СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Original Article / Оригинални рад

Svetlana Stanojlović[1,2,†], Vedrana Pejin[1], Tanja Kalezić[1,2], Jelica Pantelić[1,2], Borivoje Savić[2]

Corneal collagen cross-linking in pediatric patients with keratoconus

Корнеални колаген „крос-линкинг“ код педијатријских пацијената са кератоконусом

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Clinical Center of Serbia, Clinic for Eye Diseases, Belgrade, Serbia

Received: January 8, 2019
Revised: October 8, 2019
Accepted: November 19, 2019
Online First: November 26, 2019
DOI: https://doi.org/10.2298/SARH190108123S

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

†**Correspondence to:**
Svetlana STANOJLOVIĆ
Clinic for Eye Diseases, Clinical Center of Serbia, Pasterova 2, 11000 Belgrade, Serbia
E-mail: **stanojlovic.svetlana@gmail.com**

Corneal collagen cross-linking in pediatric patients with keratoconus

Корнеални колаген „крос-линкинг“ код педијатријских пацијената са кератоконусом

SUMMARY

Introduction/Objective The aim of this study was to report visual, refractive and tomographic outcomes of corneal collagen cross-linking (CXL) in pediatric keratoconus.

Methods This retrospective study included 17 eyes of 12 patients with progressive keratoconus who underwent epithelium-off CXL at the age ≤ 18 years. Following data were analyzed at baseline and postoperatively at one, three, six, nine, 12 months for all the patients, and annually where available: uncorrected and best spectacle-corrected distant visual acuity (UDVA and CDVA, respectively), refraction and corneal tomography.

Results Mean UDVA improved significantly from 0.52 ± 0.38 at baseline to 0.24 ± 0.29 logarithm of minimum angle resolution (log MAR) at one year (p = 0.011) and remained stable at two-year follow-up (0.21 ± 0.34 log MAR). Mean CDVA was 0.15 ± 0.21 at baseline and 0.06 ± 0.13 log MAR at one year (p = 0.248). Maximum keratometry showed a significant flattening of 1.30 ± 1.99 D (p = 0.011) at 1 year and remained stable two years after CXL. Minimum keratometry significantly decreased with a mean change of 1.34 ± 1.37 (p = 0.001). Mean reduction of corneal thickness after CXL was 55.35 ± 64.42 μm (P=0.003). At one year, seven (42%) eyes showed Kmax regression, nine (53%) stabilization, and one (5%) progression.

Conclusion In our study CXL effectively prevented progression of keratoconus in 95% of pediatric patients at one year, while improving UDVA and keratometry values. One patient with eye rubbing behavior showed signs of keratoconus progression after CXL treatment.

Keywords: corneal collagen cross-linking, keratoconus, pediatric patients, CXL

САЖЕТАК

Увод/Циљ Циљ овог рада био је да прикажемо видну оштрину, рефракционе и томографске резултате након корнеалног колаген крос-линкинга (ККЛ) због прогресивног кератоконуса код деце.

Метод Ретроспективна студија обухватила је 17 очију код 12 пацијената узраста до 18 година код којих је урађен ККЛ са уклањањем епитела. Анализирани су преоперативни и постоперативни подаци који су добијени на прегледима након 1, 3, 6, 9 и 12 месеци после урађеног ККЛа код свих пацијената, као и једном годишње код пацијената са дужим периодом праћења. Анализа је обухватила: некориговану видну оштрину (НКВО), најбоље кориговану видну оштрину (КВО), рефракцију и корнеалну томографију.

Резултати Средња НКВО значајно се побољшала од 0,52 ± 0,38 до 0,24 ± 0,29 логаритма минималног угла резолуције (логМУР) након годину дана (p = 0,011) . Ова вредност остала је стабилна до краја друге године праћења (0,21 ± 0,34 логМУР). Преоперативна средње КВО износила је 0,15 ± 0,21 логМУРа, а годину дана након ККЛа 0,06 ± 0,13 логМУРа (p = 0,248). Највећа средња кератометријска вредност апланирана је за 1,30 ± 1,99 Д (p = 0,011). Најмања кератометријска вредност смањила се за 1.34 ± 1.37Д (p = 0,001). Дебљина рожњаче смањила се за 55,35 ± 64,42 микрометара (p = 0,003). Након годину дана, 7(42%) очију показало је смањење максималне кератометријске вредности; 9 (53%) стабилизацију исте; 1(5%) око напредовање кератоконуса.

