

## LONG-TERM RESULTS OF CORNEAL COLLAGEN CROSSLINKING WITH ECTATIC FORMS OF CORNEAL DYSTROPHY

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✧ Corneal collagen crosslinking is one of the most effective methods of prophylactics and treatment of progressive corneal ectasias. In the literature, there are occasional data related to remote results concerning only the most common form of ectasias – keratoconus. In published studies, no remote results are met concerning the efficacy of corneal collagen crosslinking in other forms of corneal ectasias, which are now on the rise, including secondary ectasias that became more frequent with refractive surgery. The number of diagnosed cases of pellucid marginal degeneration increased as well. The literature shows no data on comparative analysis of remote results concerning the efficacy of this method in treatment of various forms of corneal ectasias. **The aim** of the investigation was to evaluate the efficacy of corneal collagen crosslinking based on the analysis of long-term results of this treatment method for various forms of corneal ectasias. **Materials and methods.** The results of corneal collagen crosslinking in patients with various forms of corneal ectasia 6 years after surgery were analyzed. The nosological structure of the study included patients with keratoconus, pellucid marginal degeneration, and secondary ectasia. The group of patients with keratoconus included 30 patients (30 eyes), that with pellucid marginal degeneration – 30 patients (30 eyes), and that with secondary ectasia – 30 patients (30 eyes). Corneal collagen crosslinking was performed by the same specialist, during the first or the second year of follow-up. Then changes in the state of the cornea and visual functions were monitored for 6 years. To assess the efficacy, preoperative examination results and interim data were used. **Results.** In all groups, there was an increase in the best corrected visual acuity, a decrease in the index of asymmetry of the corneal surface and its refractive power in the center of ectasia. However, best corneal collagen crosslinking results were obtained in groups of patients with keratoconus and secondary corneal ectasia.

✧ **Keywords:** collagen crosslinking; riboflavin; ultraviolet radiation.

## ОТДАЛЁННЫЕ РЕЗУЛЬТАТЫ КРОССЛИНКИНГА РОГОВИЧНОГО КОЛЛАГЕНА ПРИ ЭКТАТИЧЕСКИХ ФОРМАХ ДИСТРОФИЙ РОГОВИЦЫ

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✧ Кросслинкинг роговичного коллагена (КРК) является одним из самых эффективных методов профилактики и лечения прогрессирующих эктазий роговицы. В литературе встречаются единичные данные отдалённых результатов, посвящённые только одной наиболее часто встречающейся форме эктазии — кератоконусу. В публикациях не встречаются отдалённые результаты эффективности применения КРК при других формах эктазий роговицы, которые сегодня встречаются всё чаще. Это и вторичные эктазии, распространившиеся после рефракционных операций. Увеличилось также количество случаев диагностики пеллюцидной маргинальной дегенерации. В литературных источниках нами не найдено

данных сравнительного анализа отдалённых результатов эффективности применения этого метода для лечения различных форм эктазий роговицы. **Цель работы** — оценить эффективность КРК на основе анализа отдалённых результатов применения метода для лечения различных форм эктазий роговицы. **Материалы и методы.** Проанализированы результаты применения КРК у пациентов с разными формами эктазий роговицы через 6 лет после операции. Нозологическая структура исследования включала пациентов с кератоконусом, пеллюцидной маргинальной дегенерацией, вторичными эктазиями. В группу пациентов с кератоконусом включено 30 человек (30 глаз), с пеллюцидной маргинальной дегенерацией — 30 человек (30 глаз), с вторичными эктазиями — 30 человек (30 глаз). Кросслинкинг роговичного коллагена проводил один специалист, в первый или второй год наблюдения. Затем проводили мониторинг изменений состояния роговицы и зрительных функций в течение 6 лет. Для оценки эффективности использовали результаты обследования до операции и промежуточные данные. **Результаты.** Во всех группах выявлено повышение максимально скорректированной остроты зрения, уменьшение индекса асимметрии поверхности роговицы и её преломляющей силы в центре эктазии. Однако лучшие результаты применения КРК получены в группах пациентов с кератоконусом и вторичной эктазией роговицы.

