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ORIGINAL RESEARCH

Long Term Corneal Flattening After Corneal Crosslinking in Patients with Progressive Keratoconus

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Purpose: We evaluate the long-term visual, refractive, and keratometric outcomes after corneal crosslinking (CXL) in patients with progressive keratoconus (KC) and the incidence of an extreme corneal flattening effect.

Settings: Oftalmosalud Institute of Eyes, Lima, Perú.

Design: Retrospective cohort study.

Methods: Forty-five eyes that underwent CXL with epithelial removal between June 2006 and September 2011. Data analysis was performed at preoperative evaluation, 1 year postoperatively, and at least 10 years or more postoperatively. Outcome measures included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and Scheimpflug (Pentacam) analysis. Progression was defined by an increase in steep keratometry (Ks) of 1.5D or greater between 2 examinations. Extreme flattening effect was defined as a decrease in K values equal to or greater than 5 diopters (D).

Results: Mean follow-up time was 11 ± 1.07 years (range 10–13 years). There was a significant improvement in Ks, UCVA, CDVA, and spherical equivalent at the last visit. The overall rate of progression was 2.22% (1/45). Extreme flattening was observed in 15.5% (7/45) of the eyes, and this was associated with a loss of CDVA in 4.44% (2/45) of the eyes. One eye with corneal flattening of 11.5 D lost 7 lines of CDVA and required corneal transplantation.

Conclusion: CXL is a safe and effective procedure to stop the progression of KC with a good overall long-term success rate. Extreme corneal flattening may be more common than commonly recognized, and severe corneal flattening associated with a decrease in CDVA may occur.

Keywords: crosslinking, keratometric flattening, keratoconus, CXL

Plain Language Summary

What was Known

- Limited literature exists about the long-term effects of CXL.
- An extreme flattening effect can occur after CXL.

What this Paper Adds

- CXL is a safe and effective procedure to halt the progression of KC with long-term follow-up.
- With long-term follow-up, the incidence of severe corneal flattening is higher than previously reported.
- Extreme corneal flattening associated with a decrease in visual acuity is a rare complication of CXL.

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Introduction

Keratoconus (KC) is an ectatic disease of the cornea, typically diagnosed during the second decade of life that tends to progress, inducing irregular myopic astigmatism with impairment of functional vision.[1] Although once classified as a rare disease by the US Food and Drug Administration, more recent reports estimate prevalence rates of up to 4.79% in some places in the world.[2] Systematic review and metaanalysis report a prevalence of 1.38 per 1000 population.[3]

First reported in 2003, CXL has been adopted worldwide as an initial treatment for patients with progressive keratoconus and ectasia following LASIK. It has been shown to be safe and effective for halting the progression of these conditions short term;[3–5] however, limited literature exists regarding outcomes 10 or more years postoperatively.[6–8] Isolated cases[9–12] of extreme corneal flattening of the cornea have been reported, raising concern about the long-term effects of CXL.

The aim of this study was to evaluate the long-term visual, refractive, and keratometric outcomes after corneal crosslinking (CXL) in patients with progressive keratoconus (KC) and the incidence of extreme keratometric flattening in these patients.

Methods

This retrospective study included consecutive patients older than 18 years of age who underwent our standard Epi-OFF CXL procedure for progressive KC from June 2006 through September 2011 at Oftalmosalud Institute of Eyes, Lima, Perú and completed at least 10 years of follow-up. The study complied with the Declaration of Helsinki. The ethics committee of Oftalmosalud approved the study, and written informed consent was obtained from all participants before the CXL procedure. All participants signed a consent that allowed the publication of data from their clinical history and auxiliary test while maintaining their anonymous identity.

Included were patients with a diagnosis of KC,[13] a clear central cornea, minimum pachymetry of 450 μm at the thinnest point (TP) measured with the Pentacam (Oculus, Inc., Arlington, WA) and intraoperative ultrasonic pachymetry of at least 400 μm after de-epithelization (measured by ultrasonic pachymetry) and documented progression defined by an increase in steep keratometry of 1.5D or more between two examinations least 2 months apart (Pentacam; Oculus, Inc., Arlington, WA). Authors used 1.5D as a cutoff point for KC progression instead of 1.0 due to the high variability of Keratometrics readings in KC eyes, as suggested by Epstein et al.[14] Patients were excluded if they received any other corneal procedure (eg, PRK and intracorneal rings) before, during, or after CXL.

