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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

# Tomographic changes after corneal collagen cross-linking for progressive keratoconus – one-year follow-up study

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**SUMMARY**
**Introduction/Objective** The aim of this study was to evaluate the outcome of corneal collagen cross-linking (CXL) in patients with progressive keratoconus.
**Methods** This retrospective single-centered interventional study included 52 eyes of 41 patients who underwent epithelium-off CXL procedure at the age > 18 years. Corneal tomography data, uncorrected, and best spectacle-corrected distant visual acuity (UDVA and CDVA, respectively) were analyzed at baseline and postoperatively over the initial 12-month period. In addition, the natural course of corneal tomographic changes was demonstrated at one, three, six, nine, and 12 months after the CXL procedure.
**Results** At one year, mean UDVA improved significantly from 0.15 ± 0.22 (0.3 min – logMAR – 0 max logMAR) at baseline to 0.06 ± 0.09 logarithm of minimum angle resolution (logMAR) (0.1 min logMAR – 0 max logMAR) ($p = 0.024$). Mean CDVA was 0.45 ± 0.39 0.45 ± 0.39 logMAR (0.8 min logMAR – 0 max logMAR) at baseline and 0.06 ± 0.13 logMAR (1 min logMAR – 0 max logMAR) at one year ($p = 0.039$). Maximum keratometry showed a significant flattening of 1.36 D ± 1.53 D ($p = 0.0032$) at one year after CXL. Minimum keratometry significantly decreased with a mean change of 1.15 ± 1.20 ($p = 0.011$). Mean anterior and posterior best fit sphere (ABFS and PBFS, respectively) remained stable during the entire follow-up period. Mean reduction of corneal thickness after CXL was 47 ± 61 µm ($p = 0.003$). At one year, 29 (56%) eyes showed K max regression, 22 (53%) showed stabilization, and one (2%) showed progression. Spearman correlation coefficients were calculated to assess the correlation between difference in preoperative corneal thickness (CT), in posterior elevation corneal thickness (PECT), and minimum corneal thickness, ΔCT (PECT – minCT) and radius difference Δr (r1-r2). Spearman rs > 0.3 proved statistical significance and correlation.
**Conclusion** In our study, CXL effectively prevented progression of keratoconus in 98% of eyes at one year, while improving visual acuity. The effect of CXL can be evaluated at the earliest after six months; at that time, the stability of the corneal shape was provided by following the CXL procedure. The main limitation of this study is the small number of patients included.
**Keywords:** corneal collagen cross-linking; keratoconus; CXL

## INTRODUCTION

Keratoconus (KC) is an asymmetric, bilateral, progressive ectatic disorder, which leads to corneal thinning and protrusion. Reduced visual acuity occurs because of induced progressive myopia, irregular astigmatism and scarring. KC typically appears in the teenage years and progress until the fourth decade of life [1, 2]. The origin of this corneal ectatic disorder was believed to be multifactorial with an autosomal recessive or dominant pattern of inheritance [3, 4]. It can arise as an isolated condition or as a result of genetic predisposition triggered by environmental factors. KC is commonly associated with atopy, Down syndrome, eye rubbing habit, and the use of contact lenses [3, 5, 6]. The disease is widespread, with an annual incidence of approximately 1 in 2000, and a prevalence of 54.5 cases per 100,000 population [7].

Conservative treatment modalities, such as spectacles and gas-permeable rigid contact lenses become insufficient for visual rehabilitation in advanced stages of KC. Thus, it is important to diagnose KC as early as possible. The introduction of corneal collagen cross-linking (CXL) significantly reduced the need for corneal transplantation, which is usually required in advanced stages of KC [5].

Corneal crosslinking was introduced by Wollensak et al. [7], to slow down or stop the progression of KC. This process also occurs physiologically with aging. Spoerl and Seiler developed photochemical CXL with riboflavin (vitamin $B_2$) and ultraviolet A (UVA) (370 nm) [7]. Upon excitation by UVA, photosensitizer riboflavin generates reactive oxygen species. These free radicals induce formation of additional covalent bonds between collagen molecules resulting in corneal stiffening. Riboflavin also protects deeper ocular structures including endothelium, lens, and retina from UVA damage [8].

