Corneal Crosslinking With Riboflavin and UVA Light in Progressive Keratoconus: Fifteen-Year Results

FREDERIK RAISKUP, ROBERT HERBER, JANINE LENK, LISA RAMM, DIERK WITTIG, LUTZ E. PILLUNAT, AND EBERHARD SPOERL

• PURPOSE: To analyze the 15-year results of corneal crosslinking (CXL) in progressive keratoconus.
• DESIGN: Retrospective follow-up analysis of interventional study patients.
• METHODS: This study included keratoconic eyes with progressive disease treated from 2001 to 2006 at the Department of Ophthalmology, Carl Gustav Carus University Hospital, TU Dresden, Germany. CXL was performed by applying riboflavin and ultraviolet A (UVA) light according to a standard protocol. The best-corrected distance visual acuity (BCVA), slitlamp examination, and corneal topography as well as corneal thickness values were recorded preoperatively and 15 years after the treatment.
• RESULTS: A total of 42 eyes received a complete follow-up of 15 years. The mean age of the patients at baseline was 26.9 (95% CI: 25.0-28.8) years. The maximum keratometry was 61.6 (95% CI: 58.2 - 64.9) diopters (D) preoperatively and 55.1 (95% CI: 51.6-58.4) D postoperatively; the decrease was statistically significant ($P < .001$). The mean keratometry value changed from 50.3 (95% CI: 48.3-52.4) D to 47.5 (95% CI: 45.3-49.4) D ($P < 0.001$). Furthermore, the thinnest corneal thickness decreased statistically significantly by 40 (95% CI: 24-56) µm ($P < .001$). The BCVA improved statistically significantly from 0.4 to 0.2 logMAR after the treatment. Retreatment was needed in 14% of cases. Mild scarring of the superficial stromal corneal layers was observed in 36% of the eyes, and in 67% of them visual acuity was stable or even improved.
• CONCLUSIONS: The CXL procedure proved to be an effective method in the treatment of keratoconic eyes in the progressive stage of the disease, and achieved long-term stabilization without the occurrence of serious complications or side effects. (Am J Ophthalmol 2023;250: 95–102. © 2023 Elsevier Inc. All rights reserved.)

Frederik Raiskup and Robert Herber contributed equally to the manuscript.
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From the Department of Ophthalmology, University Hospital Carl Gustav Carus, TU Dresden, Germany
Inquiries to Robert Herber, University Hospital Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany; e-mail: robert.herber@uniklinikum-dresden.de

KERATOCONUS IS A PROGRESSIVE ECTATIC, CLINICALLY non-inflammatory corneal disease that in 84% of cases begins in the second decade of life[1] and involves bilateral conical corneal bulging and thinning of the corneal stroma.

A recent epidemiological study reported an incidence of this corneal pathology to be 13.3 new cases per 100,000 population per year. In this study, the prevalence of keratoconus in the general population was estimated to 265 cases per 100,000 population.[2] The reasons for such a large differences are probably due to the ever-increasing sensitivity of modern diagnostic instruments, regional differences, availability of health care, and/or also differences in the design and methodology of the study under investigation. Ethnic differences also influence the incidence of keratoconus.[3, 4]

A multi-center clinical trial in the United States confirmed the efficacy of treating progressive keratoconus by cross-linking the cornea with ultraviolet A (UVA) radiation and riboflavin with an excellent safety profile,[5] and, based on these results, this procedure was granted US Food and Drug Administration approval in April 2016.[6,7]

The aim of this study was to monitor the long-term efficacy, safety, and incidence of adverse effects of this procedure in the indication of progressive keratoconus after 15 years.

METHODS AND PATIENTS

This retrospective follow-up analysis of interventional study patients was performed at the Department of Ophthalmology of the University Hospital Carl Gustav Carus, TU Dresden, Germany. The Ethics committee of the TU Dresden approved the study protocol following the tenets of the Declaration of Helsinki. The study was retrospectively registered at Clinicaltrials.gov (NCT04251143, registered March 12, 2018).

