Corneal Cross-linking for Treatment of Progressive Keratoconus in Various Age Groups

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ABSTRACT

PURPOSE: To compare the effect of corneal cross-linking (CXL) for keratoconus in various age groups and to investigate the influence of the topographic cone location on the outcome of CXL.

METHODS: This cohort study included 95 patients (119 eyes) diagnosed as having progressive keratoconus who underwent epithelium-off standard protocol CXL from January 2010 through May 2012. For statistical analysis, patients were divided into three age groups: pediatric patients (< 18 years), adolescent patients (18 to 26 years), and adults (> 26 years). Visual acuity and refraction, topography, intraocular pressure, and endothelial cell counts were recorded preoperatively and postoperatively.

RESULTS: Topographic cones were located more centrally in pediatric corneas (0.85 ± 0.66 mm) compared to adolescent corneas (1.49 ± 0.76 mm, $P = .002$) and adult corneas (1.86 ± 0.99 mm, $P < .001$). Pediatric corneas flattened 1 year after CXL by a mean of 1.8 diopters (D), compared to 1.1 D in the other age groups. Central cones (0 to 1 mm) were steeper (62.3 ± 8.3 D) before treatment than peripheral cones (3 to 4 mm) (55.9 ± 8.9 D). One year after CXL, corrected distance visual acuity improved in all age groups, with the highest improvement in pediatric eyes (-0.23 ± 0.40 logMAR, $P = .044$).

CONCLUSIONS: Before CXL, cones of pediatric keratoconic corneas were located more centrally than in the two older age groups. After CXL, pediatric corneas showed more corneal flattening and more corrected distance visual acuity improvement. Pediatric CXL was equally safe compared to adolescent and adult CXL.

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Keratoconus can be progressive, leading to increased corneal weakening and thinning. The severity of the disease seems inversely correlated with age. Consequently, children with keratoconus are of specific concern when it comes to corneal changes and rate of progression.[1-3]

Keratoconus progression can be halted by corneal cross-linking (CXL). CXL consists of the application of ultraviolet-A light to corneas pretreated with riboflavin (vitamin B2) and has shown increased corneal biomechanics.[4] Until recently, CXL was primarily performed in patients older than 18 years.[5] However, because progression in pediatric patients can be rapid and requires closer clinical observation, earlier intervention by CXL could be neccessary.[6] In a small case series, our group demonstrated good results of CXL in children.[7] Another report described corneal stabilization after CXL in 95% of patients younger than 18 years.[8] Rapid visual recovery and stabilization of keratoconus after CXL in pediatric eyes are also reported in several other studies; however, the clinical effect seems to diminish 3 years after treatment.[9-13] Various reports have been published on results of CXL in the older age group. Patients older than 27 years show a positive but poorer functional response compared to other age groups.[8] CXL in patients older than 35 years seems to increase the risk of loss of Snellen lines.[14] Less successful results have been described in patients older than 40 years compared to other age groups.[15]

A valuable effect of CXL, occurring in approximately 50% of patients, is a decrease in maximal keratometry (Kmax), also

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called "flattening."[16] In 2011, a simulated CXL model showed that central and eccentric cones responded differently on different beam profiles.[17] To our knowledge, until now, CXL has only been performed with a standard beam, irradiating the center of the cornea. An investigation of clinical CXL outcome in patients treated by a standard beam showed a reduction of treated tissue depth toward the periphery of the cornea.[18,19]

In this report, we evaluated clinical CXL effects in pediatric, adolescent, and adult patients. Furthermore, we investigated whether a decrease in keratometry after CXL is influenced by the topographic cone location or age, and whether a centered beam changed cone locations.

PATIENTS AND METHODS

Study Design and Patient Population

This cohort study included all patients who consequently underwent a CXL procedure for progressive keratoconus at the University Medical Center Utrecht, the Netherlands, from January 2010 to May 2012.

Inclusion criteria for CXL treatment were documented keratometric progression of keratoconus in the previous 1 to 3 months (pediatric patients) or 6 to 12 months (adolescent and adult patients), a centrally clear cornea, a minimal corneal thickness of 400 µm prior to ultraviolet-A irradiation, no pregnancy or breastfeeding in the past 6 months, and no history of previous ocular surgery. We applied hypo-osmolar riboflavin drops during CXL when necessary to achieve the minimally required corneal thickness of 400 µm prior to ultraviolet-A irradiation.

Approval by the UMCU Ethics Review Board and the requirement for informed consent was waived because data were analyzed anonymously and were non-identifiable. The CXL treatment was in accordance with the tenets of the Declaration of Helsinki and local laws regarding research using human subjects.