The main aim of CXL is to increase corneal biomechanical stability in keratoconic eyes. Wolensak et al [9] reported an increase in corneal rigidity of the human cornea by up

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to 300% after CXL. Stiffening of the cornea flattens the corneal apex and may improve uncorrected visual acuity, whereas changes in corneal symmetry may lead to the improvement of corrected visual acuity.

The aim of this study was to report visual and tomographic outcomes of standard CXL procedure for progressive KC in Serbian patients treated at a single corneal surgical center. In addition, natural course of tomographic changes across the initial 12 months after CXL was demonstrated.

## METHODS

### Patients and methods

This retrospective single-center study included 52 eyes of 41 patients at the age > 18 years, who underwent standard corneal CXL treatment for progressive KC between November 2014 and November 2017. All the patients were followed up for at least one year. The study was performed in adherence to the tenets of the Declaration of Helsinki, and the institutional and informed consent regulation of the Clinic for Eye Diseases, University Clinical Center of Serbia.

All the patients underwent complete eye examination at all follow-ups including visual acuity measurement (Snellen chart), slit-lamp biomicroscopy, and corneal tomography. The following data were analyzed from medical records: uncorrected and corrected distant visual acuity and corneal tomography. These data were obtained at baseline (before CXL), one month, three, six, nine, and 12 months after the CXL procedure. Visual acuity was converted to logMAR values for statistical analysis.

Corneal tomography was performed using the Orbscan Topography System (Orbscan II, Bausch and Lomb, Rochester, NY, USA). The following parameters were analyzed: maximum keratometry (K max), minimum keratometry (K min), simulated keratometry (Sim K), posterior elevation height (PEH), anterior and posterior best fit sphere values (ABSF and PBFS, respectively), radius of ABFS (ABFSr) and PBFS (PBFSr). Corneal thickness was estimated in two spots including corneal thickness in the spot of the highest posterior elevation (PECT) and the spot of minimum corneal thickness (MCT). The position of these two spots was determined as the radius from the corneal apex (PECT-r1 and MCT-r2, respectively).

Changes in K max were defined as K max regression (> 1 D decrease in K max), K max stabilization (< 1 D change in K max), and K max progression (> 1 D increase in K max) in comparison with baseline values (before the CXL procedure) as described by Koller et al. [10]. In our study, this was also applied for changes in K min values. The main limitation of this study is small number of patients included.

### Surgical procedure

Standard epithelium-off (Dresden) CXL procedure was performed as previously described by Wollensak et al. [7]. Central 9-mm epithelium was removed by mechanical debridement. Isotonic 0.1% riboflavin-20% dextran solution (10 mg riboflavin-5-phosphate in 10 ml dextran solution) was administered topically at intervals of two minutes for 30 minutes. Slit lamp examination was used to confirm riboflavin absorption throughout the corneal stroma and anterior chamber. Then, central cornea was exposed to UVA irradiation (365 nm) for 30 minutes using a UV light lamp ( Intacs XL corneal crosslinking system, Addition Technology, Des Plaines, IL, USA) at irradiance of 3 mW/$cm^2$ and 5.4 J/$cm^2$ total energy dosage. During UVA exposure, isotonic riboflavin was administered every two minutes. Postoperatively, ofloxacin eye drops four times a day (quid) for one week, fluorometholone eye drops quid with taper for one month, and artificial tears quid for six months were administered. Therapeutic soft contact lens was applied until complete reepithelization of the cornea.

### Statistical analysis

The values are expressed as mean ± standard deviation in the tables and graphs. To explore normal distribution, a Shapiro–Wilk analysis was performed. Data obtained from preoperative and postoperative follow-ups were compared using the analysis of variance (ANOVA). Spearman correlation coefficients were calculated to assess the correlation between difference in preoperative corneal thickness, in PECT and MCT, ΔCT (PECT – min CT) and radius difference Δr (r1-r2). Spearman rs > 0.3 proved statistical significance and correlation. The level for statistical significance was set as less than 0.05 ($p < 0.05$) and high statistical significance as less than 0.01 ($p < 0.01$). Statistical analysis was performed using PASW Statistics, Version 18.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

In this retrospective study, 52 eyes of 41 patients with progressive KC were included. All the patients underwent standard epi-off CXL procedure. Thirty (73.17%) patients were male and 11 (26.83%) were female. Mean age at the time of surgery was 25.28 ± 5.71 years. All the patients have been followed up for at least one year.