CXL procedure: The epithelium was removed from a 9 mm diameter area in the center of the cornea, and isotonic 0.1% riboflavin in saline containing 20% dextran 500 was instilled every 5 min for 30 min. Then, UV irradiation was administered for 30 min using the CCL-VARIO cross-linking system (Peschke Ltd., Borsigstrasse, Germany) at 3 mW/cm^2 in conjunction with isotonic riboflavin 0.1% solution being re-administered to the cornea every 5 min. Post-operative medications included moxifloxacin (Vigamox, Alcon Nederland, Gorinchem, Netherlands) and nepafenac (Nevanac, Alcon Nederland) for 1 week, preservative-free artificial tears for 4 weeks, and topical fluorometholone (FML, Allergan BV) 3 times per day for 3 weeks, starting 1 week after CXL. A bandage contact lens (PureVision; Bausch & Lomb) was inserted postoperatively and removed 5 days after the procedure.

For statistical analysis, data were collected at preoperative evaluation, 1 year postoperatively, and at least 10 years or more postoperatively. The clinic protocol after CXL has a follow-up annually for all patients. However, the rate of loss of follow-up is very high, and the records indicate that most patients have follow-ups in the first year postoperatively and then very irregularly. Therefore, for the 10-year or longer follow-up, the patients were prospectively called and scheduled for control. Data from manifest refraction, uncorrected distance visual acuity (UDVA), best spectacle-corrected distance visual acuity (CDVA), slit-lamp examination, and Scheimpflug imaging analysis (Oculus Pentacam GmbH, Wetzlar, Germany) were obtained at each follow-up visit. Data from an anterior segment optical coherence tomography (AS-OCT, MS-39, CSO, Florence, Italy) were obtained in a patient with an extreme keratometric flattening. Patients who wore contact lenses were instructed to discontinue their use at least 3 days before the examination (for soft contact lenses) or 2 weeks (for rigid permeable lenses) before the examination.

KC progression after the procedure was defined as an increase of 1.5D or more in the steeper K between two examinations with at least 2 months apart. Extreme flattening was defined as a flattening of 5D or more in the maximum K reading compared with preoperative values with at least 3 months apart. For the cases in which the maximum keratometry was not available in all the follow-ups, it was decided to use the K-steeper.

Corneal densitometry analysis add-on to the standard software of the Oculus Pentacam was obtained at the last follow-up (since the Pentacam software did not have it in the preoperative evaluation). Densitometry measurements were obtained and expressed in standardized grayscale units (GSU). The 12 mm diameter area is subdivided into four concentric radial zones. The software displays the following zones for densitometry analysis: The first central zone is 2mm in diameter and centered on the apex. The second zone is an annulus extending from 2- to 6-mm diameter circle. The third zone annulus extends from 6 to 10 mm, with the final zone extending from 10 mm to a 12 mm diameter circle.

Statistical Analysis

Statistical analysis was performed using R version 4.1.3 under the terms of the Free Software Foundation's general public license (https://www.r-project.org/). Changes with respect to time were evaluated using the Wilcoxon signed-rank test. Comparison of the changes (delta) between groups was performed using the Wilcoxon Rank Sum Test or Kruskal–Wallis test. Dunn's test was used as a post hoc test to the Kruskal Wallis test. To measure the linear association between the variables, the Spearman rank correlation coefficient was used. For all comparisons, a type I error (α) equal to 0.05 was considered, declaring statistically significant any p-value less than 0.05.

In order to detect a small effect in a comparison of two means for paired samples, a sample size between 34 and 199 is required, with alpha = 0.05 and a power of 0.8. The calculations were made using the program G*Power version 3.1.9.6.

Results

Forty-five eyes were included in the study. Mean follow-up time was 11 ± 1.07 years (range 10–13 years). Table 1 shows the pre- and postoperative visual, keratometric, and pachymetric characteristics of the studied eyes.

Keratometry

Mean flattening in Ks was 2.06D ± 2.23 ($p<0.001$) at 10+ years. Figure 1A and B shows the mean change in steeper and flatter K values at 10+ years of follow-up. Keratoconus progression was observed in 2.22% (1/45) of the cases. An extreme flattening effect (equal to or greater than 5D in Ks) was seen in 15.5% (7/45) of the eyes. A flattening <1D was observed in 33.33% (15/45), ≥1<2D in 31.1% (14/45), and ≥2<5D in 20% (9/45). Table 2 shows the visual, keratometric, and pachymetric characteristics of these eyes. A flattening effect greater than 9D was observed in 4/7 of these cases. Figure 2 shows the pre- and post-operative Scheimpflug image of case 7 which experienced 11.5D of flattening in the steeper K at 13 years post CXL, as can be seen, there is an asymmetric topographic flattening that compromises the

