Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2020, 122, 4: 165–170
Received: 24.04.2020 Accepted: 10.05.2020

ORIGINAL ARTICLE

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2020.101652

Influence of corneal cross-linking on visual acuity and topometric indices in keratoconus

Magdalena Maleszka-Kurpiel[1,2], Andrzej Michalski[3], Marta Robak[1], Wojciech Warchoł[2]

[1]Optegra Eye Health Care Clinic in Poznan, Poland
[2]Department of Optometry, Chair of Ophthalmology and Optometry, Poznan University of Medical Sciences, Poland
[3]Department of Ophthalmology, Chair of Ophthalmology and Optometry, Poznan University of Medical Sciences, Poland

ABSTRACT

Aim of the study: To assess the impact of corneal cross-linking (CXL) in keratoconic eyes on uncorrected (UCVA) and best corrected (BCVA) distance visual acuity, selected corneal parameters measured with a Scheimpflug imaging system, intraocular pressure (IOP) and endothelial cell density (ECD).

Material and methods: 71 eyes of 61 patients treated with CXL were included in the study. Each patient underwent optometric and ophthalmological examination with corneal tomography. Data from the qualifying visit and 1-year post-surgery examination were analyzed.

Results: Comparative analysis of the pre-operative and 1-year post-operative evaluation showed improvement in median UCVA of –0.1 (logMAR) and median BCVA of –0.06 (logMAR). Manifest spherical equivalent showed a median change of almost 0.4 D and the power of the manifest cylinder did not change. The regression in the anterior keratometry steep meridian was greater than in the flat meridian, –0.9 D and –0.6 D respectively. The median Kmax change value was –1.2 D. Topometric indices analysis showed improvement in corneal symmetry. We did not observe changes in IOP and ECD.

Conclusions: CXL is a safe procedure, improving visual acuity, both uncorrected and corrected, and normalizing corneal parameters.

KEY WORDS: CXL, corneal cross-linking, keratoconus treatment, CXL 1-year result.

INTRODUCTION

Keratoconus (KC) is defined as a chronic, bilateral, non-inflammatory corneal disorder characterized by progressive steepening, thinning and scarring of the cornea [1].

The application of novel technologies extends this definition to abnormalities in posterior corneal elevation, corneal thickness distribution and corneal epithelium thickness profile [2, 3].

Keratoconus usually starts at puberty and progresses until the third or fourth decade of life [1]. The prevalence of KC varies widely between published studies. The lowest (0.0003%) was reported in Russia [4]. In other studies values from 0.086% in Denmark and 0.249% in Iran up to 2.3% in India were reported [5-7]. The highest prevalence, reported by Torres *et al.* in a pediatric population in Saudi Arabia, is 4.79% [8]. There are no current data available concerning the KC prevalence in Poland.

Despite numerous genetic and environmental factors which were identified as causing KC, the etiology and mechanism of progression of this ectasia remain unclear and are still under study.

In 2018 in the review publication by Loukovitis *et al.* 24 genes were described as involved in KC etiology [9]. Further investigations include examination of DNA methylation changes in keratoconic eyes [10].

Environmental factors include intensive eye rubbing. It has to be emphasized that eye rubbing is a cause of significant increase of levels of matrix metalloproteinase (MMP)-13, interleukin (IL)-6 and tumor necrosis factor α (TNF-α) in tears of healthy volunteers [11]. It is well correlated with other studies in which levels of IL-6, TNF-α, and MMP-9 are increased in tears of patients with KC [12]. Patients with keratoconus reported more frequent and intense eye rubbing during contact lens use compared to non-keratoconic contact lens (CL) users [13]. Moreover, rigid gas permeable contact lenses (RGP) use increases levels of proinflammatory cytokines and cell adhesion molecules in eyes with KC [14]. Contact lenses play an important role in visual rehabilitation but do not inhibit KC progression [2].