### Uncorrected and corrected distant visual acuity

Mean UDVA improved significantly from 0.15 ± 0.22 logMAR at baseline to 0.06 ± 0.09 logMAR at one year ($p = 0.024$). Mean spectacle CDVA was 0.45 ± 0.39 logMAR preoperatively and 0.06 ± 0.13 log MAR at one-year follow up ($p = 0.039$).

### Corneal tomography

Maximum keratometry value significantly decreased 12 months after CXL with a mean change of 1.36 ± 1.53 D in comparison with preoperative value ($p = 0.0032$). Significant flattening of K max value was observed at six

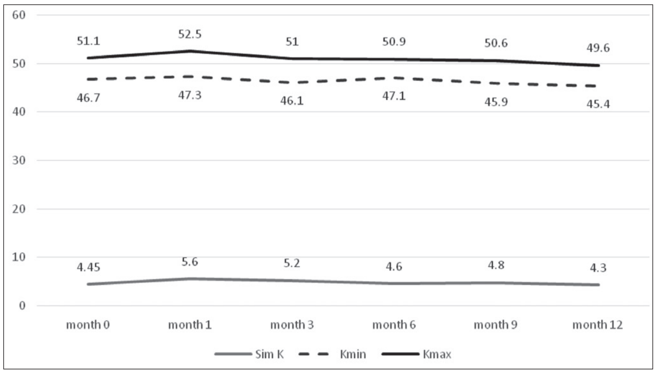


**Figure 1.** Changes in K max, K min, and Sim K over one-year follow-up period;
Sim K – simulated keratometry; K min – minimum keratometry; K max – maximum keratometry

**Table 1.** Preoperative and postoperative one-year tomographic values and their statistical significance

| Parameter | Preoperative | Postoperative (1 year) | p |
|---|---|---|---|
| Sim K | 4.45 ± 2.5 | 4.3 ± 2.4 | > 0.05 |
| K max | 51.1 ± 5.6 | 49.6 ± 5.3 | 0.003 |
| K min | 46.7 ± 4.6 | 45.4 ± 4.7 | 0.011 |
| ABFS | 43.92 ± 1.98 | 43.6 ± 2.09 | > 0.05 |
| PBFS | 55.2 ± 3.2 | 55.6 ± 2.9 | > 0.05 |
| ABFSr | 7.7 ± 0.3 | 7.8 ± 0.4 | > 0.05 |
| PBFSr | 6.1 ± 0.4 | 6.1 ± 0.3 | > 0.05 |
| PEH | 0.1 ± 0.05 | 0.14 ± 0.1 | > 0.05 |
| PECT | 432.1 ± 58.5 | 392.9 ± 71.7 | 0.003 |
| MCT | 423.5 ± 60.62 | 379.7 ± 74.3 | 0.001 |
| r1 (PECT) | 1 ± 0.4 | 1.6 ± 0.5 | > 0.05 |
| r2 (min CT) | 0.9 ± 0.4 | 0.9 ± 0.5 | > 0.05 |

K max – maximum keratometry; K min – minimum keratometry; Sim K – simulated keratometry; PEH – posterior elevation height; ABSF – anterior best fit sphere; PBFS – posterior best fit sphere; ABFSr – radius of ABFS; PBFSr – radius of PBFS; PECT – corneal thickness in the spot of highest posterior elevation; MCT – minimum corneal thickness; r1 – radius in PECT; r2 – radius in MCT; min CT – corneal thickness in the spot of the thinnest cornea

**Table 2.** Changes in Kmax and Kmin and their correlation at one year follow-up period

| | ΔK max > 1D↓ | ΔK max < 1D | ΔK max > 1D↑ | |
|---|---|---|---|---|
| ΔK min > 1D↓ | 26 (50%) | 3 (5.76%) | 0 | 29 (55.76%) |
| ΔK min < 1D | 3 (5.76%) | 18 (34.61%) | 0 | 21 (40.38%) |
| ΔK min > 1D↑ | 0 | 1 (1.92%) | 1 (1.92%) | 2 (3.84%) |
| | 29 (55.76%) | 22 (42.31) | 1 (1.92%) | |

ΔK max – change of maximal keratometry; ΔK min – change of minimal keratometry

months follow up (p = 0,0108) and remained stable afterwards (Figure 1, Table 1).