Preoperative Evaluation

Keratoconus was diagnosed or confirmed by Scheimpflug imaging and slit-lamp examination. Preoperative progression of keratoconus was documented by at least two topography measurements.

CXL Procedure

Standard CXL was performed as described before, using isotonic riboflavin 0.1% solution (Medio Cross; Peschke GmbH, Hünenberg, Switzerland) every 3 minutes for 30 minutes.[20] Ultraviolet-A irradiation was performed during 30 minutes and isotonic riboflavin solution was re-applied every 5 minutes. Finally, a bandage lens was placed and oral pain medication and antibiotic eye drops were prescribed.

Measurements and Devices

Patients were examined before and 1, 3, 6, and 12 months after CXL. Refraction, visual acuity, topography, non-contact tonometry, and slit-lamp examination were performed at each preoperative and follow-up visit. For topography measurements, a Scheimpflug device (Pentacam; Oculus Optikgeräte, Wetzlar, Germany) was used. Endothelial cell density was analyzed by specular microscopy (SP3000P; Topcon, Tokyo, Japan) preoperatively and 6 and 12 months postoperatively. The CXL device (UV-X; Peschke Meditrade, Switzerland) used an irradiance of 3 mW/cm^2.

Contact lens wearers were instructed to remove their lenses 2 weeks prior to baseline evaluation and follow-up visits.

Topographic Cone Location

The Pentacam anterior sagittal curvature map shows coordinates (distances in x and y values in mm) of the steepest corneal location (Kmax) to the corneal apex. The distance from the pupil center to Kmax was calculated by the sum of the pupil–apex distance and the Kmax–apex distance by Pythagoras' theorem (**Figure A**, available in the online version of this article).

Statistical Analysis

For statistical analysis, patients were divided into the following groups (**Table 1**): younger than 18 years, 18 to 26 years, and older than 26 years. Topographic cone location (distance pupil center to maximal keratometry) was less than 1 mm, 1 to less than 2 mm, 2 to less than 3 mm, and 3 to less than 4 mm. Change in Kmax 1 year after CXL (according to Koller et al.[16]) was defined as Kmax regression (> 1 D decrease in Kmax), Kmax stabilization (± 1 D in Kmax), and Kmax progression (> 1 D increase in Kmax). Krumeich keratometric classification[21] (referring to Pentacam mean keratometry value) was defined as I (< 48 D), II (48.1 to 53.0 D), III (53.1 to 55.0 D), and IV (> 55 D).

Normality of the data was tested using the Shapiro–Wilk test. Differences between preoperative and postoperative CXL were calculated with a paired sample *t* test. To evaluate for significant differences between groups, the one-way analysis of variance was used. Tukey's post-hoc test was used to determine which group was different. All tests were performed in SPSS version 20.0 for Windows software (SPSS, Inc., Chicago, IL). A *P* value less than .05 was considered statistically significant. Data were recorded as mean ± standard deviation.

RESULTS

Characteristics of patients and patient distribution are shown in **Table 1**. This study included 119 eyes

TABLE 1
Baseline Characteristics of Different Groups and Outcome 1 Year After Corneal Cross-Linking[a]