The most important KC-preventive measures include: instructing the patient about the harmful effects of rubbing the

CORRESPONDING AUTHOR
Magdalena Maleszka-Kurpiel, MD, Department of Optometry, Chair of Ophthalmology and Optometry, Poznan University of Medical Sciences, 5D Rokietnicka St., 60-806 Poznan, Poland, e-mail: m.maleszka-kurpiel@optegra.com.pl

Table I. Number of patients by age and gender

Gender	Median age (range)
Females ($n = 7$)	28 (16-43)
Males ($n = 54$)	26 (16-44)

eyes (including after CXL), the use of antiallergic drugs in the case of allergic eye diseases and regular moisturizing of irritated eyes to prevent rubbing [2, 15].

The therapeutic approach includes nowadays both visual function support and corneal structure stabilization. The first covers corrective glasses, CL and RGP use, the latter corneal cross-linking (CXL). Other options include intrastromal corneal ring segments and ultimately penetrating keratoplasty (PK) [16].

Until recently, in the "pre-CXL era", keratoconus treatment options were aimed at improving refraction rather than treating underlying physiopathology [17]. Since the late 1990s CXL has been proposed as a new possibility to slow progression of KC and prevent progressive visual loss and decrease the probability of corneal transplantation [17].

Corneal cross-linking is a treatment method which involves soaking the corneal tissue with vitamin B2-riboflavin and exposing it to UV-A light with a wavelength of 365 nm. As a result of this action, photopolymerization processes occur in the corneal tissue, and new connections between the amino groups are formed. It makes the cornea more rigid and resistant and less susceptible to deformation [18].

The effects of cross-linking include 300 microns of the anterior part of the corneal stroma [19, 20]. According to research the biomechanical properties of the cornea improve by 328.9% [20].

There are two basic types of CXL: epithelium-off cross-linking where epithelium of the cornea is removed to allow the riboflavin to penetrate more easily into corneal tissue; and epithelium-on cross-linking (transepithelial), a method which protects corneal epithelium, making it a less invasive procedure. Sometimes iontophoresis is used to facilitate the penetration of riboflavin through the corneal epithelium [21]. According to the length of exposure, we distinguish a standard protocol lasting 30 minutes and accelerated protocols (ACXL). At present the ACXL protocols are carried out in a shorter period such as 3, 5, or 10 minutes by using 30, 18, or 9 mW/cm^2 irradiance respectively, with a cumulative irradiation dose of 5.4 J/cm^2 [22].

Corneal cross-linking is considered as a safe procedure, but a few complications have been reported, such as wound-healing problems, infectious keratitis or noninfectious keratitis and corneal scarring with irreversible visual acuity lowering [23].

It has to be noted that the rate of PK in KC is decreasing. After analyzing documentation of 21 588 patients Sarezky *et al.* stated that for the period from 2001 to 2012 the rate of PK in KC patients was decreasing, with the most noticeable change in 2009-2012 [24]. The cause of this trend is multifactorial, but it is most likely related to progress in other therapeutic modalities including CXL [24]. It is proven that the CXL procedure achieves long-term effects of stabilization in eyes with progressive KC [25]. Thus CXL ensures clinical, financial, social and psychological advantages in KC management in comparison with other modalities including PK [18, 25].

AIM OF THE STUDY

In this study we evaluated the 1-year functional and structural results of CXL based on uncorrected (UCVA) and corrected (BCVA) distance visual acuity, selected corneal parameters measured with a Scheimpflug imaging system, intraocular pressure (IOP) and endothelial cell density (ECD).

MATERIAL AND METHODS

We included 71 eyes of 61 patients in the study – patients' characteristics are summarized in Table I. The inclusion criteria were: progressive keratoconus, or diagnosed KC in patients under 18 years old, minimal corneal thickness > 400 µm (during radiation). All eyes underwent CXL according to the Dresden Protocol.

Patients with the following criteria were excluded from the study: history of previous eye surgery, history of herpetic keratitis, corneal infection, posthydrops and corneal scarring.