Furthermore, K min value significantly decreased with a mean change of 1.15 ± 1.20 D at one year after CXL procedure (p = 0.011). A significant improvement of K min was observed at nine months (p = 0.036) and remained statistically significant until the end of the follow-up period (Table 1, Figure 1).

The mean Sim K values showed statistically significant steepening at one month after CXL (p = 0.016), becoming not statistically significant after the third month until the end of the follow-up period (Table 1, Figure 1).

K max regression at one-year follow-up, with corneal flattening ≥ 1 D in comparison with preoperative value, was found in 29 eyes (55.76 %). Stabilization of K max (ΔK max < 1 D) was observed in 22 eyes (42.31%). Interestingly, K min regression, as demonstrated in Table 2, was documented in 29 eyes (55.76%), whereas stabilization of the flatter meridian at one year was observed in 21 eyes (40.38%). Progression of KC, with an increase in both meridian, K max and K min, was found in one eye (1.92 %) (Table 2).

The baseline and follow-up measurements showed that both ABFS and PBFS values remained stable after CXL treatment (p > 0.05) (Table 1, Figure 3). As presented in Figure 4, compared with the baseline, the mean radius of both anterior and posterior BFS increased at six-months follow-up; however, this change was not statistically significant (p > 0.05). There was also no statistically significant difference between mean preoperative and postoperative posterior elevation height values until the end of the follow-up period (Table 1).

### Pachymetry

Mean values of corneal thickness in the highest posterior elevation spot (PECT) and in the spot of the thinnest cornea (MCT) at baseline at all follow-ups are shown in Table 1 and Figure 3. These measurements of corneal thickness were highly statistically decreased after CXL procedure during the entire follow up period (p < 0.01) (Figure 5 and Table 1). Furthermore, as shown in Figure 3, there was no significant difference in mean corneal thickness between these two spots following CXL procedure (p > 0.05). Mean radius values in the spot of the lowest corneal thickness (r1) and in the spot of the maximum posterior elevation height (r2) were not significantly different at any of the follow-ups as well (p > 0.05) (Table 1). However, statistically significant difference in corneal thickness between these two spots was observed at baseline in cones with mismatched position of minimum CT and maximum PEH, (p < 0.001). Preoperative difference in corneal thickness in these spots was in high correlation with the difference in their radius from corneal apex (Spearman rs = 0.3).

## DISCUSSION

The effectiveness and safety profile of standard epithelium-off CXL procedure in halting the progression of KC has been already demonstrated [11]. Cornel CXL using riboflavin as photosensitizer and UVA light increases biomechanical stiffening of the keratoconic corneas as well as its resistance to collagenase activity. The effect of CXL is limited to the anterior 300 µm [7, 9, 12].

The procedure stimulates corneal remodeling while effectively prevents KC progression. This is usually accompanied by an improvement in visual acuity and topographic indexes. The efficacy of CXL procedure in the majority of

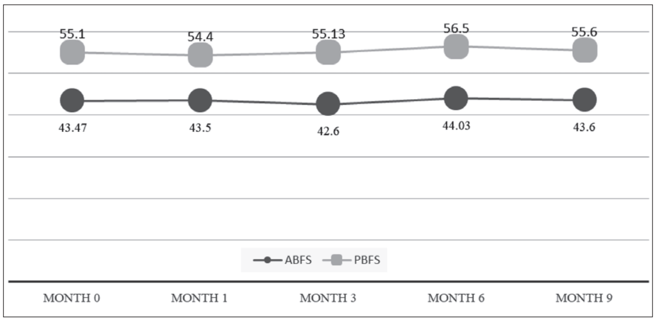


**Figure 2.** Changes in ABFS and PBFS over one-year follow-up period;
ABFS – anterior best-fit sphere; PBFS – posterior best-fit sphere

