The method of corneal collagen cross-linking for keratoconus (review of literature)

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SUMMARY

Photochemical crosslinking is widely applied in ophthalmology. Its biochemical effect is due to the release of singlet oxygen that promotes anaerobic photochemical reaction. Keratoconus is one of the most common corneal ectasia affecting 1 in 250 to 250000 persons. Currently, the rate of iatrogenic ectasia following eximer laser refractive surgery increases due to biomechanical weakening of the cornea. Morphologically and biochemically, ectasia is characterized by corneal layers thinning, contact between the stroma and epithelium resulting from Bowman's membrane rupture, chromatin fragmentation in keratocyte nuclei, phagocytosis, abnormal staining and arrangement of collagen fibers, enzyme system disorders, and keratocyte apoptosis. In corneal ectasia, altered enzymatic processes result in the synthesis of abnormal collagen. Collagen packing is determined by the activity of various extracellular matrix enzymes which bind amines and aldehydes of collagen fiber amino acids. In the late stage, morphological changes of Descemet's membrane (i.e., rupture and detachment) develop. Abnormal hexagonal-shaped keratocytes and their apoptosis are the signs of endothelial dystrophy.

The lack of analogs in domestic ophthalmology encouraged the scientists of Ufa Eye Research Institute to develop a device for corneal collagen crosslinking. The parameters of ultraviolet (i.e., wavelength, exposure time, power) to achieve the desired effect were identified. The specifics of some photosensitizers in the course of the procedure were studied. UFalink, a device for UV irradiation of cornea, and photosensitizer Dextralink were developed and adopted. Due to the high risk of endothelial damage, this treatment is contraindicated in severe keratoconus (CCT less than 400 microns). Major effects of corneal collagen crosslinking are the following: Young's modulus (modulus of elasticity) increase by 328.9% (on average), temperature tolerance increase by 5°C, and collagen fiber diameter increase by 12.2% (anterior stroma) and 4.6% (posterior stroma). In mild bullous keratopathy, corneal crosslinking provides antimicrobial effect. In moderate and severe keratopathy, crosslinking reduces pain and corneal edema and improves visual acuity immediately after the procedure. A case of HSV keratitis exacerbation was described. Amongst the complications, infection, halos, and posterior segment damage should be mentioned. Poor refractive results can be improved by the implantation of intrastromal corneal ring segments.

Keywords: corneal collagen crosslinking, keratoconus, Dextralink, UFalink.

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The concept of crosslinking involves a complicated process of formation of chemical bonds between larger molecules that can change the structure of the material, make it stronger and more resistant to decay. Physical crosslinking with ultraviolet light is used in various fields of industry and medicine for increasing the strength of the material. Chemical crosslinking methods are used in stomatology to improve the quality of a luting agent, in cardiology — for processing and strengthening bioprosthesis, in neurosurgery — in the treatment of intervertebral discs, etc. The progression of cataract is an example of a natural cross-linking of lens proteins — hardening and the loss of transparency of lens under the influence of sunlight.

Photochemical cross-linking of collagen fibers has found use in ophthalmology, which is caused by a biochemical effect of the release of singlet oxygen, promoting anaerobic type of photochemical reaction [1, 2, 3, 4, 5]. The founder of the UV cross-linking method is Gregor Wollen-

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sak. Corneal crosslinking method has different names: corneal collagen cross-linking (PSKR), UV-x-linking, C3-R, cross-linking method-UVA, CCL-method.

The purpose of the method — prevention of corneal ectasia progression, the main advantages — relative safety, possible combination with other methods and reversibility.

In recent years, the percent of keratoconus and ectasia in the structure of diagnosed diseases of the cornea has increased. The primary types of ectasias are keratoconus ectasia, keratoglobus, pellucid marginal corneal degeneration.

Keratoconus — one of the most frequent types of corneal ectasia, the frequency of which varies from 1:250 to 1:250000 of population [6, 7, 8, 9, 10]. Typically, the disease manifests in adolescence and slowly progresses for 3-4th decade of life, and then suspends in the development [1, 5, 11].

First in 1998, several authors have reported the occurrence of secondary corneal ectasia after keratorefractive interventions, the frequency of which varies from 0.04 to 0.6% [12]. Currently, number of iatrogenic ectasia is increasing after excimer laser correction of ametropia due to disorder of the biomechanics of the cornea [12].