Each patient underwent complete ophthalmological examination. Uncorrected and best corrected distance visual acuity were recorded as the Snellen value and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses. We used manifest refraction for further analysis, not objective refraction (cycloplegic autorefractometry). Slit-lamp anterior segment and dilated funduscopic examination was performed. Assessment of intraocular pressure (non-contact tonometer NT 530, Nidek, Japan) and corneal tomography with the Scheimpflug imaging system WaveLight Oculyzer II, software version 1.20r20 (Alcon, Texas, US) was done. Endothelial cell count was measured using a noncontact endothelial microscope (Specular microscope SP 3000P, Topcon, Japan). Tomographic data taken for further analysis included anterior keratometry (K1, K2), posterior keratometry (K1, K2), anterior maximal keratometry (Kmax), thinnest pachymetry (TCC), index of surface variance (ISV), keratoconus index (Ki), central keratoconus index (CKi), anterior elevation with best fit sphere (anterior BFS) and posterior elevation with best fit sphere (posterior BFS).

Corneal cross-linking was performed in accordance with the standard protocol [26, 27]. In local anesthesia the epithelium was removed before treatment using a blunt spatula, after 20 s exposure of 20% ethyl alcohol. 0.1% riboflavin solution (Riboflavin, Ricrolin, Sooft Italia, Montegiorgio, Italy) was administered every 2 minutes for 30 minutes. The corneal stroma was irradiated using an UV-A device (PXL Platinum 330, Peschke Trade, Switzerland), irradiance level of 3 mW/cm^2 for 30 minutes. Pachymetry was measured before irradiation

to confirm that the thinnest part of the stroma was not below 400 µm. After irradiation, topical antibiotics, steroids and a bandage lens were applied.

The Shapiro-Wilk test was used for testing normality of the distribution of continuous variables. All variables derived in our study were non-normally distributed, and are presented as a median and range (minimum-maximum). The Wilcoxon test was used for comparison of paired values of analyzed variables. All statistical analyses were performed using Statistica version 13 (TIBCO Software Inc. 3307 Hillview Avenue Palo Alto, CA 94304, United States).

The study was approved by the ethics committee of Poznan University of Medical Sciences.

RESULTS

At baseline the UCVA was 0.6 (logMAR), and improved to 0.5 (logMAR) at the 12-month follow-up visit. Preoperative BCVA was 0.16 (logMAR) and at 12 months after surgery improved to 0.1 (logMAR).

We observed slight changes in the subjective refraction sphere median value and no change in cylinder power. However, the spherical equivalent median value improved from –1.25 D to –0.88 D.

There was no change after surgery in median intraocular pressure.

Topographical parameters of the anterior surface of the cornea changed, flat keratometry improved by the median value of –0.6 D and steep keratometry by –0.9 D. K_{max} flattened by the median value –1.2 D.

One year after CXL curvatures of the posterior corneal surface increased by the median value of –0.1 D for both the flat and steep meridian.

Thinnest central cornea was thinner by a median value of –12 µm one year after surgery.

All analyzed corneal indices improved from the baseline values.

We noted a decrease in anterior BFS from a median value of 24 to 21 and decrease in posterior BFS from a median value of 58 to 56; both changes were statistically significant. It should be noted that we analyzed median values and the median change value for posterior BFS is 3.

There was no significant difference in endothelial cell density when compared with the baseline.

All functional and topographic parameters and their postoperative change values are summarized in Table II.

