither procedure has been found to completely halt disease progression.

Results with Intacs

Intracorneal ring segments (Intacs/ICRS) are used in the 20% of keratoconic patients who are contact intolerant. Decisions to offer this treatment modality require patients to have corneal thickness of 400 μm at corneal mid-periphery, no central corneal scarring or corneal transplants in adults [1]. While Intacs flatten the center of the keratoconic cornea and are safe and reversible in adults [86], it is not the preferred treatment in pediatric keratoconus due to the rapid progression of young corneas, eye rubbing tendencies and non-compliance [1].

However, this option should be considered in adolescent patients with end-stage keratoconus who will most likely undergo keratoplasty [1]. Limited reviewed publications document the use of Intacs in pediatric keratoconus, but few studies do indicate that Intacs are safe and effective when used in children. Dirani and associates published a case series of 4 patients (6 eyes) <14 years old with keratoconus and poor BCVA. Intacs were placed via femtosecond laser and were followed from 6 months to 6 years. Mean BCVA and UCVA improved following ICRS, while mean spherical equivalents decreased. The keratometry readings remained stable after insertion [87].

Promising results have been reported in small case series investigating combinations of ICRS and corneal cross-linking [88–92]. Intact implantation prior to

cross-linking results in greater improvement in keratoconus compared to ICRS implant after cross-linking [89]. Currently, Gaster and colleagues are conducting a clinical trial comparing cross-linking alone to cross-linking combined with Intacs in patients with keratoconus and post-LASIK ectasia [93].

While complications with ICRS implants are rare, postoperative adverse effects include ring segment extrusion, corneal neovascularization, infectious keratitis, mild channel deposits around Intacs, ring segment migration, epithelial plug at incision site, corneal haze, corneal melting, night halos, chronic pain and focal edema [86, 94–108].

Results with penetrating keratoplasty

In very advanced disease, penetrating keratoplasty (PK) is advocated in pediatric populations. Al Suhaibani et al. report that the average age for PK in our population is 19 years old, with one quarter performed in children of 15 years or younger [109]. In a 20-year study conducted by Low et al. investigating primary outcomes of pediatric keratoplasty; mean Kaplan–Meier graft survival for PK in Singaporean children was 171.7 months (95% CI 141.3–202.2). In this study, cases that underwent keratoplasty had long-term survival rate of 92.9% at 17 years [60]; however, this includes PK, ALK, lamellar corneal patch graft and DSAEK surgeries therefore is not representative of PK alone. Risk factors for corneal transplantation in pediatric keratoconus include young age of diagnosis, short duration of disease and steep keratometry values [3, 40].

High success is associated with PK in adult keratoconus; however, corneal transplantation carries poorer prognosis in children [1, 60]. Preoperative risk factors include difficult evaluation. Intra-operatively, surgeons can encounter low scleral rigidity, increased fibrin reaction and positive vitreous pressure. Postoperative follow-ups require examination under anesthesia for frequent loosening of sutures, difficulties with refraction assessments and reversal of amblyopia. Even with increased anatomic success of pediatric corneal grafts, visual rehabilitation remains a concern [110].

Whether or not young age at time of keratoplasty is a risk factor in graft survival is debated. Huang et al. [111] measured outcomes in primary pediatric keratoplasty of children ages 14 and younger between 1991 and 2006. In the median 4.4-year follow-up graft survival was similar among the different age groups. Others found no difference in graft survival based on age at the time of transplant [112, 113]. However, Lowe et al. [63] studied 765 grafts in patients younger than age 20 years at the time of graft and reported that patients younger than 5 years old have worse graft survival. Adolescents exhibited better graft survival than other age groups with 86% of grafts treating keratoconus. Aasuri et al. [62] conducted a retrospective analysis of 154 PKs age 14 and younger with average follow-up of 1.3 years and also concluded that patients younger than age 5 are at highest risk of graft rejection.

Graft failure is linked to preexisting active inflammation, a glaucoma drainage device, and/or ocular surface disease [60, 111]. Furthermore, complications from penetrating keratoplasty include deep corneal neovascularization, allograft rejection, trauma to anterior segment, infectious keratitis, epithelial defects, band keratopathy, wound leakage, retrocorneal membrane, cataract formation, secondary glaucoma and retinal detachment [37, 62, 110, 111], which too are important risk factors for graft rejection.

Conclusion

Although there is some literature published investigating pediatric keratoconus, many of the management options stem from established therapeutics in the adult population. Through reviewing the literature, it seems that pediatric keratoconus is more aggressive than in adults, most likely due to the structural differences in collagen cross-linking. Because of this, younger patients have more debilitating progression and rapid deterioration requiring more frequent follow-up and earlier intervention. The documented therapies for adults may not be appropriate for the pediatric population. The question of when to intervene with therapies beyond visual rehabilitation has not been explored in the pediatric population as standard markers used in adults may not be sufficient to halt progression in this population. From the documented research, it seems that corneal cross-linking is most promising in pediatrics, compared to the high failure rates with Intacs and penetrating keratoplasties. However, because of the dynamic

nature of the pediatric cornea, stabilization with cross-linking has also been documented to be less efficacious than in adults. It would be of interest to explore a therapeutic algorithm specific to the pediatric population in order to understand and treat pediatric keratoconus. Furthermore, the association of pediatric keratonus with inflammatory markers and hormonal etiologies should be explored further to see if they can be targeted for future therapy.

Compliance with ethical standards

Conflict of interest None of the authors have conflicts of interests with submission.

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