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

Magdalena Maleszka-Kurpiel1,2, Andrzej Michalski3, Marta Robak1, Wojciech Warchol2

1Optegra Eye Health Care Clinic in Poznan, Poland
2Department of Optometry, Chair of Ophthalmology and Optometry, Poznan University of Medical Sciences, Poland
3Department 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
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 shorter period such as 3, 5, or 10 minutes by using 30, 18, or 9 mW/cm² irradiance respectively, with a cumulative irradiation dose of 5.4 J/cm² [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 fundusscopic 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, Soofi 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/cm² 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 Hill-view 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 UCV A 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. $K_{\text{max}}$ 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      |
|-----------------------|-------------------------------|---------------------------------------|-----------------------------|--------|
| UCV A (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)      | 0.000002 |
| 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)                          | –0.25 (–5-0.25)             | 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 K1 [D]       | 44.5 (40.2-52)                | 43.8 (39.3-52.6)                      | –0.6 (–5-2.5)               | <0.000001 |
| Anterior K2 [D]       | 48.3 (42.6-59.7)              | 47 (41.1-58.2)                        | –0.9 (–4.5-4.4)             | <0.000001 |
| Anterior Kmax [D]     | 54.8 (43.9-66.2)              | 53.2 (42.8-64.8)                      | –1.2 (–6-3.8)               | <0.000001 |
| Posterior K1 [D]      | –6.4 (–7.9–5.6)               | –6.5 (–8.3-5.5)                       | –0.1 (–1.5-0.7)             | 0.021   |
| Posterior K2 [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 (–18-19)                 | <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 (1.1-1.2)                | 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 (–2-11)                  | 0.00004 |
| Posterior elevation BFS [µm] | 58 (21-107)   | 56 (20-120)                           | 3 (–19-33)                  | 0.010   |
| ECD [cells/mm²]       | 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 Goldman 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].

Kmax 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 Kohlhaas 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 μm). 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 irradiation on endothelial cells was unremarkable. The same was postulated by Kohlhaas 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.

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