DISCUSSION

Ophthalmology experts in KC from the entire world stated, in A Global Consensus on Keratoconus and Ectatic Diseases, that CXL is indicated in patients with documented disease progression or high risk of progression. 45 experts unanimously stated that CXL should be performed for all patients with keratoconus progression – regardless of age and visual acuity [2]. According to this consensus, KC progression

Table II. Functional and topometric parameters before and after CXL. Sphere, cylinder and spherical equivalent values based on subjective refraction (p: Wilcoxon test)

Parameter	Baseline Median value (range)	1 year after CXL Median value (range)	Change Median value (range)	*p*
UCVA (logMAR)	0.6 (–0.04-1.7)	0.5 (–0.04-1.3)	–0.109 (–0.806-0.301)	0.000003
BCVA (logMAR)	0.16 (–0.04-1)	0.1 (–0.08-(– 0.7))	–0.051 (–0.699-0.204)	0.00002
Sphere [D]	0 (–7-2.25)	0.25 (–4.75-(–3.75))	–0.25 (–5-3)	0.0008
Cylinder [D]	–2 (–6.5-(–0.25))	–2 (–5-(–0.25))	0 (–5.25-2.25)	0.103
Spherical equivalent [D]	–1.25 (–8.75-1)	–0.88 (–6-2.75)	0.38 (–7.13-2.13)	0.0003
IOP [mmHg]	11 (6-20)	11 (5-17)	0 (–8-4)	0.614
Anterior K_1 [D]	44.5 (40.2-52)	43.8 (39.1-52.6)	–0.6 (–5-2.5)	< 0.000001
Anterior K_2 [D]	48.3 (42.6-59.7)	47 (41.1-58.2)	–0.9 (–4-5.4)	< 0.000001
Anterior K_{max} [D]	54.8 (43.9-66.2)	53.2 (42.8-64.8)	–1.2 (–6.3-0.8)	< 0.000001
Posterior K_1 [D]	–6.4 (–7.9-(–5.6))	–6.5 (–8.3-(–5.5))	–0.1 (–1.5-0.7)	0.021
Posterior K_2 [D]	–7.3 (–9.3-(–6.1))	–7.3 (–9.3-(–6.3))	–0.1 (–2.1-0.4)	0.001
TCC [µm]	464 (388-538)	442 (329-534)	–12 (–99-16)	< 0.000001
ISV	87 (23-145)	80 (16-145)	–6 (–58-19)	< 0.000001
Ki	1.23 (1.05-1.53)	1.2 (1.03-1.49)	–0.03 (–0.34-0.08)	< 0.000001
CKi	1.04 (1-1.2)	1.03 (0.96-1.22)	–0.01 (–0.08-0.09)	0.000006
Anterior elevation BFS [µm]	24 (6-44)	21 (4-47)	–2 (–20-11)	0.00004
Posterior elevation BFS [µm]	58 (21-107)	56 (20-120)	3 (–19-33)	0.010
ECD [cells/mm^2]	2610 (1923-3203)	2573 (1900-3341)	–5 (–636-473)	0.267

UCVA – uncorrected distance visual acuity, BCVA – best corrected distance visual acuity, IOP – intraocular pressure, TCC – thinnest central cornea, ISV – index of surface variance, Ki – keratoconus index, CKi – central keratoconus index

is defined as a significant change, constant in time, of at least two of the following parameters:
– increase in the curvature of the front surface of the cornea,
– increase in the curvature of the posterior surface of the cornea,
– thinning and/or increasing the corneal thickness difference between its circumference and the thinnest point [2].

Some authors advocate performing CXL as soon as diagnosis of pediatric KC is made due to the very high rate of keratoconus progression in children (88% in some studies), without waiting for documentation of progression [15, 28]. Therefore, in our study the procedure was performed on patients under 19 years of age immediately.

In our study statistically significant improvement in distance visual acuity was found 12 months after surgery. Changes were more pronounced in UCVA – the median value decreased by 0.1 (logMAR) for UCVA and 0.06 (logMAR) for BCVA. Described values correspond to the change of one or a half of a line in Snellen visual acuity. Our observations are similar to those of Wisse *et al*., who reported that mean logMAR corrected distance visual acuity (CDVA) decreased by 0.13 after CXL [29]. Also Chang *et al.* reported improvement in BCVA above 1 line during post-operative follow-up [30], which is consistent with our observation. The greater improvement in UCVA than in BCVA can be explained by the different effects of high-order and low-order corneal aberrations on visual acuity [31], but we did not check corneal aberrations in our group. Visual acuity improvement after CXL could be related to improvement in the corneal surface regularity [32].