Pathomorphological and biochemical features in corneal ectasia include thinning of all layers, contact of the stroma with the epithelium in places of rupture of Bowman membrane, fragmentation of chromatin in the nuclei of keratocytes, the phenomenon of phagocytosis, the destruction of collagen fibrils, disorder of tinctorial properties and parallel collagen fibers, the failure of enzymatic systems and apoptosis of keratocytes [1, 4, 7, 11, 13, 14].

According to most scientists, the initial changes in keratoconus are observed in the anterior cornea — at the level of the basal layer of the epithelium and Bowman's membrane, in advanced stages — in the stroma [15, 16, 17, 18]. In areas of significant thinning of the front epithelium the Bowman's membrane undergoes degradation and disappears [3, 17].

With the progression the normal location of corneal collagen fibrils is disrupted. There are their homogenization, expansion of interfibrillar spaces, decreasing of the diameter of the fibers, the appearance of edema of the corneal stroma and the formation of scar tissue. At the same time biomechanical stability of the cornea suffers. [11, 18, 19]. In the advanced stages morphological changes of Descemet's membrane (rupture, detachment) appear. Endothelial dystrophy manifested in violation of the regular hexagonal shape of keratocytes and their apoptosis [13, 16].

Most researchers believe that in the ectasia there is a disorder of enzymatic processes in keratocytes, leading to disruption of collagen formation. The degree of packing of collagen fibers is associated with the activity of several enzymes in the extracellular matrix of the stroma, binding the amino groups and aldehyde groups of amino acids of collagen fibers between them [11, 19, 20, 21, 22]. Studies by a number of authors have established a link between the acidity of the medium and the distribution of copper in the cornea in keratoconus, which opens up new possibilities of its pathogenetic treatment [23].

Level increase of lysosomal hydrolytic enzymes and proteinase inhibitors, lysis of intracellular structures and cell death, decrease of antioxidant activity of protective enzyme systems were determined in patients with keratoconus. Last designed to inactivate oxygen free radicals [1, 23, 24, 25], the accumulation of which causes disturbance of the process of collagen formation and, accordingly, the structural integrity of the corneal collagen [18, 26, 27, 28].

G. Wollensak et al. in 2004 identified the main technical parameters of the ultraviolet radiation effect on the cornea in the presence of riboflavin. Experiments were conducted on 34 rabbits, using morphological and electron-microscopic methods. The authors studied the apoptosis of keratocytes at different depths of the cornea under the action of ultraviolet irradiation and riboflavin. After 24 hours, the area of apoptotic cells was 0,86-1,39 cm^2 with UV power of 3mVt/sm^2 was maximal at a depth of 300 microns of the cornea. According to research by the authors the emission of wavelength of 370 nm is optimal for cross-linking and safe for deeply lying segments of the eye [29]. The results obtained were the basis for the development of new devices for UVI and photosensitizers [30, 31].

First results of the treatment of keratoconus by cross-linking were published by G. Wollensak et al. in 2003 [1]. During the 3-year study of 22 patients with keratoconus in 16 eyes was suspended the progression of the disease, marked the 2,0 D decrease of refraction and improving uncorrected visual acuity in 15 eyes. In the study of long-term results of corneal collagen cross-linking in 241 eyes Raiskup-Wolf F. et al. (2008) found a decrease in the corneal refractive power on average 1,5 D in 56% of cases, improved tolerability of hard contact lenses [32].

Currently, a number of foreign companies present various devices for crosslinking UVI: UV-X (Iroc, Switzerland), UVX device (Peschke Meditrade GmbH, Germany), Vega (CSO, Italy).

Absence of analogues in the domestic ophthalmology prompted researchers of Ufa Eye Research Institute to develop a device for the procedure of corneal collagen cross-linking. The parameters of UVR (wavelength, duration of exposure, power) has been defined to achieve the desired effect, some peculiarities of photosensitizers were studied during the procedure (BIKBOV M. M., 2009). The development and introduction into clinical practice of device for UV irradiation of the cornea «UFalink» (registration certificate number FSR2010/09071) and photosensitizer «Dextralink» (registration certificate number FSR 2010/0971) was the result of the research. [30, 31, 33].

Corneal collagen crosslinking effect is based on the effect of stromal fibers photopolymerization under the influence of a photosensitive substance and a low dose of ultraviolet radiation [3, 26, 28, 32]. Cross-linking of collagen leads to biomechanical stabilization of the cornea, which is based

on an increase in the number of intra- and interfibrillary covalent bonds [18]. Crosslinking must be conducted with full saturation of the cornea with photosensitizer. As the latter, due to its safety, has been proposed riboflavin — vitamin B_2 [27]. In subsequent years, there were other substances involved in the photochemical reaction [31, 34]. Optimal parameters of UV radiation: wavelength — 365 nm, emission power 3mVt/sm^2. This minimally invasive method of treating early stages of keratoconus is used in an outpatient settings, characterized by short-term rehabilitation of patients and does not require expensive equipment.

