Long-term Evaluation of Corneal Biomechanical Properties After Corneal Cross-linking for Keratoconus: A 4-Year Longitudinal Study

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ABSTRACT

PURPOSE: To compare the long-term changes in corneal biomechanics, topography, and tomography before and 4 years after corneal cross-linking (CXL) with the Dresden protocol and correlate these changes with visual acuity.

METHODS: In this longitudinal study, 18 eyes of 18 patients with progressive keratoconus who were treated with CXL were included. All patients received a standard ophthalmological examination and were examined by Placido disc–based topography, Scheimpflug tomography, and biomechanical assessments with the Corvis ST (OCULUS Optikgeräte GmbH, Wetzlar, Germany) and Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY) before and 4 years after CXL. The main outcome measures were dynamic corneal response (DCR) parameters obtained from the Corvis ST, corneal hysteresis (CH), corneal resistance factor (CRF), visual acuity, refraction, corneal curvature, and corneal thickness.

RESULTS: There were no significant differences in mean visual acuity, refraction, intraocular pressure, corneal topography, corneal astigmatism in both corneal surfaces, maximum keratometry, corneal thickness at apical and thinnest points, thickness profile indices, corneal volume, and specular microscopy before and 4 years after CXL ($P > .05$). Significant changes were observed in many DCR parameters, including radius at highest concavity and integrated inverse radius, both of which were consistent with stiffening. The CH and CRF values after CXL were not statistically significant. The new parameters using the Corvis ST include integrated inverse concave radius, which showed a significant decrease 1.07 ± 0.93 mm^{-1}, consistent with stiffening. The corneal stiffness parameter at the first applanation, Ambrósio's Relational Thickness to the horizontal profile, deformation amplitude ratio, and Corvis Biomechanical Index as a combined biomechanical screening parameter did not show significant changes.

CONCLUSIONS: CXL is a minimally invasive treatment option to prevent keratoconus progression over 4 years. Pressure-derived biomechanical parameters obtained from the ORA did not show any change following CXL at 4 years of follow-up, whereas the Corvis ST DCR parameters detected changes in corneal biomechanical properties.

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Keratoconus is one of the most prevalent corneal ectatic disorders with a progressive nature.[1] Abnormal corneal biomechanical behavior is the most probable etiologic factor and the corneal geometrical changes are its consequences.[2] Therefore, in vivo evaluation of corneal mechanical stability and biomechanical properties might detect the ectasia in the early stages prior to the topographic/tomographic manifestations.[3] It is also useful in assessing the efficacy of therapeutic modalities, especially corneal cross-linking (CXL).

CXL is considered the only standard treatment for halting or reducing the progression of keratoectasia in the early stages and preventing deterioration by increasing the mechanical strength of the cornea.[4-7] In vitro studies confirmed increased corneal stiffness of up to 300% following CXL with no alteration in the adhesion or cohesion between the stromal laminas.[8,9] Although increased corneal rigidity has been reported following CXL in humans,[10,11] these studies were in vitro evaluations relying on the stress-strain assessments of the provided corneal strips.[12]

In recent years, the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY)[13-15] and Corvis ST (OCULUS Optikgeräte GmbH, Wetzlar, Germany)[16]

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have been introduced for in vivo evaluation of corneal biomechanics. Studies conducted using the air-puff system with the Corvis ST in ex vivo porcine eyes indicate a reduction in corneal indentation by a factor of 1.41 times, and a change in the temporal symmetry profile of corneal deformation with a coefficient of 1.65 times following CXL that confirms the viscoelastic changes in the cornea after treatment.[17]

No change in corneal hysteresis and corneal resistance factor (CRF) have been reported clinically following CXL in eyes with progressive keratoconus, although the infrared signal showed changes in morphology consistent with stiffening.[18-24]

Although non-invasive systems have also been proposed for in vivo evaluation of corneal biomechanical properties (eg, ultrasound techniques that require eye immersion or Brillouin microscopy as a non-contact technique for determining elastic modulus), the corneal deformation response measured with air-puff systems, especially the Corvis ST, provides an opportunity to examine corneal dynamic behavior and other aspects of biomechanical behavior in addition to what the previous systems measured.[17]

Therefore, this study was designed to compare the long-term changes in corneal biomechanical response before and 4 years after CXL with the standard Dresden protocol, to gain a better insight into the changes in stiffness and stability of the cornea. Also, to the best of our knowledge, there is no similar long-term study in the literature. The second purpose was to evaluate the changes in the visual and ocular status after this time period.