Refractive results showed an improvement of almost 0.4 D in the median value of spherical equivalent. This finding is statistically significant but worse than the results published by Caporossi *et al*., who claimed a 2.5 D improvement [31].

The median value of the cylinder did not change after surgery. Ghanem *et al*. also found improvement in spherical equivalent in the first postoperative year, but no change in cylinder [33]. The studies on refractive change after CXL produced different results, e.g. Sharma *et al.* found a decrease in cylinder power but not in spherical equivalent [34].

The CXL effect is sometimes unexpected. In 2015 Kymionis *et al*. published a case report of a patient who demonstrated significant corneal flattening that led to a +11.1 D change in spherical equivalent over a 5-year period [35]. The decrease in subjective refraction values suggests improvement in corneal regularity, but we have to be aware that repeatability of subjective refraction in consecutive examinations of patient with KC is low [36].

Using the non-contact tonometer no significant difference was found in the change in intraocular pressure from baseline to 12-month check-up. Several authors noted a decrease, while others reported an increase from baseline using the Goldmann applanation tonometer [37, 38]. The study of Caporossi showed that the IOP after CXL depends on the tonometry type [31].

We found that the regression in anterior K2 (steep meridian) was greater than in anterior K1 (flat meridian); –0.9 D and –0.6 D respectively. There are variable results concerning anterior corneal curvature change following CXL. Our results are similar to those published by Polat *et al*. – they reported an approximate decrease of 1.35 D for K1 and 1.9 D for K2 [39]. Steinberg *et al*. found 2 years after CXL a greater decrease in flat than steep meridian [40].

K_{max} changed statistically significantly 1 year after CXL. We noted a median change value of –1.2 D, which is similar to findings from other studies. Chang *et al*. described 1.7 D flattening of Kmax one year after CXL and Arbelaez *et al*. reported a mean 1.4 D of flattening at the apex [30, 41]. In another study the Kmax change was −1.8 ±1.8 D after surgery [42]. Results about corneal flattening were also published by Koller *et al*. They described Kmax flattening > 1 D in more than 50% of patients, and in 13% of patients the Kmax change was even > 2 D [43]. It should be mentioned that there are reported cases with delayed changes in Kmax – observed only between 24 and 36 months of observation after CXL [37, 44]. Several studies showed analysis identifying cone eccentricity as a major factor for predicting outcomes of CXL in Kmax change [29, 45, 46]. In our study we did not assess the cone location.

There are only a few scientific reports regarding the effect of CXL on the posterior surface of the cornea. We noted that in our examined group values of posterior both K1 and K2 increased by a median value of –0.1 D, which was statistically significant and is similar to the results of another study [47]. The lack of improvement in posterior K1 and K2 suggests that the CXL does not have a positive effect on back corneal surface [40, 47].

In our group TCC decreased from a median value of 464 μm to 442 μm.

One study confirmed that corneal thickness reduction is observed after CXL [48]. Also Greenstein *et al*. also observed that pachymetry slightly decreased from baseline to 12 months; they used Scheimpflug imaging [49].

Although analyses of Wittig-Sliva *et al*. indicated that ultrasound pachymetry did not reveal changes in corneal thickness in 3-year follow-up [37], Wu *et al*. proved that in keratoconic eyes Scheimpflug imaging underestimates the corneal thickness [50].

It also may represent a measurement artefact after treatment; this may be due to alterations in light transmission as the result of postoperative corneal haze when using optical methods for measuring corneal thickness [51].

We found improvement of all analyzed topometric parameters after CXL, which is similar to the results from other publications. The stabilization and improvement in corneal topometric indices were proven in previous studies. Toprak *et al*. demonstrated improvements in ISV and CKi after cross-linking with a follow-up of 12 months [52]. Sloot *et al*. found improvements in ISV and CKi one year after cross-linking [53]. Similar observations were reported by Kranitz *et al.* [54].