During the corneal collagen crosslinking the UV absorption takes place against background photosensitizers mainly in the anterior and middle parts of the stroma (300 microns), for which reason the endothelium, the retina and the lens are protected from photodamages [5, 14, 35, 36, 37, 38, 39]. The usage of this method is contraindicated in severe stages of keratoconus when corneal thickness less than 400 microns due to the risk of endothelial damage.

The main effects of corneal collagen cross-linking are the following: an increase in Young's modulus (elasticity index) by an average of 328.9%, increase in resistance to a temperature by 5°C, increasing of the diameter of the collagen fibers in the anterior stroma by 12.2% in the posterior — 4, 6% [27, 28, 35].

Clinical significance assessment of biomechanical properties of the cornea during the UV- crosslinking is important. The elastic properties of the cornea is characterized by three indicators: Corneal hysteresis (visco-elastic properties of the cornea), the factor of resistance (resistance to external impact of the cornea) and elastic modulus (mechanical resistance of the cornea).

At present there is no reliable method conventional study in vivo of biological properties of the cornea. Studies of biomechanical properties in vivo are based on changes of its shape in response to mechanical stress (by applanation of cornea by air jet or elastotonometry). However, we cannot exclude the effect of intraocular pressure on indicators of corneal biomechanics. [19, 40]. Study of the strength properties of the cornea is largely experimental, and the results of various studies are difficult for comparing. Corneal bidirectional applanation method can be used for biomechanical evaluation of its properties, which was taken as the basis of a special analyzer (Ocular Response Analyzer, ORA). And this method does not always accurately indicate the degree of elasticity of the cornea. Lack of a uniform terminology and classification of corneal biomechanical characteristics (stiffness, elasticity, viscosity, hardness) complicates the interpretation of its condition by practical ophthalmologists. Further research is need in this direction.

Research by a number of scientists have demonstrated antimicrobial efficacy of crosslinking, treatment of mild bullous keratopathy, provides pain relief in moderate and severe bullous keratopathy, decrease of corneal edema and increase of visual acuity immediately after the procedure [36, 41, 42]. At the same time described the exacerbation of herpetic keratitis after the procedure [43]. Among the complications, some authors point out the infection, the effect of halo, damage to posterior structures of the eye [38].

According to M. M. Bikbov (2012) low refractive effect of corneal cross-linking can be increased by combination with implantation of intrastromal segments or rings [44, 45, 46].

Thus, the above brief review of the literature allows us to consider the corneal collagen cross-linking as a promising minimally invasive treatment for early stages of keratectasia.