Закључак У нашој студији ККЛ је ефикасно спречио напредовање кератоконуса код 95% педијатријских пацијената уз побољшање НКВО и кератометријских вредности. Код једног пацијента, који има навику да трља очи, дошло је до напредовања кератоконуса после крос-линкинга рожњаче.

Кључне речи: корнеални колаген крос-линкинг; кератоконус; педијатријски пацијенти

INTRODUCTION

Keratoconus is a progressive, bilateral and most commonly asymmetric ectatic disorder associated with localized corneal thinning and protrusion [1]. Keratoconus usually begins in puberty and progress during adolescence. Progression of keratoconus with subsequent corneal steepening induces irregular astigmatism and myopia leading to a decrease in visual acuity. Indeed, earlier age of onset is associated with faster progression. Keratoconus severity was also greater at the time of diagnosis in children and adolescents; almost 30% of pediatric keratoconus presented at stage 4 compared with 8% of their adult counterparts [2]. Therefore,

it is critical to perform CXL as early as possible to stop progression of pediatric keratoconus. Introduction of this procedure reduced the need for penetrating keratoplasty which is usually required for advanced cases of keratoconus. This is particularly important for children since it was found that young age is associated with a seven-fold higher risk of requiring corneal transplantation [2].

The biomechanical resistance of the cornea in keratoconus is only 60% of the normal cornea [3]. Corneal CXL using ultraviolet light A and riboflavin as the photosensitizer was introduced by Wollensak et al. [4]. This treatment is aimed to increase the biomechanical stiffening of the cornea and its biomechanical resistance to collagenase activity [5, 6]. The safety and efficacy of CXL for keratoconus has already been demonstrated in both adults and children [7, 8]. However, CXL in pediatric patients with keratoconus has been significantly less studied. It was also suggested that the effect of CXL in children may be temporary [7].

The aim of this study was to evaluate visual, refractive and tomographic outcomes after standard corneal CXL for progressive keratoconus in patients younger than 19 years of age.

METHODS

Patients and methods

This retrospective study was conducted in compliance with the institutional review board regulations, informed consent regulation and adhered to the tenets of the Declaration of Helsinki. Our single-centered study comprised 17 eyes of 12 pediatric patients with progressive keratoconus who underwent an epithelium-off CXL at the age ≤ 18 between Jun 2015 and Jun 2017. These patients were followed up postoperatively at 1 month, 3 months, 6 months, 9 months, 1 year (for all patients, and annually where available).

A diagnosis of keratoconus was based on clinical findings and/or corneal images obtained by the Orbscan IIz Corneal Tomographer (Orbtek; Baush and Lomb, Salt Lake City, UT). All patients underwent a complete ophthalmic evaluation before CXL and at all follow-up visits after undergoing CXL. Data analysis included uncorrected distant visual acuity (UDVA), best spectacle-corrected distant visual acuity (CDVA), refraction (spherical equivalent, refractive astigmatism), corneal tomography, slit-lamp evaluation and particularly

associated allergic conjunctivitis. All UDVA and CDVA were recorded using Snellen chart and then converted to log MAR for statistical analysis. The following tomographic parameters were analyzed: simulated keratometry (SimK), maximum keratometry (Kmax), minimum keratometry (Kmin), minimum corneal thickness (MCT), anterior and posterior best-fit-sphere (ABFS and PBFS respectively), radius of anterior and posterior BFS, highest posterior elevation (HPE). The magnitude of highest posterior elevation was noted using the cursor within the central 8-mm zone in the best-fit-sphere map. The preoperative cone location was determined by the location of the highest posterior elevation. If it was within central 3 mm zone, it was termed a central cone. If it was was outside this zone it was termed paracentral (within central 3-5mm zone) and peripheral (outside central 5 mm zone). The Amsler-Krumeich classification based on average keratometry was used to classify keratoconus as mild (< 48 D), moderate (48-53 D) and severe (> 53 D).