Patients were included from January 2001 to October 2006 if they had keratoconus and showed significant progression of the disease during this period. Diagnosis and progression were based on clinical and corneal topographic findings. Significant progression was present if the maximum corneal keratometry value increased by more than 1

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diopter (D) or if there was deterioration of visual acuity with necessary readjustment of contact lenses within 12 months. Regarding the necessity of frequent contact lens fitting because of changes in refraction, it is normally recommended to have a new contact lens fitted every 2 years. In case the patient comes earlier with the claim that his/her visual acuity has deteriorated with the contact lens in use and the cause of the deterioration of vision has not been found on the contact lens itself (eg, scratching, breakage, coating on the lens surface), it is assumed that it is a change in the keratometric values of the cornea, and thus the dynamics of the process in terms of progression of keratoconus. Evaluation of the disease progression after initial CXL treatment was performed at least 9 months after the procedure when keratocytes repopulation (after 3-6 months) had already occurred. A re-increase in maximum keratometry (Kmax) value of more than 1 D at 2 subsequent follow-up visits (3-4 months) compared with its value during the steady-state period after the first treatment was defined as a failure (re-progression).[8] To avoid a potential influence of intra-day variability on keratometry measurements, the patients were examined commonly between 12 am and 2 pm. Within the study period, no more than 3 experienced technicians performed the topography and tomography measurements.

The severity of keratoconus was graded using the Amsler–Krumeich classification based on central mean keratometry value, corneal astigmatism, and corneal thickness.[33] Patients had to be at least 18 years of age and had to have signed the Informed Consent form after an explanation of the surgical method. A contact lens wear discontinuation of 14 days had to be observed before each examination. All patients underwent pre- and postoperative slit-lamp examination to assess clinical findings, best-corrected distance visual acuity testing (BCVA, in logMar), corneal topography measurement (C-Scan videokeratoscope, Technomed GmbH, and Pentacam HR, Oculus Optikgeräte GmbH, respectively), and thinnest corneal thickness (Pachette ultrasonic pachymeter, Technomed GmbH, and Pentacam HR Oculus Optikgeräte GmbH, respectively). Corneal topography was demonstrated as mean keratometry (Km), maximum keratometry (Kmax), and corneal astigmatism (CA). Exclusion criteria for the study were other ectatic corneal diseases, such as Pellucid Marginal Degeneration (PMD), previous corneal surgery, such as laser-assisted in situ keratomileusis (LASIK) or CXL, and current pregnancy.

• **PROCEDURE:** In all cases, the treatments were performed unilaterally and on an outpatient basis in the Department of Ophthalmology of the University Hospital Carl Gustav Carus, TU Dresden, Germany. The exact procedure has been described several times before (Table 1).[9,10]

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using SPSS (version 27, IBM Statistics). The normal distribution was examined using Q-Q plots. Due to the presence of a normal distribution, the linear mixed model was applied to evaluate the preoperative and postoperative data while also taking into account the inter-eye correlation. Because of the multiple comparisons, the Bonferroni correction was used. Mean values and 95% CIs are reported. A *P* value of less than .05 was considered as statistically significant.

TABLE 1. Description of the Applied S-CXL Protocol

Treatment target	Progressive keratoconus
Fluence, total (mJ/cm²)	5.4
Intensity (mW/cm²)	3
Treatment time, min	30
Light source	Customized UVA-light diodes
Irradiation mode	Continuous
Epithelium status	Off (mechanical abrasio)
Chromophore (centration)	Riboflavin (0.1%)
Chromophore carrier	20% Dextran

S-CXL = standard cross-linking; UVA = ultraviolet A.

RESULTS

In all, 47 eyes of 36 patients were initially included in this study and had postoperative control at 10 years (mean follow-up: 10.1 years; 95% CI: 9.6-10.6). Five of the 47 eyes dropped out after 15 years (dropout) because they could not be examined for the last follow-up appointment. The mean follow-up time was 15.4 years (95% CI: 14.9-16.0). The severity of keratoconus was defined using the Amsler–Krumeich staging, in which 42.6%, 23.4%, and 34.0% of patients were classified as stage 1, 2, and 3, respectively. Further demographic data are shown in Table 2.