Group	No.	Cone Location (mm)	Preoperative Kmax (D)	CDVA Improvement (logMAR)
Age (y)				
< 18	31 (26%)	0.85 ± 0.66[b] (0.61 to 1.09)	60.5 ± 9.2 (56.8 to 63.6)	-0.23 ± 0.4[a] (-0.38 to -0.08)
18 to 26	56 (47%)	1.49 ± 0.76 (1.28 to 1.69)	59.1 ± 8.6 (56.7 to 61.3)	-0.08 ± 0.2 (-0.14 to -0.03)
> 26	32 (27%)	1.86 ± 0.99 (1.50 to 2.21)	59.7 ± 9.3 (56.2 to 62.9)	-0.11 ± 0.19 (-0.18 to -0.03)
Cone (mm)				
< 1	44 (37%)	0.53 ± 0.28 (0.44 to 0.61)	62.3 ± 8.3 (59.8 to 64.9)	-0.19 ± 0.39 (-0.32 to -0.07)
1 to < 2	44 (37%)	1.51 ± 0.29 (1.43 to 1.60)	58.9 ± 9.8 (55.9 to 61.9)	-0.1 ± 0.18 (-0.16 to -0.05)
2 to < 3	22 (19%)	2.36 ± 0.28 (2.23 to 2.48)	56.1 ± 6.8 (53.1 to 59.1)	-0.08 ± 0.13 (-0.14 to -0.02)
3 to < 4	8 (7%)	3.28 ± 0.26 (3.06 to 3.49)	55.9 ± 8.9 (48.7 to 63.0)	-0.02 ± 0.18 (-0.19 to 0.14)
Outcome				
Regression	52 (47%)	1.17 ± 0.82 (0.94 to 1.40)	61.8 ± 7.6 (59.6 to 63.9)	-0.14 ± 0.3 (-0.23 to -0.06)
Stable	48 (43%)	1.71 ± 0.88[b] (1.44 to 1.96)	56.2 ± 8.1[b] (53.8 to 58.5)	-0 08 ± 0.20 (-0.14 to -0.02)
Progression	11 (10%)	1.48 ± 0.94 (0.85 to 2.11)	63.7 ± 12.1 (55.6 to 71.8)	-0.26 ± 0.35 (-0.49 to -0.02)
Krumeich				
I	52 (44%)	1.78 ± 0.90 (1.53 to 2.02)	52.1 ± 4.1 (50.9 to 53.2)	-0.08 ± 0.14 (-0.11 to -0.04)
II	39 (33%)	1.34 ± 0.78 (1.08 to 1.60)	61.4 ± 4.9 (59.8 to 63.0)	-0.13 ± 0.22 (-0.20 to -0.06)
III	12 (10%)	0.91 ± 0.56 (0.56 to 1.27)	67.4 ± 5.8 (63.7 to 71.1)	-0.27 ± 0.49 (-0.62 to 0.09)
IV	16 (13%)	0.86 ± 0.79 (0.43 to 1.28)	72.7 ± 6.3 (69.3 to 76.0)	-0.19 ± 0.45 (-0.44 to 0.06)

Kmax = maximal keratometry; CDVA = corrected distance visual acuity; D = diopter
[a]Values are mean ± standard deviation (95% confidence interval).
[b]Statistically significant.

of 95 patients (64 males and 31 females, age range: 12 to 49 years). A loss to follow-up of 6.7% (8 of 119 eyes) was recorded due to moving abroad (n = 2) or unknown reasons (n = 6). The mean age was 15 years (range: 12 to 17 years) in the pediatric group, 22 years (range: 18 to 26 years) in the adolescent group, and 33 years (range: 26 to 49 years) in the adult group.

Hypo-osmolar treatments were applied in 3 of 31 eyes in the pediatric group, 7 of 56 eyes in the adolescent group, and 7 of 32 eyes in the adult group.

Clinical Outcome

Visual Acuity (logMAR). Before CXL, there was no statistically significant difference in uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) between the three age groups ($P = .10$ and .935, respectively). One year after CXL, there was no statistically significant difference in UDVA ($P = .229$), whereas CDVA improved significantly in all age groups. CDVA in pediatric patients improved statistically and significantly more than in adolescents ($P = .044$). No statistically significant difference was found between adolescent and adult patients ($P = .945$) and between pediatric and adult patients ($P = .164$). In 37 of 111 eyes (33%), CDVA increased 2 lines or more.

Before CXL, CDVA was statistically significantly worse in central cones than in peripheral cones: 0.45 ± 0.41 logMAR (0 to 1 mm) versus 0.27 ± 0.29 logMAR ($P = .045$), 0.13 ± 0.16 logMAR ($P = .001$) and 0.16 ± 0.25 logMAR ($P < .090$) in cones 1 to 2 mm, 2 to 3 mm, and 3 to 4 mm, respectively. One year after CXL, there was no significant difference in CDVA improvement between the cone groups or in the three groups divided into Kmax change (**Tables 1-2**).

Cone Location. There was a statistically significant difference in cone location at baseline between the three age groups ($P < .001$); cones were more centrally located in pediatric compared to adolescent ($P = .002$) and adult ($P < .001$) corneas (**Table 1**).