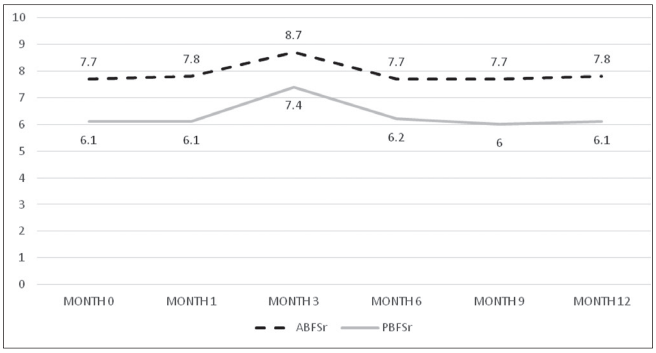


**Figure 3.** Changes in radius of anterior and posterior best fit sphere over one-year follow-up period;
ABFSr – anterior best fit sphere radius; PBFSr – posterior best fit sphere radius

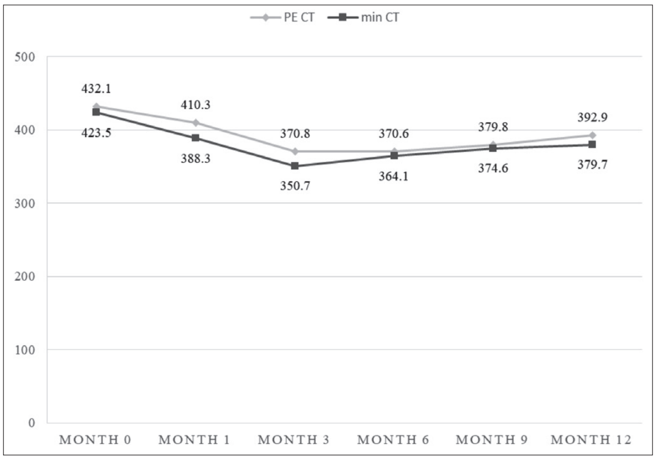


**Figure 4.** Changes in pachymetry values over one-year follow-up;
PECT – corneal thickness in posterior elevation spot; min CT – corneal thickness in the spot of the thinnest cornea

studies is determined by comparing pre- and postoperative K max values. Thus, maximum keratometry parameter is currently the standard in evaluating the efficacy of CXL for progressive KC [11, 12, 13].

In our study, standard CXL procedure halted KC progression in 98% of eyes at one-year follow-up with an average of 1.36 D decrease in K max. Nonetheless, it seems that the evaluation of both K max and K min gives better insight into postoperative regularization of the anterior corneal surface following CXL. Here, we demonstrated that 85% of cross-linked patients developed flattening of both orthogonal meridians as well. This was associated with a significant improvement in UCDVA and CDVA. Some other studies have also reported a decrease in K max while improving visual and refractive outcomes at one year after CXL procedure [8, 11, 13]. Natural course of topographic changes after CXL is important for proper visual rehabilitation. Better spectacle correction and contact lens tolerance following CXL was observed in our and similar studies [13, 14, 15]. In addition, it is of particular interest to evaluate treatment response after CXL at different time points.

Significant worsening of topographic values at one month followed by flattening until six months was observed in our patient cohort. Interestingly, there was a plateau between six and 12 months. This was also shown in the study by Chang and Hersh [16]. However, continual improvement in K max with long-term flattening was also reported in some studies [17].

The trend observed in the natural course of post-operative keratometry allows us to evaluate cross-linking efficacy at six to 12 months. In our study, KC progressed in one eye (2%) after receiving CXL. Progression of KC, defined as an increase in K max of 1 D over the preoperative value, has been reported after CXL procedure ranging 8.1–33.3% of cases [18].

According to the Global Consensus KC, KC progression is defined by "a consistent change in at least two of the following parameters where the magnitude of the change is above the normal noise of the testing system: steepening of the anterior or posterior corneal surface and thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point" [19]. However, due to the natural changes in tomographic indices after CXL, there is still no clear consensus for defining KC progression after CXL. Corneal thinning has been observed in cross-linked corneas in our and similar studies [15]. We also observed a significant decrease of corneal thickness in both spots, maximum PEH and MCT, during one-year follow-up. This is in line with other studies [20]. Mean corneal thickness in both points, PEH and MCT, was the thinnest between three and six months with subsequent improvement until the end of the follow up; however, corneal pachymetry remained significantly decreased at one-year follow-up [8].