In our population front and back elevation (BFS) median values decreased (–3 and –2 μm respectively), which is partially similar to the findings of Steinberg *et al*., who stated that

the front surface elevation decreased (–1.5 μm) and the back elevation increased (+2 μm) [40].

The Kohlhaans *et al*. studies showed that treatment of the cornea with riboflavin and UV-A stiffened the cornea in the anterior 300 μm (65% to 70% of UVA irradiation is absorbed within the anterior 200 um). This depth-dependent stiffening effect may explain the flattening in the anterior cornea and the reduction in the anterior elevation [19].

In 2011 Hashemi *et al*. concluded that examining elevation is a better way to demonstrate the long-term effects of CXL and improvements in corneal shape [55].

In our study, we evaluated the safety of standard CXL and found that ECD 1 year after surgery did not show a significant change compared with preoperative values, which indicates that the effect of increased UVA irradiance on endothelial cells was unremarkable. The same was postulated by Kohlhaans *et al*. [19]. Grewal *et al*. also proved that lens density and foveal thickness remain unchanged after CXL, which confirmed its safety [56].

Endothelial failure has been reported occasionally after CXL [57, 58].

Limitations of our study are the relatively small patient group and short observation period. It will be advisable to extend the duration of the study to check the long-term results.

CONCLUSIONS

Corneal cross-linking is the effective and safe therapeutic method of stabilization of keratoconus progression. Both functional and topographical parameters showed improvement 1 year after surgery.

DISCLOSURE

The authors declare no conflict of interest.

References

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998; 42: 297-319.
2. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. Cornea 2015; 34: 359-369.
3. Reinstein DZ, Archer TJ, Gobbe M. Corneal epithelial thickness profile in the diagnosis of keratoconus. J Refract Surg 2009; 25: 604-610.
4. Gorskova EN, Sevost'ianov EN. Epidemiology of keratoconus in the Urals. Vestnik Oftalmologii 1998; 114: 38-40.
5. Nielsen K, Hjortdal J, Nohr EA, et al. Incidence and prevalence of keratoconus in Denmark. Acta Ophthalmol Scand 2007; 85: 890-892.
6. Ziaei H, Jafarinasab MR, Javadi MA, et al. Epidemiology of keratoconus in an Iranian population. Cornea 2012; 31: 1044-1047.
7. Jonas JB, Nangia V, Matin A, et al. Prevalence and associations of keratoconus in rural maharashtra in central India: the central India eye and medical study. Am J Ophthalmol 2009; 148: 760-765.
8. Torres Netto EA, Al-Otaibi WM, Hafezi NL, et al. Prevalence of keratoconus in paediatric patients in Riyadh, Saudi Arabia. Br J Ophthalmol 2018; 102: 1436-1441.