Table 1 Pre and Postoperative Visual, Refractive, and Tomographic Data in the studied population

Variable	Pre CXL	Post CXL 1y	Post CXL +10y	P value*
UCVA (logMAR)	0.89 ± 0.64	0.73 ± 0.52	0.61 ± 0.47	0.007
BCVA (logMAR)	0.16 ± 0.15	0.12 ±0.13	0.09 ± 0.09	0.006
Steeper K (D)	49.55 ± 3.86	48.56 ±4.53	47.66 ± 4.32	< 0.001
Flattest K (D)	45.16 ± 2.62	44.68 ± 2.60	43.93 ± 3.44	< 0.001
Sphere (D)	−2.10 ± 2.16	−2.01 ± 2.43	−1.26 ± 2.75	0.008
Cylinder (D)	−3.57 ± 2.06	−2.79 ±2.16	−2.96 ± 2.00	0.100
Spherical equivalent (D)	−4.46 ± 3.50	−2.98 ± 3.02	−2.44 ±2.90	0.004
Thinnest pachy (um)	477.11 ± 31.19	462.78 ± 76.0	463.05±42.70	0.01

Note: *p value between pre and +10 postoperative for each variable.
Abbreviations: CXL, corneal collagen crosslinking; 1y, 1 year post CXL; +10y, postoperative follow up at 10 years or longer; K, keratometry; D, diopters; um, microns.

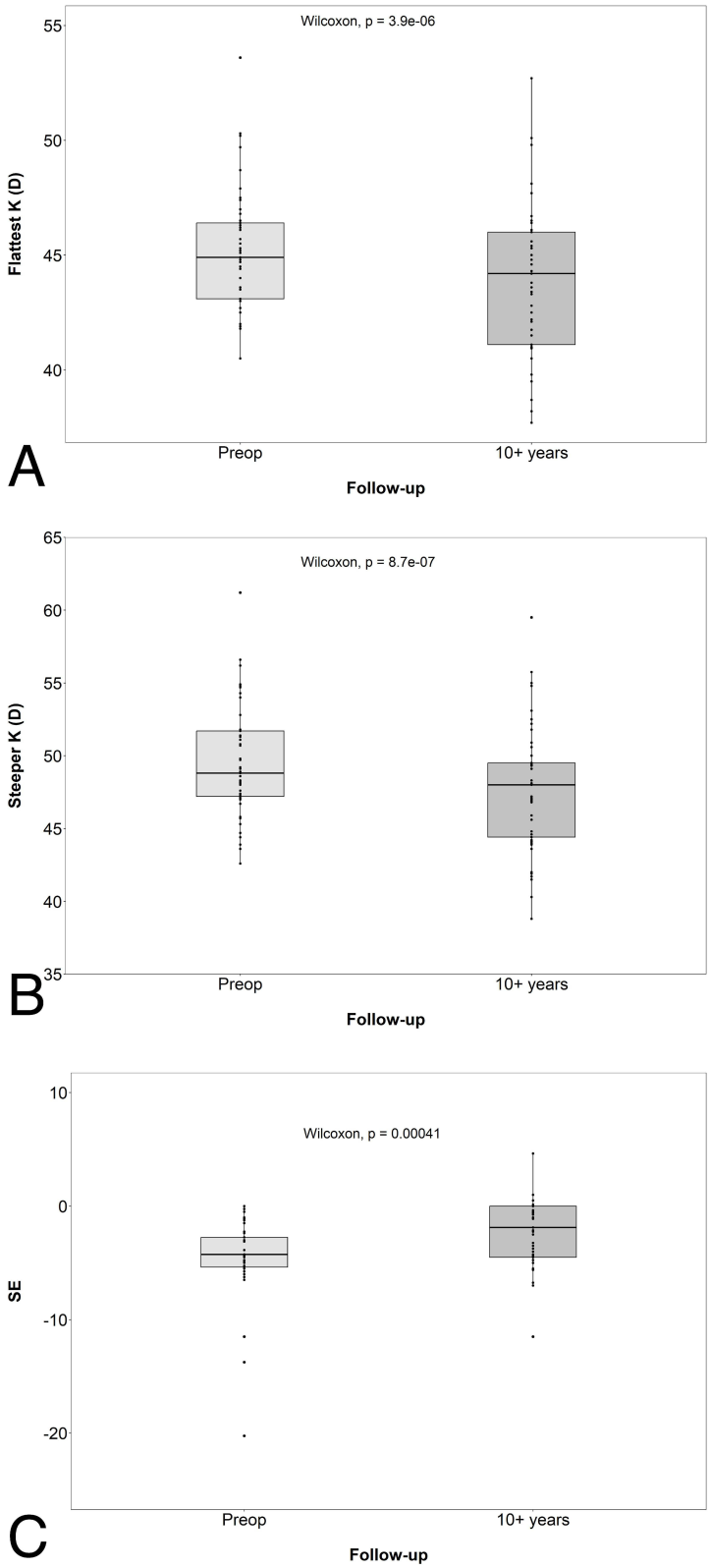

Figure 1 Pre- and post-operative steeper keratometry (**A**), flatter keratometry (**B**) and Pre- and post-operative spherical equivalent (**C**).