TABLE 2. Demographic Data of the Study Cohort

No. of eyes	47
Sex, male/female, no. (%)	28 (78%) / 8 (22%)
Eyes, right/left, no (%)	24 (51%) / 23 (49%)
Age, y, mean (CI)	26.9 (25.0-28.8)
BCVA, logMAR, mean (CI)	0.4 (0.29-0.44)
Kmax, D, mean (CI)	61.6 (58.2-64.9)
TCT, μm, mean (CI)	478.7 (462.4-495.9)
Amsler–Krumeich staging	
Stage 1, n (%)	20 (42.6%)
Stage 2, n (%)	11 (23.4%)
Stage 3, n (%)	16 (34.0%)

BCVA = best correct visual acuity; Kmax = maximal keratometry; TCT = thinnest corneal thickness.

TABLE 3. Topographic and Pachymetric Outcomes After CXL treatment

	Baseline	After 10 years	After 15 years	P^a	P^b	P^c
No. of eyes	47	47	42			
K_{mean}, D	50.3 (48.3-52.4) / 49.3	48.1 (45.8-49.9) / 46.9	47.5 (45.3-49.4) / 46.4	<.001[d]	<.001[d]	.518
K_{max}, D	61.6 (58.2-64.9) / 58.1	55.6 (52.3-59.0) / 54.6	55.1 (51.6-58.4) / 54.5	<.001[d]	<.001[d]	1.0
CA, D	6.4 (5.4-7.4) / 5.5	4.4 (3.3-5.3) / 3.9	3.7 (2.8-5.0) / 3.8	<.001[d]	<.001[d]	.887
TCT, µm	478.7 (462.4-495.9) / 481	433.7 (417.7-450.1) / 436	440.5 (422.5-455.4) / 444	<.001[d]	<.001[d]	.818

CA = corneal astigmatism; CXL = corneal crosslinking; D = diopter; K = keratometry; TCT = thinnest corneal thickness.
[a]Comparison between baseline and 10 years follow-up.
[b]Comparison between baseline and 15 years follow-up.
[c]Comparison between 10 and 15 years follow-up.
[d]Statistically significant.Data are expressed as mean (95% CI) and median.

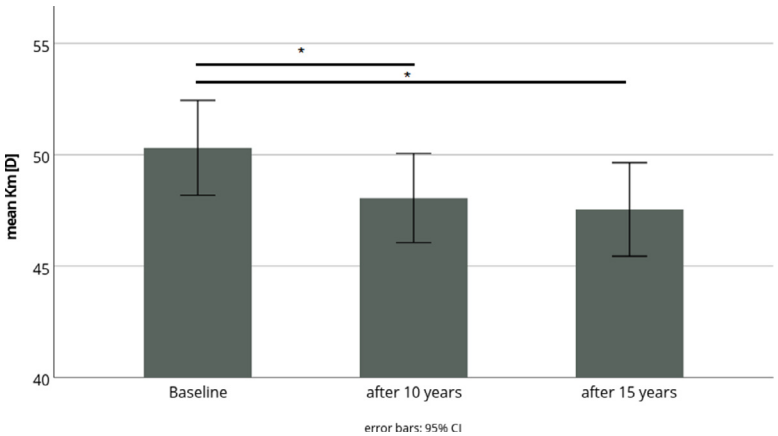

FIGURE 1. Bar graph of mean keratometry (Km) preoperatively, after 10 years, and after 15 years. Significance is marked with an asterisk (*)

Topographic and pachymetric data are shown in Table 3. There was a statistically significant decrease of −2.9 diopters (95% CI: −1.8 to −4.1, $P < .001$), −6.6 D (95% CI: −3.5 to −9.6, $P < .001$), and −2.5 D (95% CI: −1.3 to −3.7, $P < .001$) for Km (Figure 1), Kmax (Figure 2), and CA (Figure 3) at 15 years compared to the preoperative values. There was also a statistically significant decrease in all of these parameters at 10 years. However, no significant changes were observed between 10 and 15 years. The thinnest corneal thickness was statistically significantly reduced by −40 µm (95% CI: 24-56, $P <.001$) at 15 years compared to baseline (Figure 4). BCVA (in logMar) improved by −0.1 (95% CI: 0.03-0.23, $P = 0.004$) (Figure 5). There were no statically significant changes in either corneal thickness or BCVA between 10 and 15 years of follow-up (all $P < .05$).