✧ **Ключевые слова:** коллагеновый кросслинкинг; рибофлавин; ультрафиолетовое излучение.

## BACKGROUND

The introduction of effective and minimally invasive treatment methods for corneal pathologies, including ectatic dystrophies, to clinical practice is currently very important [3]. Studies of the treatment of ectatic diseases of the cornea are warranted for multiple reasons. First, there has been a steadily increasing trend in the incidence of corneal diseases in recent years, and these diseases have led to the consequent transformation and destruction of collagen, and to an increase in severe consequences of eye injuries. Second, the number of refractive surgeries has increased and diagnostic capabilities have improved because of the widespread introduction of modern computerized cornea examination methods [4].

Regarding corneal pathologies, keratectasia is a main cause of poor vision and blindness. Corneal ectasia is characterized by a progressive course characterized by corneal thinning and protrusion. Various types of keratectasias have been identified, including keratoconus, keratoglobus, pellucid marginal degeneration (PMD), pellucid marginal corneal degeneration, and iatrogenic keratectasia; of these, keratoconus is the most common [2]. As the ectatic process is frequently bilateral, often leads to visual disability and affects younger patients of working age, it is a particularly significant medical and social issue [6].

According to studies on the epidemiology of keratoconus, the reported incidence and prevalence ranges are 1.3–22.3 and 0.4–86 cases per 100,000 patients, respectively [12]. The frequency of secondary corneal ectasia after refractive surgery (e.g., Laser

Assisted in Situ Keratomileusis, LASIK) is 0.04%–0.6% [9]. PMD, which affects the lower periphery of the cornea, is less common than keratoconus. The disease refers to sporadic ones (single). Here, the cornea thins between the 4 and 8 o'clock positions at a distance of 1 mm from the limbus. In such cases, a typical “butterfly” or “crab claw” pattern with a noticeable flattening of the vertical axis is observed on the corneal topogram [10, 15].

Corneal collagen crosslinking (CXL), which uses riboflavin as a photosensitizer and initiator of photochemical modifications induced by monochromatic ultraviolet radiation, was designed and implemented by Seiler et al. in the late 1990s. CCC has since been recognized as the only treatment method that helps to slow the progression of keratoconus by improving the biomechanical properties of the cornea [2, 20]. In previous studies of CXL, researchers noted several positive biomechanical, biochemical, anti-hydration, and antimicrobial effects, as well as increases in resistance to heat and the resistance of corneal tissue to collagenase [1, 2, 13, 16, 17]. Accordingly, the indications for CXL have expanded significantly [5].

## INTRODUCTION

Ectatic forms of corneal dystrophy are among the main indications of keratoplasty. Corrective glasses and contact lenses do not affect the course of this disease. Corneal transplantation is the main treatment option for severe forms of ectasia, and this option is associated with the risk of complications [6–8, 11, 18]. Currently, CXL is the only pathogenetically

substantiated method that can block the progression of early-stage corneal ectasia [15, 19, 20, 21]. Changes in the biochemical and biophysical properties of the collagen frame of the cornea induce the development and progression of ectatic forms of corneal dystrophy. CXL is a particular example of photodynamic therapy that has been subjected to extensive study over the past 15 years. The mechanism of action of CXL is based on the photochemical effects of riboflavin and ultraviolet (UV) radiation at a wavelength of 365 nm on the cornea [20]. During CXL, photosensitive riboflavin molecules absorb UV radiation energy, reach an excited state, and produce reactive oxygen species that induce photochemical interactions in the corneal tissues. The resulting crosslinking of collagen molecules with main components of the stroma increases the mechanical strength of the cornea [2]. A similar crosslinking effect is used to increase the elasticity and strength of materials in polymer chemistry applications [12].