REFERENSES

1. Wollensak G., Spoerl E., Seiler T. Riboflavin/ultraviolet – A – induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135: 620-627.
2. Spoerl E., Mrochen M., Sliney D., Trokel S., Seiler T. Safety of UVA – riboflavin cross – linking of the cornea. Cornea 2007; 26: 385-389.
3. Wollensak G., Wilsch M., Sproel E. et al. Collagen Fiber Diameter in the Rabbit Cornea after Collagen Crosslinking by Riboflavin/UVA. Cornea 2004; 23: 5: 503-507.
4. Neroev V.V., Petuhov A.B., Gundorova R.A., Oganesjan O.G. [Sphere of clinical application of corneal collagen cross-linking]. Prakticheskaja medicina [Practical medicine], 2012; 1: 4. (in Russ.).
5. Bikbov MM, Bikbova G.M. [Corneal ectasis.] Ektazii rogovitsy. Moscow, Ophthalmology, 2011. 162 p. (in Russ.).
6. Gorskova E.N. [Prevalence of keratoconus in the Chelyabinsk region]. Vestnik mediciny [Annals of Medicine], 1995; 9:19-21 (in Russ.).
7. Grigorjan A.V., Toropygin S.G., Chashhina E.S. [Tiology and pathogenesis of various forms of cornea. A review of the literature]. Kataraktal'naja i refrakcionnaja hirurgija [Cataract Refract surgery], 2012; 4: 11-15. (in Russ.).
8. Semenova A.L., Kolidencev M.N. [Keratoconus. Prevalence, incidence, etiology, pathogenesis, classification]. Kataraktal'naja i refrakcionnaja hirurgija [Cataract Refract surgery], 2004; 4 (4): 4-7. (in Russ.).
9. Rabinovitz Y.S. Definition, etiology and diagnosis of keratoconus. Highlights of Ophthalmology, International Edition 2004; 21: 241-260.
10. Rad A., Jabbarvand M., Saif N. Progressive keratectasia after laser in situ keratomileusis. J. Refract. Surg. 2004; 20: 5: 718-722.
11. Sevast'janov E. N., Gorskova E.N. [Keratoconus plus]. Keratokonus plyus. Cheljabinsk, PIRS, 2006. (in Russ.).
12. Seiler T., Quurke A.W. Iatrogenic keratectasia after LASIK in a case of forme fruste keratoconus. J. Cataract Refract. Surg. 1998; 24: 7: 1007-1009.
13. Dumbrova N.E., Titarenko T.D. [Study of corneal depending on the stage of development of keratoconus according to the light and electronic microscopy]. Oftal'mologija [Ophthalmology], 1980;5: 309-311. (in Russ.).
14. Dhaliwal J.S., Kaufman S.C. Corneal collagen crosslinking: a confocal, electron and light microscopy study of eye bank corneas. Cornea 2009; 28: 62-68.
15. Hollingsworth J.G., Bonshek R.E., Efron N. Correlation of the keratokonis cornea in vivo by confocal microscopy and in vitro by light microscopy. Cornea 2005; 24: 4: 397-405.
16. Efron N. Contact lens – induced changes in the anterior eye as observed in vivo with the confocal microscope. Prog. Retin. Eye Res. 2007; 26: 4: 398-436.
17. Ivanovskaja E.V., Vit V.V., Golovchenko V.G. [Immunological status of patients with different stages of keratoconus and keratoglobus]. Oftal'mologicheskij zhurnal [J Ophthalmol], 2000; 5: 40-44. (in Russ.)
18. Meek K.M., S.J. Tuft, Y. Huang et al. Changes in collagen orientation and distribution in keratoconus corneas. Invest. Ophthalmol. Vis. Sci. 2005; 46: 6: 1948-1956.
19. Bubnova I.A. [Theoretical substantiation of the change of curvature of the cornea after the formation of corneal flap is formed when conducting intrastromal keratectomy]. Vestnik oftal'mologii [Annals of ophthalmology.], 2005; 6: 31-33.