Inclusion criteria were pediatric patients underwent CXL in one or both eyes at the Clinic for Eye Diseases affiliated to the University of Belgrade and being followed up for at least one year. Exclusion criteria was preoperative minimum corneal thickness less than 350 μm. Changes in Kmax were defined as Kmax regression (> 1 D decrease in Kmax), Kmax stabilization (< 1 D change in Kmax), and Kmax progression (> 1 D increase in Kmax**),** as described by Koller et al. [9].

Surgical procedure

CXL with riboflavin and ultraviolet A (UV-A) was performed according to the standard (Dresden) protocol [4]. Inclusion criteria was preoperative minimum corneal thickness ≥ 400 μm (16 eyes of 11 patients). Most children were able to successfully tolerate surgical procedure under topical anesthesia alone, while adjunctive sedation before the procedure was required in 4 eyes of 2 patients. After insertion of lid speculum, an 8-mm marker was used to mark the central corneal epithelium; then the epithelium was removed with a blunt metal spatula and isotonic 0.1% riboflavin-20% dextran solution (10 mg riboflavin-5-phosphate in 10 ml dextran solution) was applied for 30 minutes at intervals of 2 minutes. Ultrasonic pachymetry was obtained immediately after central epithelial removal and 30 minutes after the start of riboflavin drops. If the thinnest corneal thickness was less than 400 μm, hypotonic riboflavin was applied until the thinnest corneal stroma had swollen to 400 μm. Central

cornea was then exposed to UV-A irradiation using a UV light lamp (Intacs XL corneal crosslinking system, Addition Technology, Des Plaines, Ill., USA) at 3mW/cm^2 for 30 minutes (5.4 J/cm^2 total energy dosage) with reapplication of isotonic riboflavin solution every 3 min to ensure saturation. At the end of surgery, a therapeutic soft contact lens was applied until complete reepithelization of the cornea. The postoperative treatment included ofloxacin eye drops four times a day (qid) for 1 week, fluorometholone eye drops qid with taper 1 month and artificial tears qid for 6 months.

In one eye a technique of contact lens-assisted collagen cross-linking (CACXL) was applied due to the estimated preoperative corneal thickness < 400 μm (367 μm). Surgical procedure was performed as previously described by Jacob and Agarwal [10]. Briefly, after epithelial removal, isotonic 0.1% riboflavin-20% dextran solution was applied every 2 minutes for 30 minutes. An ultraviolet barrier-free soft contact lens (0.09 mm thickness, 14 mm diameter) soaked in isotonic 0.1% riboflavin for 30 minutes was placed on the cornea. Once the minimum corneal thickness with the contact lens was confirmed to be greater than 400 μm, CXL was proceeded. The UVA irradiance was performed for the next 30 minutes with reapplication of isotonic 0.1% riboflavin over and underneath the contact lens every 3 minutes. Postoperative treatment included soft contact lens and antibiotic drops as previously described for children underwent standard Dresden protocol.

RESULTS

A total of 17 eyes of 12 patients with an average age at surgery of 15 ± 1.7 years (range: 13-18) were included in this study. There were 1 (8.3%) female and 11 (91.7%) male patients. Preoperative, and follow-up data at 1, 3, 6, 9 and 12 months was available for all patients; 2-year follow-up was available for 8 patients; 3-year follow-up for 4 patients. Tomographic values from patients exceeding 1 year of follow up are presented but have not been subjected to statistical analysis as the sample size was considered insufficient. The changes in visual acuity, refractive and tomographic variables at baseline and 1 year after CXL are demonstrated in Table 1 and 2.

Eight patients (11 eyes) had a history of asthma and hay fever, 3 patients had no history of allergic eye diseases (5 eyes), whereas one patient (1 eye) had a history of eye rubbing behavior without atopy.

Interestingly, 13 eyes of ten patients (76.5%) presented at stage 2 at time of diagnosis with average Kmax of 49.67±1.48 D, whereas only 4 eyes of 3 patients (23,5%) presented at stage 3, showing average Kmax of 55.62 ± 1.50 D. All patients had cone located inside the central 3 mm topographic zone.

Visual acuity and refraction

Mean UDVA improved significantly from 0.52 ± 0.38 at baseline to 0.24 ± 0.29 log MAR at 1 year (P = 0.011) (Table 1) and remained stable at 2 year follow-up (0.21 ± 0.34 log MAR). Mean spectacle CDVA was 0.15 ± 0.21 at baseline and 0.06 ± 0.13 log MAR at 1-year. However, this improvement was not significant (P = 0.248).