When comparing mean cone location in the overall patient group between baseline (1.43 ± 0.88 mm) and 1 year after CXL (1.58 ± 0.95 mm), a statistically significant difference was found ($P = .015$). Central cones (group < 1 mm) decentered significantly by 0.33 ± 0.63 mm, and the other three groups remained unchanged ($P = .093$) (**Table 3**). There was no statistically significant

TABLE 2

Visual Acuity and Keratometry Outcomes in Three Different Age Groups 1 Year After Corneal Cross-linking[a]

Group	UDVA (logMAR)	CDVA (logMAR)	Kmax (D)	Ksteep (D)	Kflat (D)	Kmean (D)
<18 years						
Preoperative	0.83 ± 0.58 (0.62 to 1.04)	0.41 ±0.47 (0.24 to 0.58)	60.5 ± 9.2 (56.8 to 63.6)	52.5 ± 5.6 (50.4 to 54.6)	48.3 ± 4.8 (46.5 to 50.1)	50.3 ± 5.0 (48.4 to 52.1)
12 months postoperative	0.65 ± 0.62 (0.42 to 0.89)	0.19 ±0.29 (0.08 to 0.30)	58.7 ± 8.4 (55.5 to 61.9)	52.2 ± 5.7 (50.0 to 54.4)	47.9 ± 4.7 (46.1 to 49.7)	49.9 ± 5.0 (48.0 to 51.8)
P	.012[b] (.04 to .32)	.003[b] (.08 to .39)	.014[b] (.40 to 3.20)	.06 (-.20 to 1.0)	.085 (-.05 to .80)	.032[b] (.00 to .80)
18 to 26 years						
Preoperative	0.79 ± 0.46 (0.66 to 0.91)	0.25 ± 0.25 (0.18 to 0.31)	59.1 ± 8.6 (56.7 to 61.3)	51.0 ± 5.3 (49.6 to 52.4)	47.1 ± 4.4 (45.8 to 48.2)	48.9 ± 4.6 (47.7 to 50.1)
12 months postoperative	0.74 ± 0.50 (0.60 to 0.88)	0.17 ± 0.24 (0.10 to 0.24)	57.9 ± 8.3 (55.7 to 60.2)	50.4 ± 5.5 (48.9 to 51.9)	47.0 ± 4.7 (45.8 to 48.3)	48.6 ± 4.8 (47.3 to 49.9)
P	.444 (-.07 to .16)	.004[b] (.03 to .14)	< .001[b] (.70 to 1.60)	.001[b] (.30 to 1.00)	.667 (-.30 to .40)	.026[b] (.00 to .60)
> 26 years						
Preoperative	0.80 ± 0.55 (0.59 to 1.00)	0.32 ± 0.33 (0.20 to 0.44)	59.7 ± 9.3 (56.2 to 62.9)	51.4 ± 5.4 (49.5 to 53.3)	47.5 ± 4.9 (45.8 to 49.3)	49.4 ± 4.9 (47.6 to 51.1)
12 months postoperative	0.83 ± 0.52 (0.63 to 1.03)	0.21 ± 0.27 (0.10 to 0.31)	58.6 ± 9.3 (55.0 to 62.2)	51.0 ± 6.0 (48.7 to 53.4)	46.9 ±5.3 (44.8 to 49.0)	49.1 ± 5.8 (46.9 to 51.4)
P	.927 (-.17 to .19)	.008[b] (.03 to .18)	.033[b] (.10 to 2.10)	.374 (-.50 to 1.20)	.199 (-.30 to 1.30)	.802 (-.80 to 1.10)

UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; Kmax = maximal keratometry; D = diopters; Ksteep = steepest central keratometry; Kflat= flattest central keratometry; Kmean = mean central keratometry
[a]Values are mean ± standard deviation (95% confidence interval).
[b]Statistically significant.

TABLE 3

Change in Topographic Cone Location in Different Groups After Corneal Cross-linking[a]

Cone	No.	Preoperative (mm)	12 Months Postoperative (mm)	Change (mm)	*P*
0 to < 1 mm	44 (37%)	0.53 ± 0.28 (0.44 to 0.61)	0.85 ± 0.63 (0.65 to 1.05)	0.33 ± 0.63 (0.13 to 0.54)	.002[b]
1 to < 2 mm	44 (37%)	1.51 ± 0.29 (1.43 to 1.60)	1.60 ± 0.64 (1.40 to 1.80)	0.09 ± 0.63 (-0.10 to 0.29)	.354
2 to < 3 mm	22 (19%)	2.36 ± 0.28 (2.23 to 2.48)	2.33 ± 0.72 (2.00 to 2.66)	-0.04 ± 0.58 (-0.30 to 0.22)	.747
3 to < 4 mm	8 (7%)	3.28 ± 0.26 (3.06 to 3.49)	3.28 ± 0.63 (2.70 to 3.86)	-0.01 ± 0.47 (-0.45 to 0.42)	.930

Cone = distance pupil center to maximal keratometry
[a]Values are mean ± standard deviation (95% confidence interval).
[b]Statistically significant.

difference between the age groups in change of cone location after CXL.