Table 2 Cases with Intense Keratometric Flattening Effect

Case	Age	UCVA Pre	UCVA Post	BCVA Pre	BCVA Post	Kmax Pre	Kmax Post	Steeper K Pre	Steeper K Post	Pachy TP Pre	Pachy TP Post	Procedure
1	14	1.30	0.70	0.40	0.04	55.3	49.2	52.8	47.2	485	441	CXL only
2	14	1.30	0.70	0.40	0.04	58.6	48.9	54.8	48.0	463	452	CXL only
3	37	1.30	1.00	0.30	0.18	52.6	43.4	48.8	38.8	488	355	CXL only
4	26	1.00	0.30	0.30	0.00	55.4	45.7	49.8	44.0	540	517	CXL only
5	22	2.00	1.30	0.18	0.10	60.1	55.1	54.9	52.5	429	431	CXL only
6	35	0.18	0.40	0.0	0.1	50.8	45.8	44.7	44.4	509	476	CXL only
7	24	1.00	2.00	0.18	1.30	–	44.1	47.1	35.6	512	415	CXL only

Abbreviations: Pre, preoperative evaluation; post, postoperative evaluation at 10 years or longer; UCVA, uncorrected visual acuity; BCVA, best-corrected visual acuity; K, keratometry; Kmax, maximum K; Ks, steeper K; Pachy, pachymetry; TP, thinnest point, CXL-PRK, CXL associated with photorefractive keratectomy.

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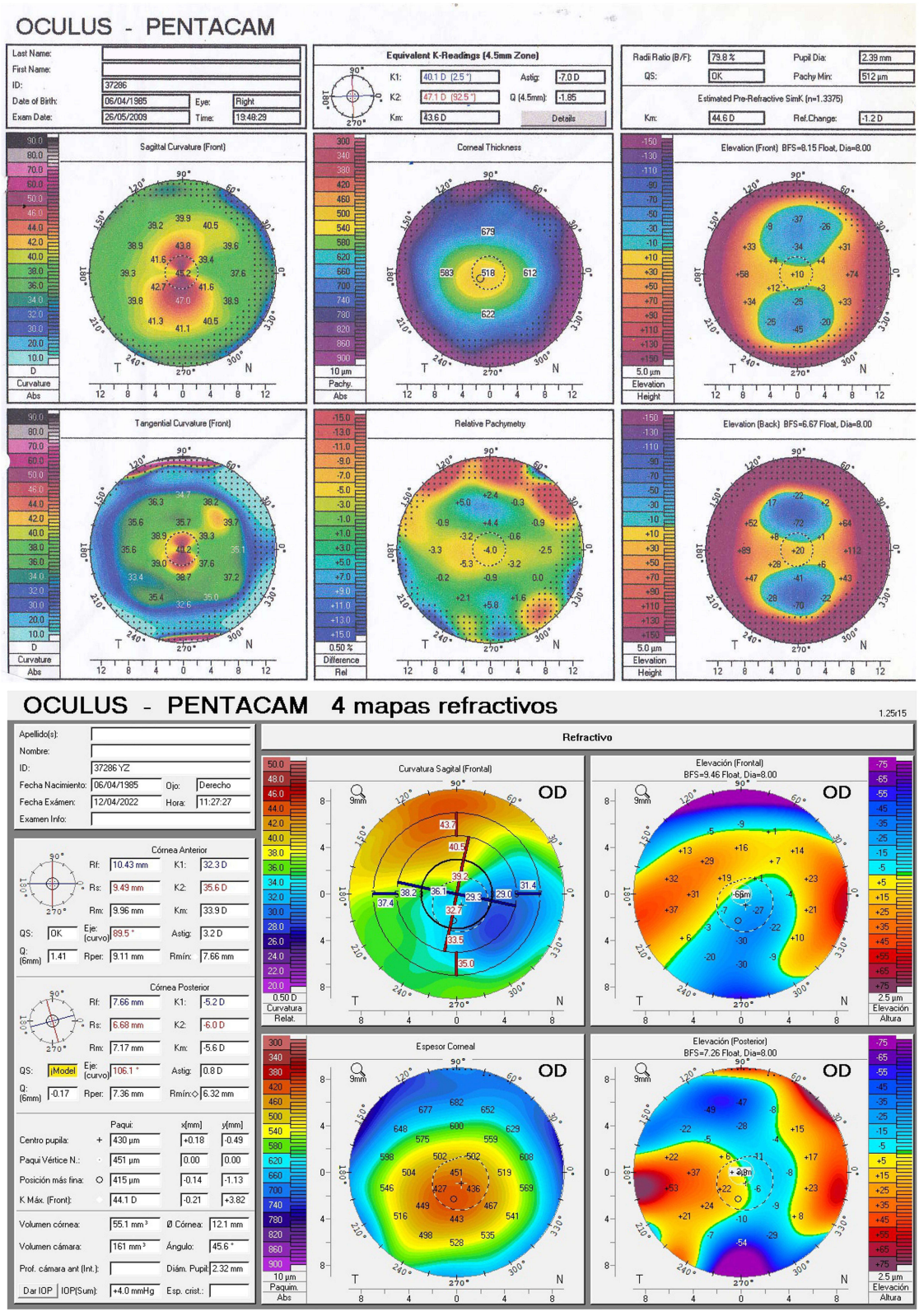