The mean preoperative and postoperative spherical equivalent and refractive astigmatisms data are shown in Table 1. There was no significant difference between the preoperative and postoperative refractive values as well (P > 0.05). Mean spherical equivalent was 2.42 ± 1.89 D (P = 0.67); mean refractive cylinder was 4.0 ± 1.64 D (P = 0.61) at 1 year.

Tomography

Maximum keratometry value showed a significant flattening of 1.30 ± 1.99 D (P = 0.011) at 1 year and remained stable at 2 year follow-up (Figure 1). The baseline and follow-up measurements demonstrated that Kmax value decreased significantly 6 months after CXL and this improvement remained stable afterwards (Figure 1). Minimum keratometry value significantly decreased with a mean change of 1.34 ± 1.37 at 1 year compared with baseline (P = 0.001). A significant flattening of Kmin was observed at 3 month (P = 0.039) and remained statistically significant along the entire follow-up period (Figure 1). The SimK average values showed statistically significant worsening at 3 month after CXL (P = 0.036), becoming not statistically significant after the sixth month until the end of follow-up period (Table 2).

As presented in Table 2, compared with the baseline, the mean anterior elevation BFS decreased significantly 1 year after CXL (P<0.01). In contrast, a significant steepening of posterior elevation BFS was observed 1 year after CXL treatment (p<0.01).

At 1 year, in comparison with baseline values, 7 (42%) eyes showed Kmax regression; 9 (53%), stabilization; and 1(5%), progression. Keratoconus progressed in one eye with steepening of >1D in both orthogonal meridians at 1 year. Interestingly, at 1 year majority of treated eyes (12 out of 17) showed flattening of Kmin in combination with either stabilization (6 eyes) or regression (6 eyes) of the steeper orthogonal meridian. At 2 year follow up, 5 eyes out of 8 showed stabilization of both orthogonal meridians, whereas in 3 eyes regression ≥ 1D of both, Kmax and Kmin meridian, was observed.

Pachymetry

Average preoperative pachymetry at the thinnest point as measured by Orbscan was 460.94 ± 44.95 μm. Only one patient had pachymetric value less than 400 μm (368 μm). The changes of pachymetry over time are shown in Figure 2. There was a significant reduction of minimum corneal thickness after CXL in comparison with baseline values, with a mean reduction of 55.35 ± 64.42 μm at 1 year (P=0.003) (Table 2).

Statistical analysis

Statistical analysis was performed using Statistical Package software (version 23.0; SPSS). The significance of the difference between the preoperative and postoperative variables was tested using a 2-tailed paired samples Student t test. The value of $p < 0.5$ was considered statistically significant. All values were expressed as mean ± SD. Visual acuity was converted to logMAR for statistical analysis.

DISCUSSION

Different studies have confirmed that standard epithelium-off CXL protocol is safe and effective for the treatment of pediatric keratoconus [11]. Due to the less corneal stiffness in pediatric population CXL is not as effective in children as it is in adults [12]. Recently, a 24% regression rate was contemplated in patients who were aged 15 years and younger at the time of inclusion in the treatment protocol [13].

In our study we evaluated visual, refractive and tomographic results in a group of pediatric patients with a mean age of 15 ± 1.7 years who had been treated with corneal CXL for progressive keratoconus. Majority of eyes (76.5%) presented at stage 2 at time of diagnosis with average Kmax of 49.67 ± 1.48D. Both UDVA and CDVA improved at 1 year follow-up and remained stable 2 years after CXL procedure; however, the improvement in CDVA was not statistically significant. Similar to other studies [7, 8, 14], spherical equivalent and refractive astigmatism did not show any significant differences in comparison with preoperative values. Although the main objective of CXL treatment is to prevent keratoconus progression, flattening of the cornea is commonly reported [7, 15]. In ours and similar studies [8, 16] initial steepening of both keratometric indices, Kmax and Kmin was observed during the first 3 months. This has been suggested to be the result of early epithelial remodeling [17]. We also demonstrated continuous improvement in corneal topographic values with significant flattening of both Kmax and Kmin at 1 year following CXL procedure; however, slight steepening was noticed at 2 years for available patients (8 eyes). This is in line with the results of previous studies with a follow-up duration ranging from 1 to 3 years [16]. Improvement in keratometric values was associated with significant decrease of ABFS suggesting global corneal flattening as well. Although PBFS increased at 1 year follow up, no significant variation of highest posterior elevation has been observed indicating the effectiveness of the CXL treatment.