Six of the 42 (14%) eyes received re-crosslinking within the study period of 15 years. The mean time period between initial CXL and re-treatment (in case of treatment failure) was 9 years. The mean age of these 6 eyes was 24 years at baseline. In 1 patient, re-treatment was performed in both eyes. This female patient had Amsler−Krumeich grade 3 and was also obese (World Health Organization grade III) as well having thrombotic thrombocytopenic purpura. Except for 1 eye (stage 1), the other re-crosslinked eyes all had an Amsler−Krumeich stage of 3. In addition, the patients had allergies or rheumatism. A summary of characteristics of patients who underwent repeated CXL is shown in Table 4.

Mild scaring in superficial corneal layers was also present in 15 eyes (36%). Among these eyes, 3 of them showed scars already before the CXL procedure was performed. Corneal scars developed in 33%, 20%, and 47% of cases with stage 1, 2, and 3, respectively. Ten of 15 patients (67%) with scarring were stable or even improved their visual acuity after 15 years. A loss in visual acuity did not exceed of more than 2 lines in 33% of cases. These patients had a keratoconus stage of 1 and 3. Between 10 and 15 years, the Kmax value increased by more than 1 D in 8% of the eyes. However, this progression was not observed within 12 months, so no further re-intervention has been planned so far.

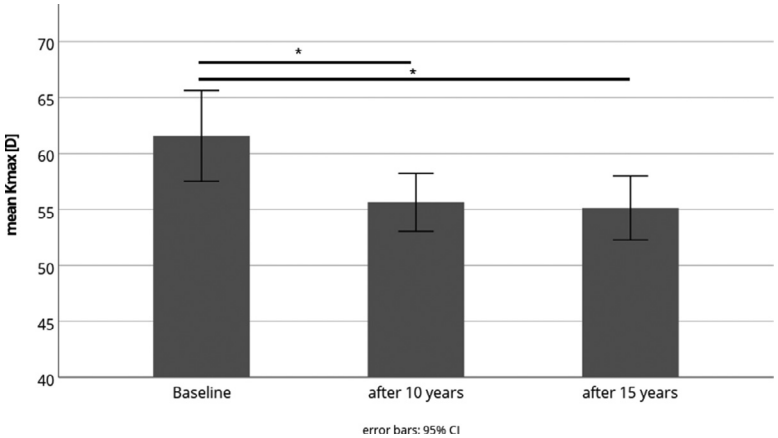

FIGURE 2. Bar graph of maximum keratometry (Kmax) preoperatively, after 10 years, and after 15 years. Significance is marked with an asterisk (*).

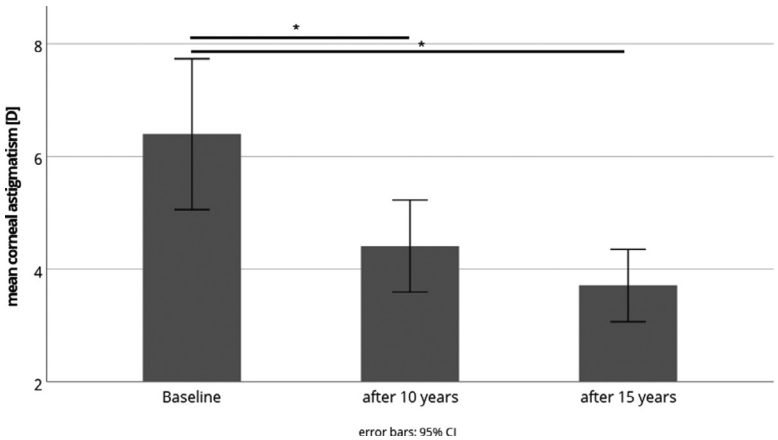

FIGURE 3. Bar graph of corneal astigmatism (CA) preoperatively, after 10 years, and after 15 years. Significance is marked with an asterisk (*).