Figure 2 Top: preoperative Scheimpflug analysis; Bottom: 13 years postoperative Scheimpflug analysis of the case presenting an extreme flattening of 11.5D in the steeper keratometry.

pupillary area. Figure 3 shows the postoperative AS-OCT of the same patient showing the central haze and the corresponding high densitometric values.

Correlations between preoperative age, preoperative pachymetry, preoperative Kmax and postoperative flattening were performed, as well as correlations between postoperative densitometric measurements and postoperative keratometric flattening. There was a significant negative correlation between age (at the time of the CXL procedure) and the flattening effect at 10 years post-operative ($r = -0.51$, $p = 0.01$). There was no significant correlation between preoperative

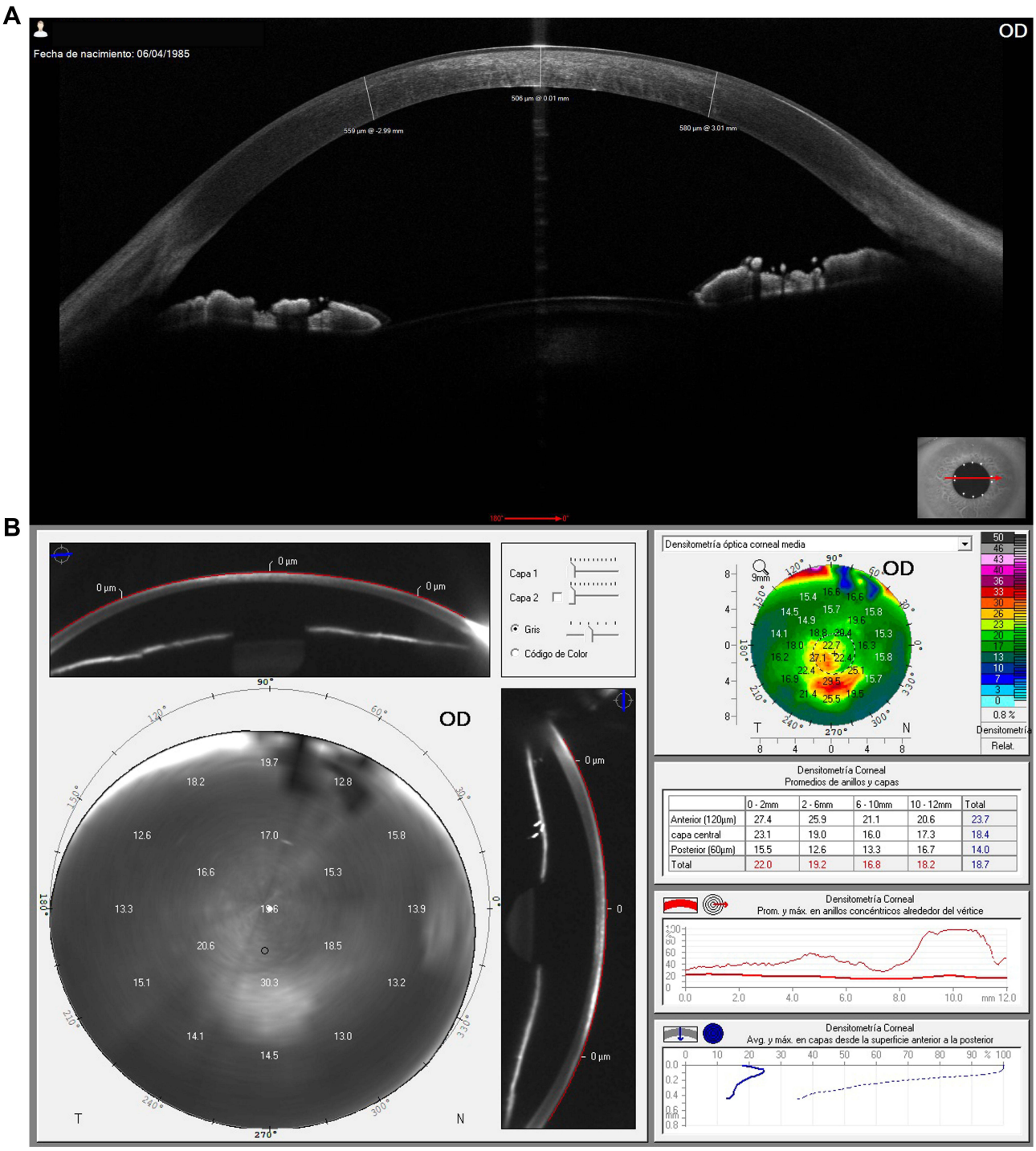

Figure 3 (**A**) Postoperative anterior segment optical coherence tomography of the case presenting an extreme flattening of 11.5D in the steeper keratometry; (**B**) Pentacam densitometric values of the same patient.

pachymetry and the keratometric flattening (r = −0.14, p = 0.42). There was no significant correlation between the preoperative Kmax or steeper K and the keratometric flattening (r = 0.04, p = 0.79 and r = −0.013, p = 0.94 respectively).

Visual Acuity

Mean improvement in the UDVA and CDVA was 0.46 ± 0.42 logMAR and 0.1 ± 0.12 logMAR (p = 0.007, p = 0.006 respectively) at 10+ years follow-up. Two cases had worsening of the CDVA (2/45, 4.4%). Case 6 lost one line of CDVA and has 5 diopters of Kmax flattening. Case 7 lost seven lines of CDVA and has 11.5D of flattening on steeper K (Table 2).

Refractive Error