Steepening of the anterior and posterior corneal surface has been generally considered a sign of KC progression in untreated patients. Interestingly, Sedaghat et al. [20] showed that ABFS had not been changed significantly after CXL, but posterior BFS increased six months postoperatively, and remained stable afterwards. In contrast, Grewal et al. [21] reported neither of BFS changes following CXL. Likewise, in our study, there was no significant change in ABFS and PBFS mean values during the initial 12 months after CXL. Furthermore, mean values of posterior elevation height remained stable during the follow up period. These data indirectly indicate biomechanical corneal stability in keratoconic eyes after receiving CXL procedure. We also demonstrated regularization of corneal shape following CXL; baseline difference in mean preoperative radius between the spot of maximum PEH and the spot of minimum CT was lost following CXL.

## CONCLUSION

In summary, here we reported visual and tomographic outcomes of CXL for progressive KC in Serbian patients treated at a single corneal surgical center. Standard CXL procedure effectively halted KC progression in 98% of eyes at one-year follow-up. We also confirmed efficacy of CXL in regularisation of anterior corneal geometry while improving visual acuity. The effect of CXL can be evaluated at the earliest after six months, at which time the stability of corneal shape is the result of the natural course of topographic changes following CXL procedure.

**Conflict of interest:** None declared.

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# Томографске промене након корнеалног колагенског *крос-линкинга* код прогресивног кератоконуса – студија једногодишњег праћења

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**САЖЕТАК**

**Увод/Циљ** Циљ ове студије је да се анализира исход корнеалног *крос-линкинга* (ККЛ) код болесника са прогресивним кератоконусом.

**Метод** Ова ретроспективна једноцентрична студија интервенције обухватила је 52 ока код 41 болесника, старијих од 18 година, који су подвргнути ККЛ-у са уклањањем епитела. Вредности корнеалне томографије, некоригована и коригована видна оштрина анализирани су преоперативно и током 12 месеци постоперативно. Такође, природни ток корнеалних томографских промена приказан је један месец, три, шест, девет и 12 месеци после процедуре ККЛ.

**Резултати** Средња коригована видна оштрина значајно се побољшала од 0,45 ± 0,39 до 0,06 ± 0,13 (0,8 мин. логМАР – 0 макс. логМАР) логаритма минималног угла резолуције (логМАР) након годину дана ($p$ = 0,011). Такође, значајно се побољшала и средња некоригована видна оштрина од 0,15 ± 0,22 до 0,06 ± 0,09 логМАР (0,3 мин. логМАР – 0 макс. логМАР). Максимална кератометрија показала је значајно заравњење од 1,36 Д ± 1,53 Д ($p$ = 0,0032) годину дана после процедуре. Минимална кератометрија значајно се смањила, са променом средње вредности од 1,15 Д ± 1,20 Д ($p$ = 0,011). Средња вредност дебљине рожњаче после процедуре смањила се за 47 ± 61 микрометара ($p$ = 0,003). После годину дана 29 (56%) очију показало је регресију максималне кератометријске вредности, 22 (42,31%) стабилизацију, а једно (2%) прогресију кератоконуса. Спирманов коефицијент корелације је коришћен да би се израчунала корелација између разлике у преоперативној дебљини рожњаче (ДР), у дебљини рожњаче на задњој елевацији (ДРЗЕ) и минималној дебљини рожњаче, ΔДР (ДРЗЕ – мин. ДР) и разлике полупречника Δр (р1-р2), и доказао је статистичку значајност и корелацију ($p$ > 0,3).

**Закључак** У нашој студији прогресија кератоконуса ефикасно је спречена код 98% очију уз побољшање видне оштрине. Ефекат ККЛ-а може се анализирати најраније после шест месеци с обзиром на то да се тада постиже стабилност облика рожњаче након процедуре ККЛ. Највећи ограничавајући фактор ове студије је мали број укључених болесника.

**Кључне речи:** корнеални колагенски *крос-линкинг*; кератоконус; ККЛ