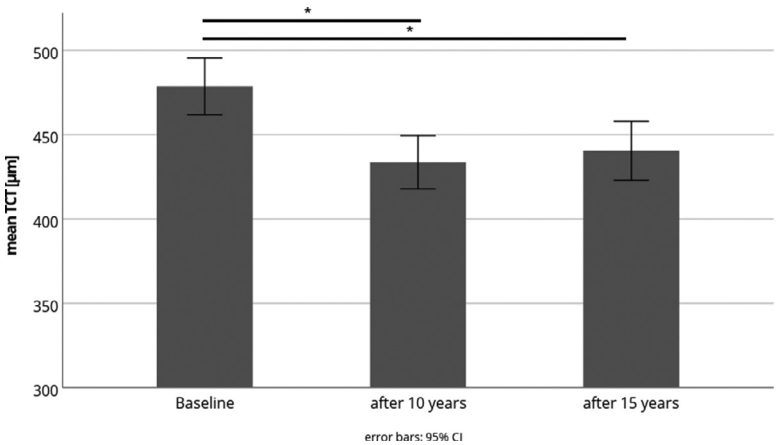

FIGURE 4. Bar graph of thinnest corneal thickness (TCT) preoperatively, after 10 years, and after 15 years. Significance is marked with an asterisk (*).

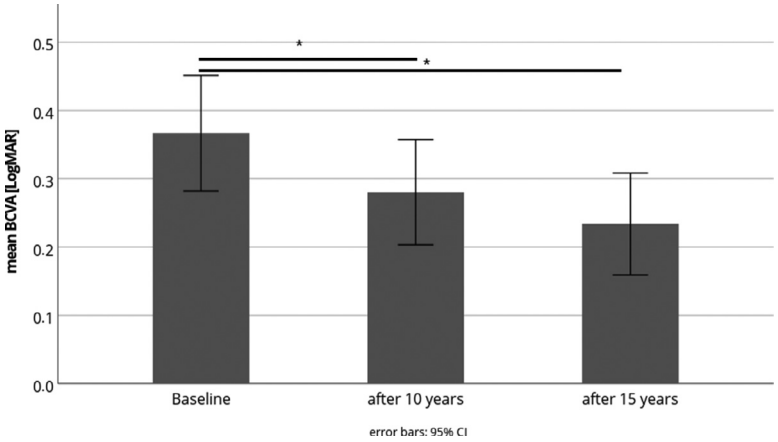

FIGURE 5. Bar graph of best-corrected visual acuity (BCVA) preoperatively, after 10 years, and after 15 years. Significance is marked with an asterisk (*).

TABLE 4. Patients characteristics of necessary re-treatments.

Patient ID	eye	time to re-treatment	Baseline			Before re-treatment			After 15 years		
			K mean	K max	VA	K mean	K max	VA	K mean	K max	VA
1	right	11 years	53.2	64.7	0.2	48.6	57.8	0.5	48.4	56.0	0.6
1	left	12 years	62.7	95.3	0.5	57.6	72.7	0.2	57.2	68.4	0.2
2	right	7 years	40.4	46.2	0.8	34.7	43.2	0.5	32.6	42.6	0.6
3	left	11 years	52.4	63.7	0.4	48.8	67.3	0.5	43.5	54.9	0.5
4	left	12 years	54.9	66.8	0.6	49.6	58.1	0.5	48.3	54.8	0.8
5	Left	9 months	57.1	72.1	0.1	57.7	73.8	0.5	51.9	65.1	0.5

K, keratometry; VA, visual acuity.

DISCUSSION

Clinical data obtained in recent years from several research centers in Europe, Australia, and the United States have shown that corneal crosslinking is an effective and safe method for the treatment of progressive keratoconus. In 2008, the Dresden team described the largest published case series to date, consisting of 241 eyes in 130 patients who were monitored over a period of 6 years after corneal crosslinking. This retrospective study confirmed previous observations that had revealed statistically significant improvement in astigmatism, best correctable vision, and better keratometric values at the apex of the keratoconus (Kmax).[10] The stability of the results and the safety of this treatment method were also confirmed by analyzing the results of another long-term study after 10 years.[11]

The main outcome of this study was the continuous stabilization of the keratoconic cornea also after 15 years, confirmed by flattening of the mean central and maximal keratometry as well as visual acuity. Furthermore, keratometry values, corneal thickness, and visual acuity did not change between 10 and 15 years, indicating that an ongoing remodeling process, such as corneal flattening, is not endless. To the best of our knowledge, this is the first study to provide extensive long-term data.