9. Loukovitis E, Sfakianakis K, Syrmakesi P, et al. Genetic aspects of keratoconus: a literature review exploring potential genetic contributions and possible genetic relationships with comorbidities. Ophthalmol Ther 2018; 7: 263-292.
10. Kabza M, Karolak JA, Rydzanicz M, et al. Multiple differentially methylated regions specific to keratoconus explain known keratoconus linkage loci. Invest Ophthalmol Vis Sci 2019; 60: 1501-1509.
11. Balasubramanian SA, Pye DC, Willcox MD. Effects of eye rubbing on the levels of protease, protease activity and cytokines in tears: relevance in keratoconus. Clin Exp Optom 2013; 96: 214-218.
12. Lema I, Durán JA. Inflammatory molecules in the tears of patients with keratoconus. Ophthalmology 2005; 112: 654-659.
13. McMonnies CW. Eye rubbing type and prevalence including contact lens 'removal-relief' rubbing. Clin Exp Optom 2016; 99: 366-372.
14. Lema I, Durán JA, Ruiz C, et al. Inflammatory response to contact lenses in patients with keratoconus compared with myopic subjects. Cornea 2008; 27: 758-763.
15. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric [corrected] corneal collagen cross-linking in children and adolescents [published correction appears in J Refract Surg 2013; 29: 72]. J Refract Surg 2012; 28: 753-758.
16. Mohammadpour M, Heidari Z, Hashemi H. Updates on managements for keratoconus. J Curr Ophthalmol 2017; 30: 110-124.
17. Raiskup F, Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A. I. Principles. Ocul Surf 2013; 11: 65-74.
18. Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg 2008; 34: 796-801.
19. Kohlhaas M, Spoerl E, Schilde T, et al. Biomechanical evidence of the distribution of cross-links in corneas treated with riboflavin and ultraviolet A light. J Cataract Refract Surg 2006; 32: 279-283.
20. 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: 1780-1785.
21. Caporossi A, Mazzotta C, Paradiso AL, et al. Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results. J Cataract Refract Surg 2013; 39: 1157-1163.
22. Wen D, Li Q, Song B, et al. Comparison of standard versus accelerated corneal collagen cross-linking for keratoconus: a metaanalysis. Invest Ophthalmol Vis Sci 2018; 59: 3920-3931.
23. Bödemann M, Kohnen T. Ulcus corneae durch MRSA nach UV/Riboflavin-Crosslinking bei Keratokonus [Corneal ulcer caused by MRSA after UV/riboflavin cross-linking in a patient with bilateral keratoconus]. Ophthalmologe 2012; 109: 1112-1114.
24. Sarezky D, Orlin SE, Pan W, et al. Trends in corneal transplantation in keratoconus. Cornea 2017; 36: 131-137.
25. Raiskup F, Theuring A, Pillunat LE, et al. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. J Cataract Refract Surg 2015; 41: 41-46.
26. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135: 620-627.
27. Brittingham S, Tappeiner C, Frueh BE. Corneal cross-linking in keratoconus using the standard and rapid treatment protocol: differences in demarcation line and 12-month outcomes. Invest Ophthalmol Vis Sci 2014; 55: 8371-8376.