Interestingly, majority of eyes in our study (12 out of 17) demonstrated flattening of Kmin in combination with either stabilization or regression of the Kmax. Corneal response to CXL treatment showed vide variability in reported studies and this was also observed in ours. Vinciguerra [8] reported significant flattening of the flatter meridian but not of the steeper meridian at 2 year follow up. Some other studies and ours also demonstrated no significant differences in simulated keratometry at 1-year follow-up.

In pediatric patients, keratoconus is often more advanced in the worst eye at diagnosis as compared with their adult counterpart [2]. Chatzis and Hafezi [7] found a preoperative progression rate of 88% and recommended CXL treatment as soon as the diagnosis of keratoconus has been estimated in children. In our study, all children subjected to CXL treatment had history of significant visual impairment accompanying keratoconus progression. We generally perform pediatric corneal CXL at presentation in the eye with with more advanced stage of keratoconus, rather than to wait for documented progression. Until

the age of 16, all patients were followed at 3 months intervals. Serial tomographies were performed for both treated and untreated eyes to identify early keratoconus progression which may occur after CXL as well. Chatzis and Hafezi [7] also observed that an initially significant improvement in Kmax in the first 2 years was lost at the third year in pediatric keratoconus.

In our case series, 42% of eyes showed keratoconus regression at 1 year after the standard epi off CXL treatment, which was manifested as flattening of the steepest keratometry meridian more than 1D; whereas, 53% of treated eyes remained stable with average changes in Kmax less than 1D. One patient with compulsive eye rubbing behavior (5%), showed signs of keratoconus progression after CXL treatment with an increase of both orthogonal meridians. Allergy, atopy and eye rubbing are identified as a possible cause of keratoconus progression after CXL treatment [2, 18]. Therefore, patients should be counseled to avoid eye rubbing. Paracentral cone location and the thinnest corneal thickness below 450 μm were also linked to possible keratoconus progression [19]. However, all patients in our case series exhibited central topographic pattern. The average minimum pachymetry corneal thickness was 460.94 ± 44.95μm. The CXL procedure was well tolerated by all patients with corneal re-epithelization completed at 3 days postoperatively. We did not observe any side effects of the procedure. Mild temporarily corneal haze was noticed in all patients. This was also described in similar studies [13, 20].

For pediatric keratoconus, it is of vital importance to avoid more aggressive procedure such as keratoplasty, even in patients with more advanced form of disease. Jacob and coauthors have recently described CACXL technique for performing cross-linking in thin corneas with less than 400 microns after epithelial abrasion. Endothelial cell counts have been shown to remain unaffected after CACXL [10]. Here we also observed that CACXL was effective and safe in stabilization of keratoconus progression at 1 year follow up in a patient with minimum corneal thickness of 367 microns. Alternative protocols such as transepithelial CXL may also be effective in stabilizing corneal topography [21]; however, several studies showed inferior efficacy of the epithelium on CXL procedure in comparison with standard CXL treatment [22, 23]. Due to the reduced treatment time, accelerated CXL is also likely to be better tolerated in pediatric patients than standard CXL treatment. The long-term efficacy of accelerated pediatric CXL is yet to be determined.

CONCLUSION

We confirmed efficacy and good safety profile of pediatric corneal CXL. In this age group, keratoconus remained stable without signs of progression in 95% of eyes following standard epithelium off CXL treatment at 2 year follow up. Keratoconus in young age is often more aggressive and the effect of CXL may be temporary. Progression of pediatric keratoconus after CXL may also be related to the intense eye rubbing habit. Furthermore, special attention should be given to the pediatric population with more advanced stages of keratoconus. Alternative protocols, such as contact lens assisted CXL might be considered in eyes with thin cornea.

NOTE

This work was presented in part at the annual meeting of the Serbian Society of Ophthalmology, Kopaonik, 2018.

Conflict of interest: None declared.