Mean sphere was significantly reduced by 1.44 D ± 1.25 at +10 years post-operative (p = 0.008). Mean cylinder change was not significant (p = 0.1) at 10 years postoperative. Mean spherical equivalent (SE) had a significant reduction at +10 years postoperative (Figure 1C). There was a hyperopic shift in 11.11% (5/45) of the eyes.

Corneal Densitometry

Table 3 shows the corneal densitometry values at the last follow-up. Although the group that experienced extreme flattening presented densitometric values higher (0–2 mm and 2–6 mm of corneal diameter) than those eyes with a Kmax flattening less than 5D between, these differences were not significant (p = 0.35 and p = 0.30 respectively). The anterior

Table 3 Corneal Densitometry Measurements at 10 Years or More After CXL

Densitometry (GSU)	Anterior	Central	Posterior	Total
0–2 mm				
Flattening Kmax ≥ 5 D	28.9 ± 9.69	18.0 ± 5.02	12.5 ± 4.11	19.3 ± 5.16
Flattening Kmax < 5 D	24.8 ± 6.86	15.3 ± 2.69	10.3 ± 1.75	16.8 ± 3.26
P value*	0.25	0.21	0.26	0.35
r	−0.30	−0.038	−0.22	−0.15
P value**	0.064	0.82	0.19	0.36
2–6 mm				
Flattening Kmax ≥ 5 D	23.4 ± 5.38	14.5 ± 2.63	10.6 ± 1.38	16.2 ± 2.92
Flattening Kmax < 5 D	20.7 ± 4.22	13.0 ± 1.88	10.3 ± 1.40	14.7 ± 2.20
P value*	0.18	0.17	0.64	0.30
r	−0.24	−0.0013	−0.12	−0.11
P value**	0.14	0.99	0.47	0.51
6–10 mm				
Flattening Kmax ≥ 5 D	18.5 ± 2.39	13.0 ± 1.57	11.0 ± 1.30	14.2 ± 1.53
Flattening Kmax < 5 D	19.6 ± 4.45	13.5 ± 2.82	11.5 ± 1.95	14.9 ± 2.95
P value*	0.97	0.94	0.55	0.88
r	−0.023	0.11	0.02	0.018
P value**	0.89	0.53	0.91	0.92
Total				
Flattening Kmax ≥ 5 D	22.7 ± 2.83	14.7 ± 1.99	11.1 ± 1.58	16.2 ± 1.87
Flattening Kmax < 5 D	22.2 ± 4.21	14.4 ± 2.24	11.5 ± 1.52	16.0 ± 2.40
P value*	0.51	0.72	0.43	0.71
r	−0.17	0.037	0.05	−0.078
P value**	0.31	0.83	0.77	0.64