Kmax. One year after CXL, Kmax decreased statistically significantly in all age groups without significant difference between the three age groups (**Table 2**). A topographic flattening (ie, a decrease in Kmax by > 1 D, 1 year after CXL) was observed in 52% of eyes in the pediatric group compared to 43% in the adolescent and 50% in the adult group.

Before CXL, there was a statistically significant difference in Kmax between the cone location groups; central cones showed higher Kmax values (**Table 1**). One year after CXL, Kmax decreased significantly in central cones (0 to 1 mm) by 2.0 ± 3.3 D ($P < .001$) and 1.1 ± 1.9 D (cones 1 to 2 mm, $P = < .001$), and non-significantly by 0.6 ± 2.1 D (cones 2 to 3 mm, $P = .226$) and 0.5 ± 1.8 D (cones 3 to 4 mm, $P = .481$). This difference in Kmax decrease was non-significant between the cone location groups ($P = .133$).

Patients with stable Kmax 1 year after CXL showed statistically significant flatter and more peripheral

cones before CXL compared to patients with regression or progression of Kmax (P = .001).

Endothelial Cell Density. No statistically significant difference was found in endothelial cell density by age group and between the groups (P = .439) 1 year after CXL (**Table A**, available in the online version of this article).

Corneal Thickness. One year after CXL, corneal thickness decreased statistically significantly in the three age groups with a significant difference between the three age groups only at the thinnest location of the cornea (P = .046) (**Table A**). Corneal thickness in adult corneas decreased statistically significantly more (-17 ± 33 µm, P = .036) than in adolescent corneas (-4 ± 13 µm), and corneas in adults remained statistically significantly thinner than in the other age groups (P = .005).

Epithelial Healing. Epithelium healed after 1 week in 89 of 119 eyes (75%), between 1 and 2 weeks in 25 eyes (21%), and after 2 weeks in 3 eyes (3%) (2 in the pediatric and 1 in the adolescent group). In 2 eyes (2%), the timing of epithelial healing was unknown due to a consult elsewhere. There was no significant difference in epithelial healing time between the age groups (P = .456).

Complications

Two eyes (1 adolescent and 1 adult eye) developed sterile infiltrate(s) 1 week postoperatively. The antibiotics and fluorometholone drops were increased to four times daily for 6 weeks. In 1 eye, decimal CDVA increased from 0.2 (before CXL) to 0.4 after 1 year, with less dense white opacities (**Figure B**, available in the online version of this article). In the other eye, CDVA remained stable (1.25 decimal preoperatively and postoperatively), presenting a totally clear cornea after 1 year.

One adolescent patient developed a herpes simplex keratitis de novo 1 week (right eye) and 2 months (left eye) after CXL, confirmed by polymerase chain reaction testing. Decimal CDVA remained stable after 1 year (0.8).

Two eyes in the adolescent group developed a deep stromal haze, one presenting 3 months after CXL, resulting in a stable decimal CDVA of 0.1 compared to preoperatively. From the other eye, the time of onset is unclear due to follow-up loss. Decimal CDVA improved from 0.16 to 0.3 after 1 year.

One year postoperatively, CDVA decreased two or more lines in 1 of 29 (3%) pediatric eyes, 3 of 54 (6%) adolescent eyes, and 2 of 28 (7%) adult eyes. Kmax increased by more than 1 D in 4 of 29 (14%) pediatric eyes, 3 of 54 (6%) adolescent eyes, and 4 of 28 (14%) adult eyes.

DISCUSSION

This study compared the 1-year outcome of CXL for keratoconus in pediatric, adolescent, and adult patients. We found more visual improvement and corneal flattening of Kmax in pediatric patients compared to the older patient groups. Furthermore, this study showed that, in keratoconus, the steepness of the cone is related to the topographical location; centrally located cones were steeper than peripherally located cones. This finding is consistent with the results of Greenstein et al.[19]

In addition, we found that pediatric patients showed more centrally located cones before CXL and that adult patients showed more peripherally located cones. This is in line with Léoni-Mesplié et al., who investigated the severity of keratoconus in children.[22] Their study showed that corneas were significantly steeper in children at the time of diagnosis compared to adults; however, cone locations were not investigated. Our study showed a trend to steeper Kmax values in pediatric compared to adolescent and adult patients. Caporossi et al. also compared CXL in three age groups.[8] Their pediatric group showed flatter corneas and better UDVA and CDVA than the older age groups, whereas in our pediatric group and in the children in the study by Léoni-Mesplié, corneas were steeper than in adults. An explanation why corneal steepness was different between these three study groups remains unclear. Ertan and Muftuoglu investigated clinical keratoconus findings according to age and expected to find more progressed keratoconus and steeper corneas in the older population, but found no significant correlation between age and keratometry values.[1]