## MATERIALS AND METHODS

This study was conducted at St. Petersburg City Diagnostic Center No. 7. The sample included 90 eyes of 90 patients aged 13–50 years (mean age:  $26.53 \pm 7.69$  years). Written informed consent for the processing of personal data was obtained from each patient. All patients were divided into three groups depending on the diagnosed ectatic process: keratoconus, secondary ectasia and PMD of the cornea. The first two groups each included 30 eyes of 30 patients. In the third group, the treatment results of 30 eyes of 30 patients with PMD were analyzed. Patients with a corneal thickness <400 microns, stage 3–4 keratoconus, or a history of herpetic keratitis, parallel infectious or autoimmune disease and/or an abnormal endocrine profile were excluded.

CXL was performed during the first or second year of follow-up, after which the corneal state and visual acuity were monitored for 6 years. All patients underwent a comprehensive examination, including biomicroscopy, ophthalmoscopy, ophthalmometry, refractometry, visometry, tonometry, perimetry, and ultrasound pachymetry. Particular attention was paid to the results of corneal topography performed on a TOMEY TMS-4 corneal topograph. CXL was performed using a UV-X device (version 1000; IROC Innocross, Switzerland) with a UV wavelength of 365 nm and a radiation power on the corneal surface of  $3 \text{ mW/cm}^2$  when used with a solution of 0.1%

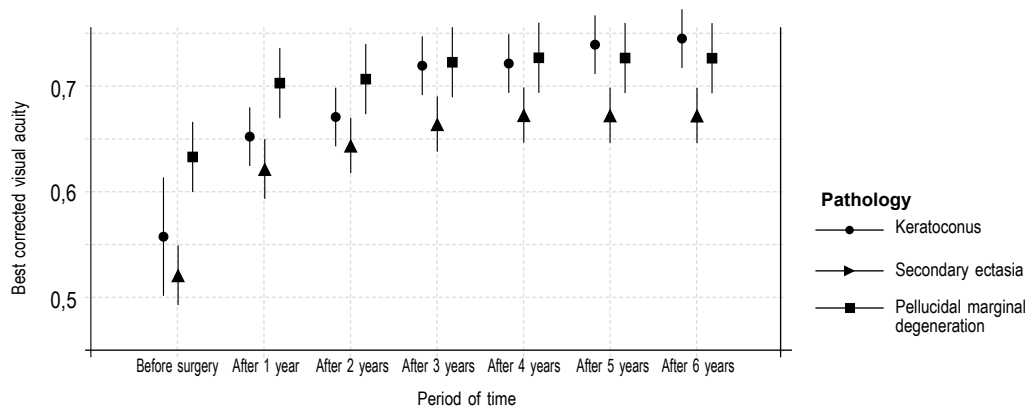
riboflavin in 20% solution of dextran (Dextralink, Ufa) according to the standard method (Dresden protocol). Silicone hydrogel soft contact lenses were prescribed to all patients before re-epithelialization. Data from the first visit and from 6 years of subsequent annual examinations were included in the analysis. The best corrected visual acuity, corneal surface asymmetry index (SAI) and refractive corneal power in the center of the corneal ectasia were evaluated.

The Wilcoxon test (*V*-statistics) was used to assess the dynamics of changes over 6 years since the time of surgery. A mixed-effects beta regression analysis was used to provide a comprehensive description of the dynamics of the studied variables after adjustment for the pathology, sex and age of the patients [14]. The beta regression analysis was selected because an initially strong assumption about the normal distribution of residues was not needed. Beta regression is used to model data distributed in an interval of (0; 1). The characteristics of the random effect and the additional parameter are presented as values with corresponding 95% confidence intervals. The Benjamini–Hochberg adjustment was used to correct *p*-values when multiple hypotheses were tested. The results were considered statistically significant at a *p* value < 0.05. All calculations were performed using the R programming language v3.6.1. Data are presented as medians and quartiles (Me [Q<sub>1</sub>; Q<sub>3</sub>]).