Abbreviations: CXL, corneal collagen crosslinking; GSU, grayscale units; Kmax, maximum keratometry; P value*, p value for Groups comparison using Wilcoxon sum range test; r, Spearman rank correlation coefficient between the densitometric value and the amount of keratometric flattening (expressed in negative values); p value**, from the Pearson correlation coefficient; D, Diopters.

central 0–2 mm corneal diameter was the location where these differences were more evident between groups (28.9 ± 9.69 versus 24.8 ± 6.86, p = 0.06). There was no significant correlation between the degree of flattening and the postoperative densitometric value.

Of the two cases with loss of CDVA lines (Table 2), case 6 had no associated haze (densitometric values at 0–2 and 2–6 mm were 15.1 and 13.4, respectively), and case 7 (Figure 3) had associated haze (densitometric values of 22.9 and 19.2, respectively).

Loss to Follow-Up and Complications

A total of 149 eyes of 92 patients over 18 years old with progressive KC underwent CXL from 2006 to 2011. Of these, 78 eyes of 56 patients were examined at least 10-year postoperatively. Of the remaining 36 patients who were not seen for 10 or more years postoperatively, 29 was reached by telephone and denied any surgery during the postoperative time or worsening of their visual acuity; however, they could not attend their postoperative 10-year follow-up visit for personal reasons. Seven patients could not be reached by telephone. In addition, the clinical history of these 36 patients were reviewed and reveals that none of these patients had an additional surgery or worsening of their visual acuity at their last follow-up, which ranged between 5 and 9 years.

Seventy-eight eyes (56 patients) had a follow-up of 10 years or more, but 42.30% (33/78) were excluded from analysis because they underwent another refractive procedure. The refractive procedures were photorefractive keratectomy in 13/33 of the eyes; intrastromal corneal rings implantation in 9/33 of the eyes; and cataract extraction with intraocular lens implantation in 11/33 of the eyes.

46.66% (21/45) of the eyes developed mild corneal haze at the 1-year post-operative exam, and 2.2% (1/45) of eyes had permanent haze at 10 years, same eye 2.22% (1/45) underwent deep anterior lamellar keratoplasty (DALK) for loss of CDVA due to extreme flattening, haze, and corneal irregularity 13 years after CXL (topography shown in Figures 2 and 3). No corneal transplants or repeat CXL was needed by any patients who underwent CXL because of KC progression, so this study is not biased by the fact that they were selectively excluded from inclusion in the study cohort. Further, subjective histories obtained from patients who had not been seen 10 or more since CXL confirms that selective loss to follow-up did not induce study bias. There were no incidents of infectious keratitis, sterile infiltrates, corneal melting, stem cell deficiency, corneal decompensation, or ICRS extrusion at the most recent follow-up among these patients, either.

Discussion

With 10–13 years of follow-up, this study demonstrates that CXL is a safe and effective procedure to halt the progression of KC. Consistent with previously published studies of CXL in KC adults, we found a significant improvement in UDVA,[8] CDVA,[6–8] flatter K,[6–8] steeper K,[7] and spherical equivalent.[8] The rate of progression was only 2.22% (1/45) which is similar to that previously reported after 10y of follow-up in adults: 8.8%,[6] 7.4%,[7] and 0%,[8] demonstrating the efficacy of the procedure in halting the progression of the disease. Serious complications such as infection,[6–8] sterile infiltrate,[7] limbal stem cell insufficiency,[6] and endothelial decompensation[6] were not observed at 10+ postoperatively in our study, which is consistent with previous publications.

Radial keratotomy (RK) was one of the first and most commonly performed refractive surgical procedures of the twentieth century, early publications were optimistic, and there were few reported complications. However, progressive corneal flattening in some of these patients required visual rehabilitation in later life. More than a decade has passed since our group began to routinely perform CXL in our patients with progressive KC in 2006. It is therefore appropriate to conduct long-term follow-up of patients who have undergone CXL to discover any undesirable long-term effects such as those we now know are seen after RK.