One year after CXL, Kmax decreased significantly in all age groups, with more corneal flattening in pediatric patients. Corneal flattening has been previously described by Koller et al., but that report showed no impact of age on the amount of corneal flattening.[16] An interesting finding in our study is that patients with stable Kmax 1 year postoperatively showed flatter corneas and more peripherally located cones before CXL compared to patients with flattening or even keratometric progression. This finding is in line with another study we recently published, in which we demonstrated more pronounced postoperative CXL flattening in advanced cases of keratoconus.[20]

According to Greenstein et al., more corneal flattening seems to occur after CXL in eyes with centrally located cones, whereas peripherally located cones seem to show the least corneal flattening.[19] The authors divided the groups differently than in our study: less than 3 mm, 3 to 5 mm, and greater than 5 mm, whereas none of the cones exceeded the 4-mm zone in our

patient groups. Possibly, some patients with a different corneal thinning disorder, such as pellucid marginal degeneration, were included, which involves more peripherally located cones.[23] Frequently, topographic patterns of keratoconus and pellucid marginal degeneration overlap, which can make it challenging to distinguish between them.[24] Nonetheless, in our study, patients with centrally located cones showed a trend toward more flattening after 1 year (-2.0 D in central cones [0 to 1 mm]) versus -0.5 D in peripheral cones (3 to 4 mm).

As investigated by Roy and Dupps, central and eccentric cones seem to respond differently to CXL.[17] In our study, corneas were irradiated with a standard ultraviolet-A beam, centered on the central cornea. One year after CXL, centrally located cones (group: 0 to 1 mm) had decentered by an average of 0.33 mm, whereas the location of peripheral cones remained unchanged. These clinical findings are in contrast to the results of the theoretical model by Roy and Dupps[17] and to a report of Tu and Aslanides, who both reported a centralization of peripheral cones.[25] The authors attributed the anterior elevation changes to the anisotropy of collagen distribution. In our opinion, a beam that solely irradiates the cone is probably not feasible in daily practice, because irradiation is generally performed in patients who are awake during treatment and try to keep their eyes as still as possible during 30 minutes. A beam that only irradiates the cone seems impossible without an integrated eye-tracker.

We found that the pediatric group showed the highest CDVA improvement after CXL. Recently, our study group published a prediction model that showed that CDVA 1 year after treatment can be predicted based on CDVA before CXL.[26] Patients with worse CDVA are likely to improve, and this effect diminishes and seems to reverse in patients with a decimal CDVA of 0.8 or better. In the current study, the pediatric group showed worse CDVA at baseline compared to the older age groups, which could explain why this group improved most after CXL. Another explanation for the higher CDVA improvement in pediatric patients could be the improvement of optical aberration values, such as coma. Caporossi et al. described this improvement of coma in pediatric but also older patients after CXL.[8] Because we did not analyze changes in optical aberrations, this should be considered a weakness of our study.

One year after CXL, corneal thickness had significantly decreased in all patient groups. This finding is in accordance with Greenstein et al.[27] Caporossi et al.[28] and O'Brart et al.[29] concluded that corneal thickness returns to baseline values at much longer follow-up time points than in our study (4 to 6 years).

Regarding the safety of the CXL procedure, we found no difference in amount of complications (eg, epithelial healing problems and corneal infiltrates), visual loss, or treatment failure between the age groups.

Pediatric patients seem to benefit more from CXL in terms of visual improvement. Before CXL, their cones are located more centrally than in older patients, and their corneas flatten more after CXL. CXL seems to be an equally safe treatment, independent of age. Sustainability of the CXL effect in pediatric patients needs further investigation because keratoconus in young patients can progress rapidly.