PATIENTS AND METHODS

This longitudinal study included 18 patients with progressive keratoconus who had received CXL at a clinic in Iran by an experienced corneal fellowship-trained surgeon (M-RS) and were called back for a thorough 4-year follow-up examination. Criteria for keratoconus diagnosis were based on slit-lamp findings (eg, Fleischer ring or Vogt striae) and abnormal topographic patterns on the sagittal (axial) front curvature map and distortion of the retinoscopic reflex, and were confirmed by an experienced corneal specialist.

Progression was confirmed initially based on a change of 1.00 diopter (D) or greater in maximum keratometry or corneal astigmatism in topography, greater than 30 µm reduction in the corneal thinnest point, or subjective report of visual deterioration after ruling out other causes of visual impairment during 1 year. The study followed the tenets of the Declaration of Helsinki and informed consent was obtained from all patients after an explanation of the nature and purpose of this study. The local ethics committee approved this study.

Inclusion criteria were no history of herpetic keratitis, diabetic mellitus, and connective tissue disorders; a corneal thickness of at least 400 µm at the thinnest point; no severe dry eye and corneal scarring; and no history of pregnancy during the past 4 years after CXL due to the effects of hormonal changes on the progression of keratoconus.

Along with standard ophthalmological examination, all patients were examined by Placido disc–based topography with the TMS-4 (Tomey Corporation, Nagoya, Japan) and Scheimpflug tomography and biomechanical assessments with the Pentacam HR, Corvis ST, and ORA, respectively, and specular microscopy (SP2000; Topcon Corporation, Tokyo, Japan) before and 4 years (48 months) after CXL.

CXL Technique

CXL was done based on the standard Dresden protocol (S-CXL [3*30]) including mechanical debridement of the corneal epithelium in the central 9 mm. Riboflavin 0.1% in 20% dextran was administered topically every 2 minutes for 30 minutes for appropriate saturation of the corneal stroma. Absorption of riboflavin in the stroma and the anterior chamber was confirmed by checking its fluorescence using slit-lamp examination. Ultraviolet-A light with a wavelength of 365 nm and irradiance of 3 mW/cm^2 was applied to the central 8 mm of the cornea for 30 minutes using an optical system (UV-X; Peschke Meditrade GmbH, Huenenberg, Switzerland). Administration of riboflavin was continued every 5 minutes when exposed to ultraviolet-A light (**Table 1**).

Postoperative Regimen

An antibiotic eye drop (Oftaquix; Santen UK Ltd., St. Albans, United Kingdom), a topical corticosteroid (betamethasone 0.1%), and a preservative-free artificial drop (Artelac Advanced; Bausch & Lomb, Rochester, NY) were administered. A soft bandage contact lens was fitted until complete corneal reepithelialization.

Follow-up Evaluations

Early postoperative visits were at 1, 3, and 5 days after surgery until complete epithelial healing. Subsequent follow-up visits were planned at 1, 6, and 12 months after CXL and then annually, which included visual acuity, refraction, and keratometry. Imaging data were acquired only preoperatively and at 4 years postoperatively. In this study, the preoperative imaging data were compared with 4-year postoperative assessments.

All measurements with the ORA and Corvis ST were taken by the same experienced and qualified technician to avoid any bias and the automatic release of both devices ensured no effect of user dependency.

Only examinations with acceptable quality were included in the final analysis.

Included Variables

Visual acuity in logMAR notation (uncorrected [UDVA] and corrected [CDVA] distance visual acuity), refractive data (sphere, cylinder, and axis), and noncontact intraocular pressure (IOP) were included. The corneal topography–derived variables were simulated keratometry in flat and steep meridians, corneal astigmatism, and mean keratometry. Endothelial cell density and coefficient of variation in the cell area were assessed using specular microscopy.