(in Russ.).
20. Rodin A.S., Brizhak P.E. [Prospects of application of a method corneal cross-linking corneal collagen in the treatment of keratoconus and кератоэктазий]. Kataraktal'naja i refrakcionnaja hirurgija [Cataract Refract surgery], 2008; 4: 14-23. (in Russ).
21. Radner W., Zehemayer M., Skorpik Ch., Mallinger R. Altered Organization of Collagen in Apex of Keratoconus Corneas. Ophthalmic Res. 1998; 30: 327-332.
22. Wollensak G., Herbst H. Significance of the lacunar hydration pattern after corneal crosslinking. Cornea 2010; 29: 8: 899-903.
23. Avetisov S.Je. [The role of acidity tears and CU-cofactor of the enzyme activity лизилоксидазы in the pathogenesis of keratoconus]. Vestnik oftal'mologii [Annals of ophthalmology.]. 2011; 2: 3-8 (in Russ.).
24. Brian S., Wachler B. Corneal Collagen Crosslinking with Riboflavin. Cataract and Refract. Surg. 2005; 73-74.
25. Coskunseven E., Jankov MR, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. J Refract Surg 2009; 25: 371-376.
26. Caporossi A., Baiocchi S. et al. Parasurgical therapy for keratoconus by riboflavin – ultraviolet type A rays induced cross – linking of corneal collagen: Preliminary refractive results in an Italian study. J. Cataract Refract. Surg. 2006; 32: 5: 837-845.
27. Spoerl E., Huhle M., Seiler T. Induction of cross – links in corneal tissue. Exp. Eye Res. 1998; 66: 97-103.
28. Wollensak G., Iomdina E. Long – term biomechanical properties of rabbit cornea after photodynamic collagen crosslinking. Acta Ophthalmol 2009; 87: 48-51.
29. Wollensak G., Spoerl E, Wilsch M., Seiler T. Keratocyte apoptosis after corneal collagen cross-linking using riboflavin UVA treatment. Cornea. – 2004. 23: 43-49.
30. Bikbov M.M., Bikbova G.M., Khalimov A.R. [The results of clinical use of corneal collagen crosslinking device «Ufalink»]. Kataraktal'naja i refrakcionnaja hirurgija [Cataract Refract surgery]. 2009; 7 (2): 14-17. (in Russ.).
31. Bikbov M.M., Bikbova G.M., Khalimov A.R. [A new cornea protector for crosslinking «Dextralink»]. Sbornik nauchnyh trudov nauchno-prakticheskoj konferencii s mezhdunarodnym uchastiem po oftal'mohirurgii «VOSTOK-ZAPAD». [Collection of scientific papers of the scientific and practical conference with international participation «EAST – WEST»]. Ufa, 2011: 60-61. (in Russ.).
32. Raiskup – Wolf F., Hoyer A., Spoerl E., Pillunat L.E. Collagen crosslinking with riboflavin and ultraviolet – A light in keratoconus: long – term results. J. Cataract Refract. Surg. 2008; 34: 796-801.
33. Bikbov M.M., Bikbova G.M., Khabibullin A.F. [Corneal collagen crosslinking in keratoconus treatment]. [Annals of ophthalmology.] Vestnik oftal'mologii, 2011; 5: 21-25. (in Russ.).
34. Hafezi F., Mrochen M., Iseli H.P., Seiler T. Collagen cross-linking with ultraviolet – A and hypoosmolar riboflavin solution in thin corneas. Journal of Cataract and Refractive Surgery 2009; 35: 4: 621-624.
35. Raiskup-Wolf F., Spoerl E. Reply: long-term results of collagen crosslinking with riboflavin and UVA in keratoconus. J. Cataract Refract. surg. 2008; 34:1617.
36. Yuksel N., Bilgihan K., Hondur A.M. Herpetic keratitis after corneal collagen cross-linking with riboflavin and ultraviolet – A for progressive keratoconus. Int Ophthalmol 2011; 31: 513-515.
37. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. Curr Opin Ophthalmol 2006; 17: 356-360.
38. Dhawan S., K. Rao, Natrajan S. Complications of corneal collagen cross-linking. J Ophthalmol 2011. – Article ID: 869015. Available at: http: www.ncbi.nlm.gov/pmc/articles/PMC3255294/pdf/JOP201. –869015.pdf.Accessed February 2, 2013.
39. Witting – Silva C., Whiting M., Lamoureux E., Lindsay RG, Sullivan LJ, Snibson GR A randomized controlled trial of corneal collagen cross – linking in progressive keratoconus: preliminary results. J Refract Surg. 2008; 24: 720-725.
40. Bubnova I.A., Antonov A.A., Novikov I.A., Sukhanova E.V., Petrov C.Y., Avetisov K.S. [Comparison of different IOP indices in patients with altered biomechemical properties of the cornea]. Glaukoma [Glaucome], 2011; 1:10-14. (in Russ.).
41. Bikbov M.M., Bikbova G.M. [Curative potential of crosslinking in bullous keratopathy treatment]. Oftal'mohirurgija [Ophthalmosurgery]. 2009; 2: 30-33. (in Russ.).
42. Bikbov M.M., Bikbova G.M., Khabibullin A.F. [The usage of corneal collagen crosslinking in bullous keratopathy treatment]. Oftal'mohirurgija [Ophthalmosurgery], 2011; 1: 24-27. (in Russ.).
43. Ferrari G., Luliano L., Vigano M., Rama P. Impending corneal perforation after collagen cross-linking for herpetic keratitis. J. Cataract Refract Surg. 2013; 39: 4: 638.
44. Bikbov M.M., Bikbova G.M. [The results of «MyoRing» intrastromal corneal ring segment implantation combined with corneal collagen crosslinking for keratoconus treatment]. Oftal'mohirurgija [Ophthalmosurgery]. 2012; 4 (4): 6-9. (in Russ.).
45. Bikbov M.M., Usubov E.L., Iskhakova A.K. [KeraRing intrastromal corneal ring segment implantation combined with one-step corneal collagen crosslinking for corneal ectasia]. Kataraktal'naja i refrakcionnaja hirurgija [Cataract Refract surgery]. 2012; 9 (4): 27-30. (in Russ.).
46. Bikbov M.M., Bikbova G.M., Iskhakova A.K. [The results of KeraRing intrastromal corneal ring segment implantation for keratoconus]. Oftal'mohirurgija [Ophthalmosurgery]. 2013; 2 (7): 55-58. (in Russ.).