## RESULTS

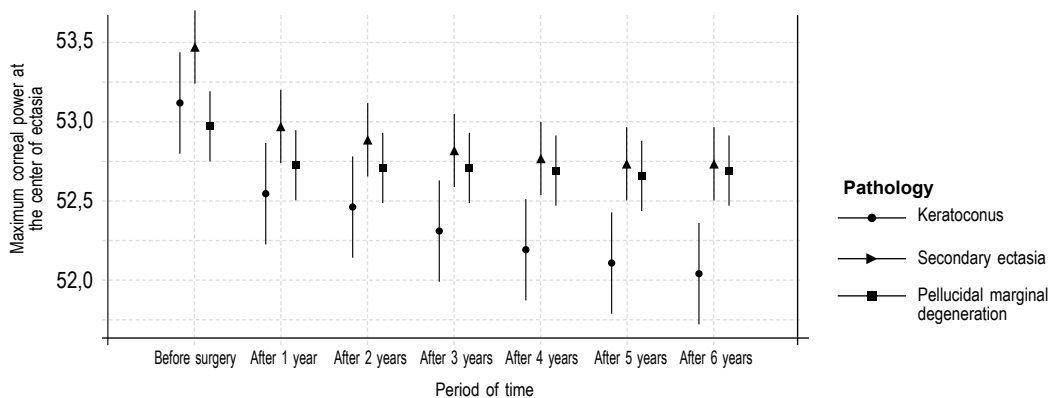
Our data demonstrated an increase in the best corrected visual acuity, a decrease in the refractive corneal power in the center of ectasia, and a decrease in the SAI index in all groups of patients. However, most significant results were observed in the group of patients with keratoconus (Fig. 1–3). Our results were consistent with those obtained by Raiskup-Wolf et al. [14] in an analysis of the results of CXL in patients with keratoconus.

In patients with keratoconus, best corrected visual acuity (BCVA) values before and 6 years after surgery were 0.55 [0.42; 0.70] and 0.75 [0.70; 0.80], respectively (*V* = 0.0, *p* < 0.001). In patients with secondary ectasia, BCVA values before and 6 years after CXL were 0.50 [0.40; 0.60] and 0.70 [0.60; 0.70], respectively (*V* = 0.0, *p* < 0.001). In patients with PMD before surgery, BCVA values before and 6 years after CXL were 0.60 [0.52; 0.70] and 0.70 [0.60; 0.80], respectively (*V* = 0.0, *p* < 0.001).



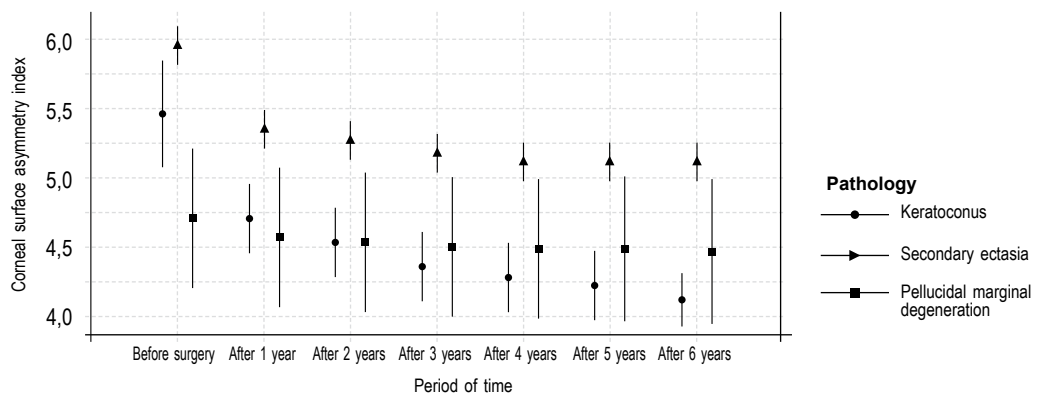
**Fig. 1.** The dynamics of the most corrected visual acuity

**Рис. 1.** Динамика максимально корригированной остроты зрения. Вертикальные линии — 95 % доверительный интервал среднего



**Fig. 2.** The dynamics of the refractive power of the cornea in the center of ectasia

**Рис. 2.** Динамика преломляющей силы роговицы в центре эктазии. Вертикальные линии — 95 % доверительный интервал среднего



**Fig. 3.** The dynamics of the topographic index of the asymmetry of the cornea

**Рис. 3.** Динамика топографического индекса асимметрии поверхности роговицы. Вертикальные линии — 95 % доверительный интервал среднего