REFERENCES

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998; 42(4):297–319. PMID: 9493273
2. Léoni-Mesplié S, Mortemousque B, Touboul D, Malet F, Praud D, Mesplié N, et al. Scalability and severity of keratoconus in children. Am J Ophthalmol. 2012; 154(1):56–62.e1. doi: 10.1016/j.ajo.2012.01.025.
3. Andreassen TT, Simonsen AH, Oxlund H. Biomechanical properties of keratoconus and normal corneas. Exp Eye Res. 1980; 31(4):435–41. PMID: 7449878
4. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003; 135(5):620–7. PMID: 12719068
5. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. J Cataract Refract Surg. 2003; 29(9):1780–5. PMID: 14522301
6. Spoerl E, Wollensak G, Seiler T. Increased resistance of crosslinked cornea against enzymatic digestion. Curr Eye Res. 2004; 29(1):35–40. PMID: 15370365
7. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric corneal collagen cross-linking in children and adolescents. J Refract Surg. 2012; 28(11):753–8. doi: 10.3928/1081597X-20121011-01.
8. Vinciguerra P, Albé E, Frueh BE, Trazza S, Epstein D. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. Am J Ophthalmol. 2012; 154(3):520–6. doi: 10.1016/j.ajo.2012.03.020.
9. Koller T, Pajic B, Vinciguerra P, Seiler T. Flattening of the cornea after collagen crosslinking for keratoconus. J Cataract Refract Surg. 2011; 37(8):1488–92. doi: 10.1016/j.jcrs.2011.03.041.
10. Jacob S, Kumar DA, Agarwal A, Basu S, Sinha P, Agarwal A. Contact lens-assisted collagen cross-linking (CACXL): A new technique for cross-linking thin corneas. J Refract Surg. 2014; 30(6):366–72. doi: 10.3928/1081597X-20140523-01.
11. McAnena L, Doyle F, O'Keefe M. Cross-linking in children with keratoconus: a systematic review and meta-analysis.Acta Ophthalmol. 2017; 95(3):229–39. doi: 10.1111/aos.13224
12. Kamiya K, Shimizu K, Ohmoto F. Effect of aging on corneal biomechanical parameters using the ocular response analyzer. J Refract Surg. 2009; 25:888–93. PMID: 19835329
13. Mazzotta C, Traversi C, Baiocchi S, Bagaglia S, Caporossi O, Villano A, et al. Corneal Collagen Cross-Linking With Riboflavin and Ultraviolet A Light for Pediatric Keratoconus: Ten-Year Results. Cornea. 2018; 37(5):560–6. doi: 10.1097/ICO.0000000000001505.
14. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R, Balestrazzi A. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. Cornea 2012; 31(3):227–31. PMID: 22420024
15. Chunyu T, Xiujun P, Zhengjun F, Xia Z, Feihu Z. Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis. Sci Rep. 2014; 10(4):5652. doi: 10.1038/srep05652.
16. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, Natarajan R, Iyer G, Srinivasan B, et al. Corneal Collagen Cross-Linking for Keratoconus in Pediatric Patients-Long-Term Results.Cornea. 2017; 36(2):138–43. doi: 10.1097/ICO.0000000000001102.
17. Rocha KM, Perez-Straziota CE, Stulting RD, Randleman JB. Epithelial and stromal remodeling after corneal collagen cross-linking evaluated by spectral-domain OCT. J Refract Surg. 2014; 30(2):122–7. doi: 10.3928/1081597X-20140120-08. 11.
18. Léoni-Mesplié S, Mortemousque B, Mesplié N, Touboul D, Praud D, Malet F, et al. Epidemiological aspects of keratoconus in children. J Fr Ophtalmol. 2012; 35(10):776–85. doi: 10.1016/j.jfo.2011.12.012.
19. Sarac O, Caglayan M, Cakmak HB, Cagil N. Factors Influencing Progression of Keratoconus 2 Years After Corneal Collagen Cross-Linking in Pediatric Patients. Cornea. 2016; 35(12):1503–7. doi: 10.1097/ICO.0000000000001051.
20. Knutsson KA, Paganoni G, Matuska S, Ambrosio O, Ferrari G, Zennato A, et al. Corneal collagen cross-linking in paediatric patients affected by keratoconus. Br J Ophthalmol. 2018; 102(2):248–52. doi: 10.1136/bjophthalmol-2016-310108.