AUTHOR CONTRIBUTIONS

Conception and design (NS, NGT); data collection (NS); analysis and interpretation of data (NS, RV, NGT); writing the manuscript (NS, RV, NGT); critical revision of the manuscript (RV, NGT); statistical expertise (NS); supervision (RV, NGT)

REFERENCES

1. Ertan A, Muftuoglu O. Keratoconus clinical findings according to different age and gender groups. *Cornea*. 2008;27:1109-1113.
2. Reeves SW, Stinnett S, Adelman RA, Afshari NA. Risk factors for progression to penetrating keratoplasty in patients with keratoconus. *Am J Ophthalmol*. 2005;140:607-611.
3. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. *Ophthalmology*. 1994;101:439-447.
4. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res*. 1998;66:97-103.
5. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a–induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620-627.
6. Randleman JB. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. *Am J Ophthalmol*. 2013;155:612-613.
7. Soeters N, Van der Lelij A, van der Valk R, Tahzib NG. Corneal crosslinking for progressive keratoconus in four children. *J Pediatr Ophthalmol Strabismus*. 2011;48:e26-e29.
8. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R. Age-related long-term functional results after riboflavin UVA corneal cross-linking. *J Ophthalmol*. 2011;2011:608041.
9. Zotta PG, Moschou KA, Diakonis VF, et al. Corneal collagen cross-linking for progressive keratoconus in pediatric patients: a feasibility study. *J Refract Surg*. 2012;28:793-799.
10. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric corneal collagen cross-linking in children and adolescents. *J Refract Surg*. 2012;28:753-758.
11. Vinciguerra P, Albé E, Frueh BE, Trazza S, Epstein D. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. *Am J Ophthalmol*. 2012;154:520-526.
12. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R, Balestrazzi A. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. *Cornea*. 2012;31:227-231.
13. Arora R, Gupta D, Goyal JL, Jain P. Results of corneal collagen cross-linking in pediatric patients. *J Refract Surg*. 2012;28:759-762.

14. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg*. 2009;35:1358-1362.
15. Vinciguerra R, Romano MR, Camesasca FI, et al. Corneal cross-linking as a treatment for keratoconus: four-year morphologic and clinical outcomes with respect to patient age. *Ophthalmology*. 2013;120:908-916.
16. Koller T, Pajic B, Vinciguerra P, Seiler T. Flattening of the cornea after collagen crosslinking for keratoconus. *J Cataract Refract Surg*. 2011;37:1488-1492.
17. Roy AS, Dupps WJ. Patient-specific computational modeling of keratoconus progression and differential responses to collagen cross-linking. *Invest Ophthalmol Vis Sci*. 2011;52:9174-9187.
18. Koller T, Schumacher S, Fankhauser F II, Seiler T. Riboflavin/ultraviolet a crosslinking of the paracentral cornea. *Cornea*. 2013;32:165-168.
19. 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.
20. Sloot F, Soeters N, van der Valk R, Tahzib NG. Effective corneal collagen crosslinking in advanced cases of progressive keratoconus. *J Cataract Refract Surg*. 2013;39:1141-1145.
21. Krumeich JH, Daniel J, Knülle A. Live-epikeratophakia for keratoconus. *J Cataract Refract Surg*. 1998;24:456-463.
22. Léoni-Mesplié S, Mortemousque B, Touboul D, et al. Scalability and severity of keratoconus in children. *Am J Ophthalmol*. 2012;23:1-8.
23. Wang M. Keratoconus vs pellucid marginal degeneration. In: Wang M, ed. *Keratoconus and Keratoectasia: Prevention, Diagnosis, and Treatment*. Thorofare, NJ: SLACK Incorporated; 2010:39.
24. Lee BW, Jurkunas UV, Harissi-Dagher M, et al. Ectatic disorders associated with a claw-shaped pattern on corneal topography. *Am J Ophthalmol*. 2007;144:154-156.
25. Tu KL, Aslanides IM. Orbscan II anterior elevation changes following corneal collagen cross-linking treatment for keratoconus. *J Refract Surg*. 2009;25:715-722.
26. Wisse RP, Godefrooij DA, Soeters N, Imhof SM, Van der Lelij A. A multivariate analysis and statistical model for predicting visual acuity and keratometry one year after crosslinking for keratoconus. *Am J Ophthalmol*. 2014;157:519-525.
27. Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:691-700.
28. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. 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.
29. O'Brart DPS, Kwong TQ, Patel P, McDonald RJ, O'Brart NA. Long-term follow-up of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linking to halt the progression of keratoconus. *Br J Ophthalmol*. 2013;97:433-437.