In patients with keratoconus, refractive corneal power values before and 6 years after CXL were 53.06 [52.52; 53.72] and 52.06 [51.44; 52.67], respectively ( $V = 465.0$ ,  $p < 0.001$ ). In patients with secondary

ectasia, refractive power values before and 6 years after CXL were 53.20 [53.08; 54.01] and 52.80 [52.16; 52.98], respectively ( $V = 465.0$ ,  $p < 0.001$ ). In patients with PMD, refractive power values before

and 6 years after CXL were 53.13 [52.53; 53.30] and 52.81 [52.14; 53.05], respectively ( $V = 438.0$ ,  $p < 0.001$ ).

In patients with keratoconus, SAI index values before and 6 years after CXL were 5.89 [4.19; 6.01] and 4.13 [3.69; 4.77], respectively ( $V = 465.0$ ,  $p < 0.001$ ). In patients with secondary ectasia, SAI index values before and 6 years after CXL were 5.94 [5.89; 6.09] and 5.11 [4.89; 5.29], respectively ( $V = 465.0$ ,  $p = 0.008$ ). In patients with PMD, SAI index values before and 6 years after CXL were 5.38 [3.97; 5.82] and 5.12 [3.80; 5.73], respectively ( $V = 465.0$ ,  $p < 0.001$ ).

## CONCLUSION

Our analysis of the long-term effectiveness of CXL revealed positive outcomes in all groups, as evidenced by both the suspension of progression and, in many cases, a complete stabilization of the pathological process and improvements in visual functions. Significant flattening of the ectasia zone and increases in the BCVA were noted in some cases. However, no significant flattening of ectasia or increases in BCVA were observed in patients with PMD. These results will facilitate the development of criteria for the monitoring of cases and staging of therapeutic measures.

## SUMMARY

CXL can effectively treat ectatic forms of corneal dystrophy. This technique yields additional benefits by enhancing visual function and improving young patients' quality of life and ability to work.

*Transparency of financial activity:* None of the authors has a financial interest in the materials or methods presented.

*There are no conflicts of interest.*

*Authors' contributions:* S.Yu. Astakhov and S.A. Novikov created the research concept and design; O.A. Frolov collected and processed the materials, analyzed the data and wrote the manuscript.