The first prospective, randomized, controlled study was performed by Wittig-Silva and colleagues using the so-called "Dresden protocol."[12] This study provided findings on refractive, topographic, and clinical outcomes in 46 eyes with progressive keratoconus after corneal crosslinking. A group of an additional 48 eyes served as a control group over a 3-year follow-up period. A statistically significant increase in Kmax values, a worsening of astigmatism, and a decrease in uncorrected visual acuity were measured in eyes in the control group after 3 years. In contrast to the control group, a statistically significant decrease in keratometric Kmax values and improvement in uncorrected and corrected visual acuity were observed in the cross-linked corneas. These achievements were comparable to the 6-year results by our group.[10]

Another prospective, randomized, and multi-center study conducted in accordance with Food and Drug Administration guidelines demonstrated improvement in uncorrected and corrected vision, Kmax values, and mean keratometric values after 1 year.[13] The study design of the U.S.

multi-center clinical trials of crosslinking has demonstrated the safety and efficacy of this technique for the treatment of progressive keratoconus and corneal ectasia, thus making this important medical advance available to patients in the United States.[5,7]

In another prospective study, in the United Kingdom, significant improvement in topographic and aberrometric parameters was observed over a 5-year follow-up period. Corneal stability persisted up to 7 years after corneal crosslinking.[14]

The results of our current study show that long-term stabilization of progressive keratoconus can be achieved. The CXL treatment significantly reduced the Km and the Kmax in our study cohort after 15 years. Corrected distance visual acuity (CDVA) also improved significantly, because of a reduction in corneal astigmatism and corneal keratometry, as well as better contact lense fitting due to regularization of the corneal surface. The long-term follow-up results by the Italian authors also showed that the standard protocol represents a safe and effective treatment of progressive keratoconus over 13 years of follow-up.[15] Concerning the corneal topographical and tomographical results, the authors found that Kmax remained statistically unchanged, demonstrating the stabilization of the keratoconus. However, an index representing the anterior curvature of a 3-mm area around the thinnest location was reduced, indicating an improvement of the steeper area of the cornea.[15] In contrast, long-term results from Nicula et al confirmed the continuous flattening of central keratometry values up to 10 years.[16] In their study population, visual acuity, refractive cylinder, and spherical equivalent improved significantly as well. In another long-term study, a reduction of central keratometry was found to be significant after 10 years.[17] A quantitative comparison between different studies is difficult, as various measuring devices were used and different study cohorts were investigated. Corneal alterations induced by CXL depend on preoperative values, such as Kmax, or the observed follow-up interval. It is known that a stronger corneal flattening occurred more in advanced cases.[18-20] Therefore, the higher decrease of Km and Kmax in our study might be explained by the fact that nearly half of the eyes presented with Amsler–Krumeich stage 3.

The thinnest corneal thickness was still reduced after 10 or more years following CXL, as was found in the current study.[15,17].

In the present study, keratometry values, corneal thickness, and visual acuity did not change between 10 and 15 years, indicating that an ongoing remodeling process, such as corneal flattening, might be not endless. Only 8% of the eyes showed an increase of more than 1 D between 10 and 15 years. The increase did not proceed within 12 months; thus a re-treatment was not indicated. The long stabilization effect can also be explained by the naturally stiffening of the cornea,[21] in which older persons have a higher Young's modulus compared to younger persons.[22] Mazzotta et al demonstrated, in their long-term results of pediatric keratoconus patients, that the CXL effect on topography and tomography remained successful up to 7 years, at which point a further progression was observed in 21% of eyes between 7 and 10 years.[23] The authors assumed a loss in efficacy due to the corneal collagen turnover resuming a renewed instability of the cornea.

In our study, 14% of eyes needed a re-treatment with a mean follow-up period of 9 years, although 1 re-CXL was necessary after only 9 months. Therefore, the lower failure rates and the lasting stabilization between 10 and 15 years might be due to the natural tissue aging effect. Nevertheless, treatment failure occurred mostly in patients with advanced keratoconus or those with allergies and rheumatism. Previously, we observed a cumulative prediction rate of success of 92.5% (failure rate, 7.5 %) after 3 years in a large cohort of 120 eyes, in which a higher preoperative Kmax was a predictor for re-CXL.[24] In addition, Vinciguerra et al found a failure rate of 7.4% in their long-term study.[15] They used the ABCD progression display to evaluate progression after CXL. The reason for using the ABCD progression display was to overcome the lack of the high noise level of the Kmax value before and after CXL.[25] Therefore, it is recommended to use the display as an objective method to standardize the assessment of treatment failures.[15,26,27]