21. Filippello M, Stagni E, O'Brart D. Transepithelial corneal collagen crosslinking: bilateral study. J Cataract Refract Surg. 2012; 38(2):283–91. doi: 10.1016/j.jcrs.2011.08.030.
22. Soeters N, Wisse RP, Godefrooij DA, Imhof SM, Tahzib NG. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. Am J Ophthalmol. 2015; 159(5):821–8.e3. doi: 10.1016/j.ajo.2015.02.005.
23. Leccisotti A, Islam T. Transepithelial corneal collagen cross-linking in keratoconus. J Refract Surg. 2010; 26(12):942–8. doi: 10.3928/1081597X-20100212-09.

Table 1. Preoperative and postoperative one-year visual acuity and refractive values and their statistical significance

Parameter	Preoperative	Postoperative (1 year)	p
UDVA (logMAR)	0.52 ± 0.38	0.24 ± 0.29	0.011
CDVA (logMAR)	0.15 ± 0.21	0.06 ± 0.13	0.248
Spherical Eq., D	-2.83 ±2.15	-2.42 ±1.89	0.67
Refractive astig., D	-2.69 ± 3.6	-4.0 ± 1.64	0.61

UDVA – uncorrected distance visual acuity; CDVA – corrected distance visual acuity; Spherical Eq. – spherical equivalent; Refractive astig. – refractive astigmatism

Table 2. Preoperative and postoperative one-year corneal tomography values and their statistical significance

Parameter	Preoperative	Postoperative (1 year)	p
SimK, D	5.52 ± 2.04	5.68 ± 1.89	0.702
Kmax, D	51.07 ± 2.97	49.69 ± 3.11	0.011
Kmin, D	45.23 ± 2.31	43.89 ± 2.57	0.011
MCT, µm	460.94 ± 44.94	405.58 ± 86.86	0.003
ABFS, D	42.79 ± 1.01	42.23 ± 1.33	0.003
ABFSr, mm	7.88 ± 0.2	7.95 ± 0.23	0.002
PBFS, D	53.70 ± 2.03	55.25 ± 1.95	0.008
PBFSr, mm	6.29 ± 0.23	6.11 ± 0.26	0.008
HPE, mm	0.20 ± 0.29	0.09 ± 0.04	0.658

SimK – simulated keratometry; Kmax – maximum keratometry; Kmin – minimum keratometry; MCT – minimal corneal thickness; ABFS – anterior best-fit-sphere; ABFSr – radius of the anterior best-fit-sphere; PBFS – posterior best-fit-sphere; PBFSr – radius of the posterior best-fit-sphere; HPE – highest posterior elevation