## REFERENCES

1. Бикбов М.М., Бикбова Г.М. Эктазии роговицы (патогенез, патоморфология, клиника, диагностика, лечение). – М.: Офтальмология, 2011. – 168 с. [Bikbov MM, Bikbova GM. Ektazii rogovitsy (patogenez, patomorfologiya, klinika, diagnostika, lecheniye). Moscow: Oftal'mologiya; 2011. 168 p. (In Russ.)]
2. Бикбов М.М., Халимов А.Р., Усубов Э.Л. Ультрафиолетовый кросслинкинг роговицы // Вестник РАМН. – 2016. – Т. 71. – № 3. – С. 224–232. [Bikbov MM, Khalimov AR, Usubov EL. Ultraviolet corneal crosslinking. *Annals of the Russian Academy of Medical Sciences*. 2016;71(3):224–232. (In Russ.)]. <https://doi.org/10.15690/vramn562>.
3. Новиков С.А., Кольцов А.А., Данилов П.А., Федотова К. К вопросу о стандартизации и оптимизации офтальмологического обследования пациентов // Современная оптометрия. – 2016. – № 10. – С. 30–49. [Novikov SA, Koltsov AA, Danilov PA, Fedotova K. About standardization and optimization of vision examination procedure. *Actual Optometry*. 2016;(10):30–49. (In Russ.)]
4. Слонимский А.Ю. Тактика ведения больных при остром кератоконусе // РМЖ. Клиническая офтальмология. – 2004. – Т. 5. – № 2. – С. 75–77. [Slonimskiy AYU. Taktika vedeniya bol'nykh pri ostrom keratokonuse. *RMZh. Klinicheskaya oftal'mologiya*. 2004;5(2):75–77. (In Russ.)]
5. Нероев В.В., Петухова А.Б., Гундорова Р.А., Оганесян О.Г. Сферы клинического применения кросслинкинга роговичного коллагена // Практическая медицина. – 2012. – № 4–1. – С. 72–74. [Neroev VV, Petukhova AB, Gundorova RA, Oganesyana OG. Sphere of clinical application of corneal collagen cross-linking. *Practical Medicine*. 2012;(4-1):72–74. (In Russ.)]
6. Gordon MO, Steger-May K, Szczotka-Flynn L, et al. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. *Am J Ophthalmol*. 2006;142(6):923–930. <https://doi.org/10.1016/j.ajo.2006.07.026>.
7. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34(5):796–801. <https://doi.org/10.1016/j.jcrs.2007.12.039>.
8. Edwards M, Clover GM, Brookes N, et al. Indications for corneal transplantation in New Zealand: 1991–1999. *Cornea*. 2002;21(2):152–155. <https://doi.org/10.1097/00003226-200203000-00004>.
9. Kymionis GD, Portaliou DM, Diakonis VF, et al. Management of post laser in situ keratomileusis ectasia with simultaneous topography guided photorefractive keratectomy and collagen cross-linking. *Open Ophthalmol J*. 2011;5:11–13. <https://doi.org/10.2174/1874364101105010011>.
10. Panos GD, Hafezi F, Gatzoufas Z. Pellucid marginal degeneration and keratoconus; differential diagnosis by corneal topography. *J Cataract Refract Surg*. 2013;39(6):968. <https://doi.org/10.1016/j.jcrs.2013.04.020>.
11. Millodot M, Shneor E, Albou S, et al. Prevalence and associated factors of keratoconus in jerusalem: a cross-sectional study. *Ophthalmic Epidemiol*. 2011;18(2):91–97. <https://doi.org/10.3109/09286586.2011.560747>.
12. Rabinowitz YS. Keratoconus. *Survey of Ophthalmology*. 1998;42(4):297–319. [https://doi.org/10.1016/s0039-6257\(97\)00119-7](https://doi.org/10.1016/s0039-6257(97)00119-7).
13. Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA – induced cross-linking in keratoconus. *J Refract Surg*. 2009;25(9): S824–828. <https://doi.org/10.3928/1081597X-20090813-12>.

14. Rizopoulos D. Joint models for longitudinal and time-to-event data: with applications in R (Chapman & Hall/CRC Biostatistics Series, Book 6). Chapman and Hall/CRC; 2012. 275 p.
15. Spadea L. Corneal collagen cross-linking with riboflavin and UVA irradiation in pellucid marginal degeneration. *J Refract Surg.* 2010;26:375-377. <https://doi.org/10.3928/1081597x-20100114-03>.
16. Spoerl E, Wollensak G, Seiler T. Increased resistance of crosslinked cornea against enzymatic digestion. *Curr Eye Res.* 2004;29(1):35-40. <https://doi.org/10.1080/02713680490513182>.
17. Spoerl E, Wollensak G, Dittert DD, Seiler T. Thermomechanical behavior of collagen-cross-linked porcine cornea. *Ophthalmologica.* 2004;218(2):136-140. <https://doi.org/10.1159/000076150>.
18. Owens H, Gamble GD, Bjornholdt MC, et al. Topographic indications of emerging keratoconus in teenage New Zealanders. *Cornea.* 2007;26(3):312-318. <https://doi.org/10.1097/ICO.0b013e31802f8d87>.
19. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Curr Opin Ophthalmol.* 2006;17(4):356-360. <https://doi.org/10.1097/01.icu.0000233954.86723.25>.
20. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135(5):620-627. [https://doi.org/10.1016/s0002-9394\(02\)02220-1](https://doi.org/10.1016/s0002-9394(02)02220-1).
21. Ziaei M, Barsam A, Shamie N, et al; ASCRS Cornea Clinical Committee. Reshaping procedures for the surgical management of corneal ectasia. *J Cataract Refract Surg.* 2015;41(4):842-872. <https://doi.org/10.1016/j.jcrs.2015.03.010>.

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