Complications such as prolonged epithelialization, infections, limbal stem cell insufficiency, and endothelial cell decompensation were not observed. Concerning the development of corneal scars after the treatment, we found that these clinical findings could be observed at all stages of keratoconus. However, these scars did not affect the vision in two-thirds of treated eyes, as the visual acuity remained stable or improved after 15 years. A loss of vision (no more than 2 lines) was observed in cases that were classified as Amsler–Krumeich stage 1 and 3, indicating that all patients undergoing CXL must be informed about the possibility of corneal scars developing.

In 2004, keratoconus was the cause of 15.1% of the more than 30,000 corneal transplantations performed in the United States.[28] These patients have the best prognosis after corneal transplantation[29]; however, sometimes corneal transplantation may not be the best option because patients with this disease are often young and very active, which has implications for their overall quality of life. In addition, patients' perception of success may not reflect the clinical success criteria (eg, clear corneal graft), as some patients report dissatisfaction with visual acuity and are handicapped by limitations in "daily functioning" despite achieving good CDVA and a clear graft.[29]

The implementation of CXL procedure in the standard treatment algorithm for progressive keratoconus has made it possible to reduce the necessity of indications for corneal transplantation in this disease.[30,31] The economic consequences of the introduction of this CXL treatment are also important. Because CXL is a relatively simple outpatient procedure, the effectiveness of which we have been able to

confirm in our long-term results, a reduction in the necessity of corneal transplants reduces the financial costs for patients with this diagnosis, which has significant economic consequences for the national health system.[32-34]

The results of this study are limited by the different measurement devices that were used to assess corneal topography and tomography both pre- and post-operatively. However, the technological development of ophthalmic devices has become a comprehensive gain in the last decade. The current standard to measure corneal topography and tomography is the Scheimpflug technology that was released in 2005, after the procedure was introduced. Therefore, the amount of flattening in Km and Kmax might be influenced by the systematic bias of both the C-Scan videokeratoscope and the Pentacam HR. However, it can be assumed that keratometry values of both devices were at least strongly correlated. Nevertheless, the success of the treatment is also confirmed, if no further clinically significant progression can be observed.

In conclusion, the corneal crosslinking procedure is an effective, minimally invasive method to halt progression of the keratoconus over a long-term period. The safety and efficacy of this treatment were maintained over a period of 15 years. Re-treatment was necessary in 13% of cases, which makes follow-up examinations very important in clinical practice.