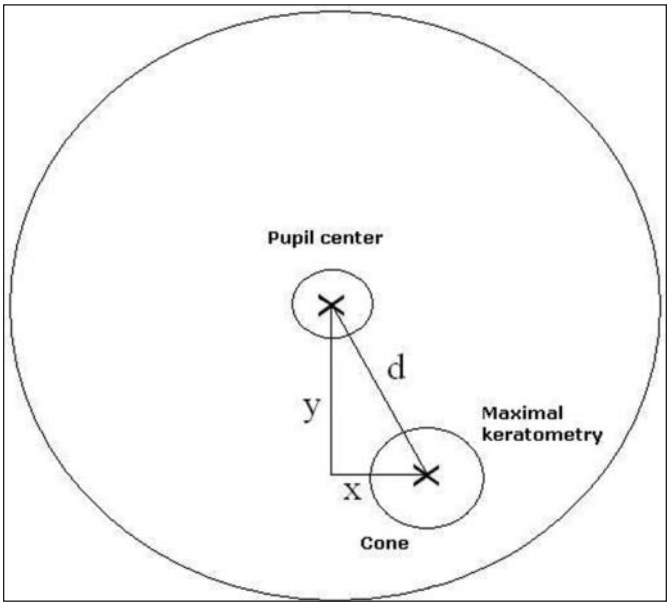

Figure A. Cone location: the distance from pupil center to maximal keratometry location, measured by Pentacam topography (Oculus Optikgeräte, Wetzlar, Germany).

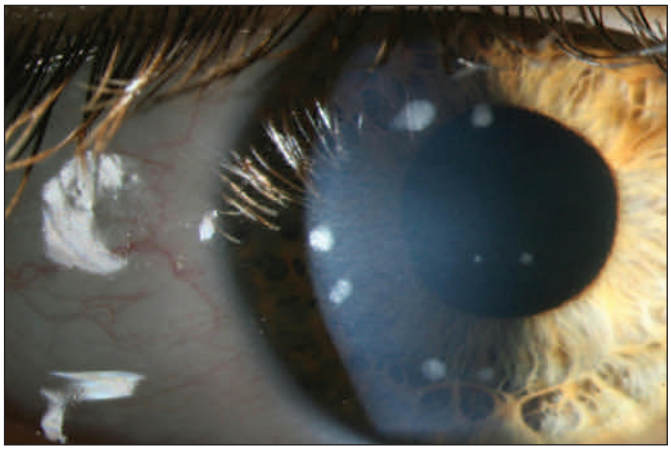

Figure B. Cornea 1 month after corneal cross-linking. Multiple sterile infiltrates developed 1 week after treatment.

TABLE A

Corneal Thickness, Endothelium, and Cone Location Outcome in Three Different Age Groups 1 Year After Corneal Cross-linking

Group	CCTCenter (μm)	CCTApex (μm)	CCTThin (μm)	ECD (cells/mm²)	Cone Location (mm)
<18 years					
Preoperative	482 ± 38 (469 to 496)	475 ± 40 (460 to 489)	461 ± 41 (447 to 476)	2,832 ± 241 (2,712 to 2,951)	0.85 ± 0.7 (0.6 to 1.1)
12 months postoperative	472 ± 38 (457 to 487)	464 ± 42 (448 to 480)	451 ± 41 (435 to 466)	2,787 ± 310 (2,633 to 2,941)	1.06 ± 0.7 (0.8 to 1.3)
P	.009[b] (3 to 16)	.007[a] (3 to 16)	.010[b] (2 to 16)	.391 (-63 to 154)	.055 (-.5 to .0)
18 to 26 years					
Preoperative	486 ± 40 (475 to 497)	476 ± 45 (464 to 488)	459 ± 45 (447 to 471)	2,851 ± 243 (2,753 to 2,950)	1.50 ± 0.8 (1.3 to 1.7)
12 months postoperative	483 ± 41 (473 to 495)	474 ± 45 (462 to 486)	457 ± 46 (444 to 469)	2,895 ± 261 (2,790 to 3,000)	1.55 ± 0.9 (1.3 to 1.8)
P	.025[b] (1 to 8)	.044[b] (0 to 8)	.013[b] (1 to 8)	.363 (-140 to 53)	.215 (-.2 to .1)
> 26 years					
Preoperative	484 ± 38 (71 to 498)	459 ± 46 (41 to 477)	438 ± 47 (420 to 456)	2,708 ± 370 (2,473 to 2,943)	1.94 ± 1.0 (1.6 to 2.3)
12 months postoperative	468 ± 44 (51 to 485)	445 ± 51 (425 to 464)	421 ± 52 (401 to 441)	2,735 ± 351 (2,512 to 2,958)	2.11 ± 1.0 (1.7 to 2.5)
P	.020[b] (2 to 23)	.015[b] (3 to 26)	.012[b] (4 to 29)	.680 (-166 to 112)	.270 (-.5 to .1)

CCT = central corneal thickness (measured at the center, apex, or thinnest point); ECD = endothelial cell count
[a]*Values are mean ± standard deviation (95% confidence interval).*
[b]*Statistically significant.*