In our study population, 15.5% (7/45) of the eyes experienced extreme keratometric flattening greater than 5 D, and one case (2.22%) required a corneal transplant due to an asymmetric flattening of 11.5D in Ks and a decrease of 7 lines in CDVA (Figures 2 and 3). Isolated cases of severe flattening have previously been reported. Santhiago et al[9] reported two cases with a flattening up to 14D; Nor et al[10] reported three cases that continued to flatten for up 12 years following CXL. In 2008, Raiskup et al[11] reported corneal flattening between 1 and 3 years, followed by a phase of stability at 6 years of follow-up, indicating long-term stabilization of topography following CXL; however, only 33 eyes were included at 3

years of follow-up and 5 eyes at 6 years of follow-up. More recently, Padmanaban et al[12] reported extreme corneal flattening greater than 5D in Kmax in 7.85% (43/502) of a cohort of KC patients in a case–control retrospective study with a mean follow-up time of 4.3±2.1 years. In our study, 15.5% (7/45) of the cases experienced extreme flattening. To the best of our knowledge, this is the highest incidence reported to date. One possible cause of these differences is that our study has the longest follow-up of these reports. It is also possible that patients with good outcomes were selectively lost to follow-up. It is important to emphasize that excessive keratometric flattening is not always a complication as it is more frequently associated with an improvement in CDVA and UDVA (5/7 cases) than with a reduction in CDVA (2/7 cases).

A mild significant negative correlation was observed between preoperative age and the magnitude of flattening 10 years after CXL in our study. This may be explained, at least in part, by the fact that corneas become stiffer, and perhaps less susceptible to the effect of CXL, in older eyes.[15] Unlike other studies, we found no significant correlation between preoperative Kmax and postoperative flattening. Regarding the influence of postoperative haze and the extreme post-operative keratometric flattening, our study shows that the group that experienced extreme flattening in Kmax presented higher densitometric values than the group with less than 5D flattening in Kmax; however, these differences were not significant. The anterior central 0–2 mm corneal diameter was the location where these differences were more evident between groups (28.9 ± 9.69 versus 24.8 ± 6.86, $p = 0.06$, $r = -0.30$, $p = 0.25$).

Our study is not without limitations. Among them was the small sample size.

In conclusion, our study demonstrates that CXL is a safe and effective procedure to stop the progression of KC, providing an excellent visual outcome for the vast majority of eyes. Extreme corneal flattening associated with loss of CDVA is a complication of CXL to be aware that may require corneal transplantation or rigid contact lens.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42(4):297–319.
2. 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(10):1436–1441. doi:10.1136/bjophthalmol-2017-311391
3. Hashemi H, Heydarian S, Hooshmand E, et al. The prevalence and risk factors for keratoconus: a systematic review and meta-analysis. *Cornea*. 2020;39(2):263–270. doi:10.1097/ICO.0000000000002150
4. 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(5):13. doi:10.1167/tvst.10.5.13
5. O'Brart DPS. Corneal collagen crosslinking for corneal ectasias: a review. *Eur J Ophthalmol*. 2017;27(3):253–269.
6. 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(1):41–46. doi:10.1016/j.jcrs.2014.09.033
7. 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(12):838–843. doi:10.3928/1081597X-20201021-01
8. 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;2019:828564.
9. Santhiago MR, Giacomin NT, Medeiros CS, Smadja D, Bechara SJ. Intense early flattening after corneal collagen cross-linking. *J Refract Surg*. 2015;31(6):419–422. doi:10.3928/1081597X-20150521-09
10. Noor IH, Seiler TG, Noor K, Seiler T. Continued long-term flattening after corneal cross-linking for keratoconus. *J Refract Surg*. 2018;34(8):567–570. doi:10.3928/1081597X-20180607-01
11. 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(5):796–801.
12. Padmanabhan P, Belin MW, Padmanaban V, Sudhir RR. Extreme corneal flattening following collagen crosslinking for progressive keratoconus. *Eur J Ophthalmol*. 2021;31(4):1546–1552. doi:10.1177/1120672120947664
13. Izquierdo L, Henriquez M, Mannis MJ. *Keratoconus, E-Book: Diagnosis and Management*. Elsevier Health Sciences; 2022:595.

14. Epstein RL, Chiu YL, Epstein GL. Pentacam HR criteria for curvature change in keratoconus and postoperative LASIK ectasia. *J Refract Surg*. 2012;28(12):890–894. doi:10.3928/1081597X-20121115-04
15. Henriquez M, Cocche K, Quezada F, Rojas R, Chauca J, Izquierdo L. Age related variation in corneal biomechanics in healthy subjects. *ASCRS*. 2022;28:117–122.