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REFERENCES

1. Zadnik K, Barr JT, Edrington TB, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Invest Ophthalmol Vis Sci*. 1998;39:2537–2546.
2. Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM, Wisse RP. Age-specific incidence and prevalence of keratoconus: a nationwide registration study. *Am J Ophthalmol*. 2017;175:169–172.
3. Cozma I, Atherley C, James NJ. Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asian and white patients. *Eye (Lond)*. 2005;19:924–925 author reply 925-926.
4. Pearson AR, Soneji B, Sarvananthan N, Sandford-Smith JH. Does ethnic origin influence the incidence or severity of keratoconus? *Eye (Lond)*. 2000;14(Pt 4):625–628.
5. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK. United States Crosslinking Study Group. United States multicenter clinical trial of corneal collagen crosslinking for keratoconus treatment. *Ophthalmology*. 2017;124:1259–1270.
6. Belin MW, Lim L, Rajpal RK, Hafezi F, Gomes JAP, Cochener B. Corneal cross-linking: current USA status: report from the Cornea Society. *Cornea*. 2018;37:1218-1225.
7. Greenstein SA, Hersh PS. Corneal crosslinking for progressive keratoconus and corneal ectasia: summary of US multicenter and subgroup clinical trials. *Transl Vis Sci Technol*. 2021;10:13.
8. Raiskup F, Spoerl E. Reply: To PMID 25532633. *J Cataract Refract Surg*. 2015;41:1337–1338.
9. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
10. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34:796–801.
11. Raiskup F, Theuring A, Pillunat LE, Spoerl E. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg*. 2015;41:41–46.
12. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology*. 2014;121:812–821.
13. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:149–160.
14. O'Brart DP, Patel P, Lascaratos G, et al. Corneal cross-linking to halt the progression of keratoconus and corneal ectasia: seven-year follow-up. *Am J Ophthalmol*. 2015;160:1154–1163.
15. Vinciguerra R, Pagano L, Borgia A, et al. Corneal cross-linking for progressive keratoconus: up to 13 years of follow-up. *J Refract Surg*. 2020;36:838–843.
16. Nicula C, Pop R, Rednik A, Nicula D. 10-Year results of standard cross-linking in patients with progressive keratoconus in Romania. *J Ophthalmol*. 2019;2019:8285649.
17. Salman A, Ali A, Rafea S, et al. Long-term visual, anterior and posterior corneal changes after crosslinking for progressive keratoconus. *Eur J Ophthalmol*. 2022;32:50–58.
18. 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.
19. 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.
20. Padmanabhan P, Belin MW, Padmanaban V, Sudhir RR. Extreme corneal flattening following collagen crosslinking for progressive keratoconus. *Eur J Ophthalmol*. 2021;31:1546–1552.
21. Seiler TG, Shao P, Eltony A, Seiler T, Yun SH. Brillouin spectroscopy of normal and keratoconus corneas. *Am J Ophthalmol*. 2019;202:118–125.
22. Knox Cartwright NE, Tyrer JR, Marshall J. Age-related differences in the elasticity of the human cornea. *Invest Ophthalmol Vis Sci*. 2011;52:4324–4329.
23. Mazzotta C, Traversi C, Baiocchi S, et al. Corneal collagen cross-linking with riboflavin and ultraviolet a light for pediatric keratoconus: ten-year results. *Cornea*. 2018;37:560–566.

24. Lenk J, Herber R, Oswald C, Spoerl E, Pillunat LE, Raiskup F. Risk factors for progression of keratoconus and failure rate after corneal cross-linking. *J Refract Surg*. 2021;37:816–823.
25. Belin MW, Alizadeh R, Torres-Netto EA, Hafezi F, Ambrosio Jr R, Pajic B. Determining progression in ectatic corneal disease. *Asia Pac J Ophthalmol (Phila)*. 2020;9:541–548.
26. Vinciguerra R, Fossati G, Sorrentino T, et al. Corneal cross-linking for progressive keratoconus in patients older than 40 years: long-term follow-up. *J Refract Surg*. 2021;37:338–342.
27. Vinciguerra R, Legrottaglie EF, Tredici C, Mazzotta C, Rosetta P, Vinciguerra P. Transepithelial iontophoresis-assisted cross linking for progressive keratoconus: up to 7 years of follow up. *J Clin Med*. 2022:11.
28. Eye Bank Association of America. Statistical report on eye banking activity for 2004. Washington, DC: Eye Bank Association of America; 2005.
29. Mendes F, Schaumberg DA, Navon S, et al. Assessment of visual function after corneal transplantation: the Quality of Life and Psychometric Assessment After Corneal Transplantation (Q-PACT) study. *Am J Ophthalmol*. 2003;135:785–793.
30. Sandvik GF, Thorsrud A, Raen M, Ostern AE, Saethre M, Drolsum L. Does corneal collagen cross-linking reduce the need for keratoplasties in patients with keratoconus? *Cornea*. 2015;34:991–995.
31. Godefrooij DA, Gans R, Imhof SM. Wisse RP. Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of cross-linking. *Acta Ophthalmol*. 2016;94:675–678.
32. Lindstrom RL, Berdahl JP, Donnenfeld ED, et al. Corneal cross-linking versus conventional management for keratoconus: a lifetime economic model. *J Med Econ*. 2021;24:410–420.
33. Krumeich JH, Daniel J, Knulle A. Live-epikeratophakia for keratoconus. *J Cataract Refract Surg*. 1998;24(4):456–463. doi:10.1016/s0886-3350(98)80284-8.
34. Leung VC, Pechlivanoglou P, Chew HF, Hatch W. Corneal collagen cross-linking in the management of keratoconus in canada: a cost-effectiveness analysis. *Ophthalmology*. 2017;124:1108–1119.