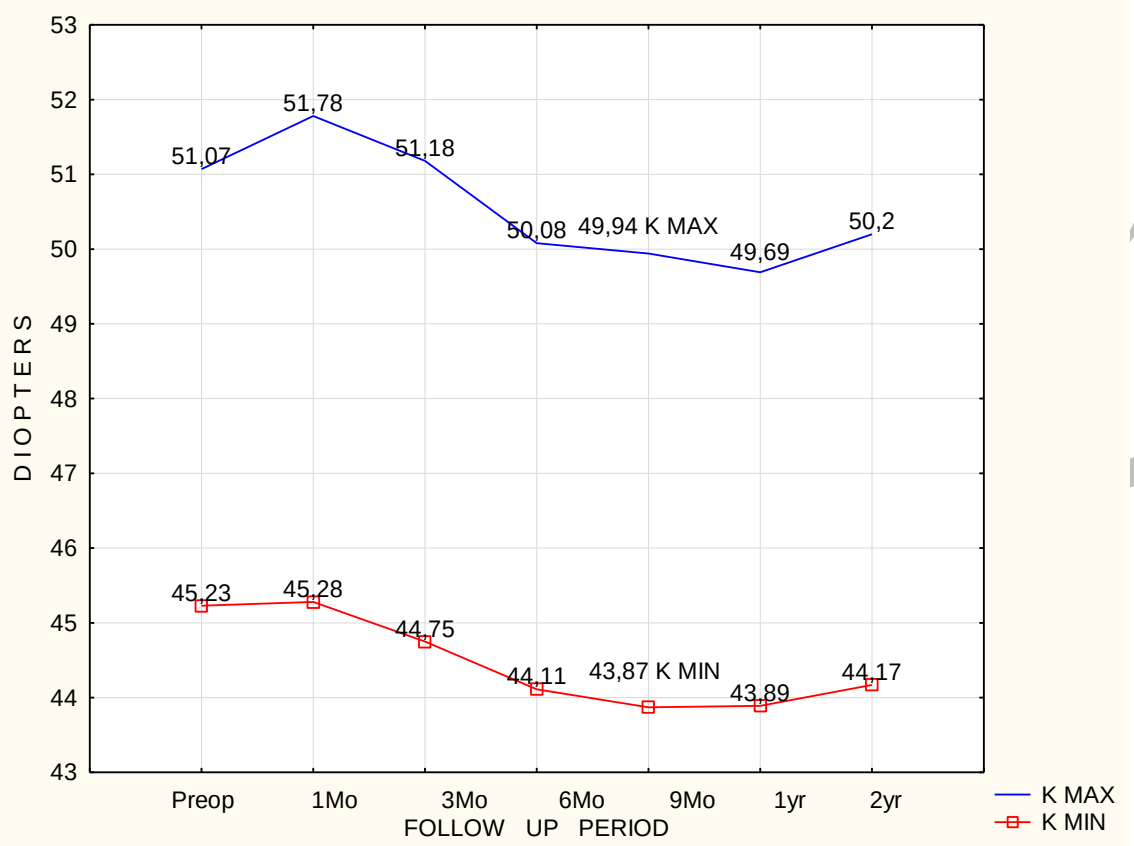

Figure 1. Changes in Kmax and Kmin over a two-year follow-up period;

Kmax – maximum keratometry; Kmin – minimum keratometry

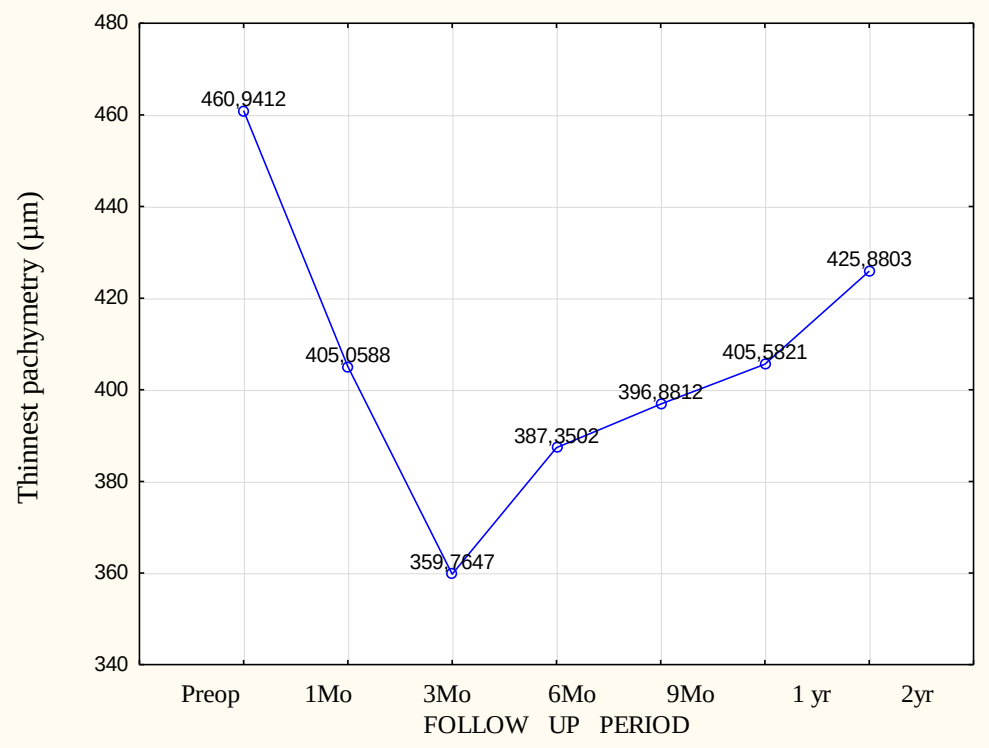

Figure 2. Changes in the thinnest corneal pachymetry over a two-year follow-up period