28. Soeters N, van der Valk R, Tahzib NG. Corneal cross-linking for treatment of progressive keratoconus in various age groups. J Refract Surg 2014; 30: 454-460.
29. Wisse RP, Godefrooij DA, Soeters N, et al. A multivariate analysis and statistical model for predicting visual acuity and keratometry one year after cross-linking for keratoconus. Am J Ophthalmol 2014; 157: 519-525.e252.
30. Chang CY, Hersh PS. Corneal collagen cross-linking: a review of 1-year outcomes. Eye Contact Lens 2014; 40: 345-352.
31. Caporossi A, Baiocchi S, Mazzotta C, 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: 837-845.
32. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg 2011; 37: 1282-1290.
33. Ghanem RC, Santhiago MR, Berti T, et al. Topographic, corneal wavefront, and refractive outcomes 2 years after collagen crosslinking for progressive keratoconus. Cornea 2014; 33: 43-48.
34. Sharma N, Suri K, Sehra SV, et al. Collagen cross-linking in keratoconus in Asian eyes: Visual, refractive and confocal microscopy outcomes in a prospective randomized controlled trial. Int Ophthalmol 2015; 35: 827-832.
35. Kymionis GD, Tsoulnaras KI, Liakopoulos DA, et al. Excessive corneal flattening and thinning after corneal cross-linking: single-case report with 5-year follow-up. Cornea 2015; 34: 704-706.
36. Raasch TW, Schechtman KB, Davis LJ, et al. Repeatability of subjective refraction in myopic and keratoconic subjects: results of vector analysis. Ophthalmic Physiol Opt 2001; 21: 376-383.
37. Wittig-Silva C, Chan E, Islam FM, et al. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. Ophthalmology 2014; 121: 812-821.
38. Kymionis GD, Grentzelos MA, Kounis GA, et al. Intraocular pressure measurements after corneal collagen crosslinking with riboflavin and ultraviolet A in eyes with keratoconus. J Cataract Refract Surg 2010; 36: 1724-1727.
39. Polat N, Gunduz A, Colak C. The influence of corneal collagen cross-linking on anterior chamber in keratoconus. Indian J Ophthalmol 2017; 65: 271-275.
40. Steinberg J, Ahmadiyar M, Rost A, et al. Anterior and posterior corneal changes after crosslinking for keratoconus. Optom Vis Sci 2014; 91: 178-186.
41. Arbelaez MC, Sekito MB, Vidal C, et al. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One-year results. Oman J Ophthalmol 2009; 2: 33-38.
42. Ng AL, Chan TC, Cheng AC. Conventional versus accelerated corneal collagen cross-linking in the treatment of keratoconus. Clin Exp Ophthalmol 2016; 44: 8-14.
43. Koller T, Pajic B, Vinciguerra P, et al. Flattening of the cornea after collagen crosslinking for keratoconus. J Cataract Refract Surg 2011; 37: 1488-1492.
44. Vinciguerra P, Albè E, Trazza S, et al. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. Am J Ophthalmol 2012; 154: 520-526.
45. Lamy R, Netto CF, Reis RG, et al. Effects of corneal cross-linking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. Cornea 2013; 32: 591-596.
46. Greenstein SA, Fry KL, Hersh PS. Effect of topographic cone location on outcomes of corneal collagen cross-linking for keratoconus and corneal ectasia. J Refract Surg 2012; 28: 397-405.
47. Safarzadeh M, Nasiri N, Doostdar A, et al. Comparative study of changes of corneal curvatures and uncorrected distance visual acuity prior to and after corneal collagen crosslinking: 1-year results. Taiwan J Ophthalmol 2016; 6: 127-130.
48. Koller T, Iseli HP, Hafezi F, et al. Scheimpflug imaging of corneas after collagen cross-linking. Cornea 2009; 28: 510-515.
49. Greenstein SA, Shah VP, Fry KL, et al. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg 2011; 37: 691-700.
50. Wu W, Wang Y, Xu L. Meta-analysis of Pentacam vs. ultrasound pachymetry in central corneal thickness measurement in normal, post-LASIK or PRK, and keratoconic or keratoconus-suspect eyes. Graefes Arch Clin Exp Ophthalmol 2014; 252: 91-99.
51. Caporossi A, Mazzotta C, Baiocchi S, et al. Long-term results of riboflavin ultraviolet A corneal collagen cross-linking for keratoconus in Italy: the Siena Eye Cross Study. Am J Ophthalmol 2010; 149: 585-593.
52. Toprak I, Yildirim C. Effects of corneal collagen cross-linking on corneal topographic indices in patients with keratoconus. Eye Contact Lens 2013; 39: 385-387.
53. Sloot F, Soeters N, van der Valk R, et al. Effective corneal collagen crosslinking in advanced cases of progressive keratoconus. J Cataract Refract Surg 2013; 39: 1141-1145.
54. Kránitz K, Kovács I, Miháltz K, et al. Changes of corneal topography indices after CXL in progressive keratoconus assessed by Scheimpflug camera. J Refract Surg 2014; 30: 374-378.
55. Hashemi H, Seyedian MA, Miraftab M, et al. Corneal collagen cross-linking with riboflavin and ultraviolet a irradiation for keratoconus: long-term results. Ophthalmology 2013; 120: 1515-1520.
56. Grewal DS, Brar GS, Jain R, et al. Corneal collagen crosslinking using riboflavin and ultraviolet-A light for keratoconus: one-year analysis using Scheimpflug imaging. J Cataract Refract Surg 2009; 35: 425-432.
57. Hafezi F, Kanellopoulos J, Wiltfang R, et al. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. J Cataract Refract Surg 2007; 33: 2035-2040.
58. Gokhale NS. Corneal endothelial damage after collagen cross-linking treatment. Cornea 2011; 30: 1495-1498.