Pentacam-derived variables were keratometry in flat and steep meridians in the central 3 mm of the front and back corneal surfaces, the mean keratometry readings in a 5-mm zone around the steepest point (5 mm), the magnitude and axis of the front and back corneal astigmatism, corneal asphericity expressed as Q-value in the central 8 mm of the cornea on both surfaces, corneal thickness at the apex (CCT) and the thinnest point (CTP), displacement of CTP along the y-axis from the apex (TPy), corneal volume at 10 mm around the corneal apex, and average and maximum pachymetric progression indices (PPIave, PPImax) calculated for average of all meridians over the entire 360° of the cornea, starting from the thinnest point and meridian with maximum pachymetric increase, respectively, and Ambrósio Relational Thickness maximum (ART max) calculated as dividing the thinnest pachymetric value by the maximum pachymetric progression.

The provided parameters using the Corvis ST (software version 1.4r1755) were dynamic corneal response (DCR) parameters associated with IOP and CCT. DCR parameters included: first applanation length (A1: the flattened length of the cornea at the first applanation), second applanation length (A2: the flattened length of the cornea at the second applanation), applanation velocity 1 (AV1: velocity of corneal apex during the first applanation), applanation velocity 2 (AV2: velocity of corneal apex during the second applanation), peak distance (distance between the two peaks at the highest concavity phase), highest concavity radius (central corneal radius of curvature at the highest concavity phase), and deformation amplitude (the largest anterior-posterior displacement of at the corneal apex at the highest concavity phase).

Derived data from the ORA were corneal hysteresis, CRF, corneal compensated IOP (IOPcc), and Goldmann correlated IOP (IOPg).

The new parameters obtained from the Corvis ST were stiffness parameter at the first applanation (SP-A1: resultant pressure [adjusted pressure at A1 (adj AP1) – biomechanically compensated IOP (bIOP)] divided by deflection amplitude at A1), Ambrósio's Relational Thickness to the horizontal profile (ARTh: ART in the horizontal [temporal-nasal] meridian), integrated radius (area under the inverse concave radius curve), deformation amplitude ratio (DAR: the ratio between deformation amplitude at the apex and the average of deformation amplitude at 2 mm around the center in temporal and nasal directions), and the Corvis Biomechanical Index (CBI: combination of DCR parameters and corneal thickness profile in the horizontal meridian based on the regression analysis).

TABLE 1
CXL Methods

Parameter	Variable
Treatment target	Primary ectasia (keratoconus)
Fluence (total) (J/cm^2)	5.4
Soak time and interval (minutes)	30(q2)
Intensity (mW)	3
Treatment time (minutes)	30
Epithelium status	Off
Chromophore	Riboflavin
Chromophore carrier	Dextran
Chromophore osmolality	Iso-osmolar
Chromophore concentration	0.1%
Light source	UV-X; Peschke Meditrade, GmbH, Huenenberg, Switzerland
Irradiation mode (interval)	Continuous
Protocol modification	No
Protocol abbreviation in manuscript	S-CXL(3*30) (Standard)

CXL = corneal cross-linking

Statistical Analysis

Data were analyzed in SPSS software (version 22; SPSS, Inc., Chicago, IL) using the paired-samples *t* test and its non-parametric equivalent (Wilcoxon signed-rank test) for variables with no Gaussian distribution to analyze the changes before and after CXL. A *P* value of less than .05 was considered significant in all tests.

RESULTS

Eighteen eyes of 18 patients with progressive keratoconus were included in this study. The mean age at the preoperative and postoperative assessments were 19.61 ± 3.16 years (range: 15 to 25 years) and 23.88 ± 2.96 years (range: 19 to 29 years), respectively ($P < .001$).

Mean and standard deviation of visual acuity, refraction, IOP, corneal topography, and specular mi-

TABLE 2

Mean ± SD Corneal Biomechanical Parameters Using Corvis ST and ORA Before and After CXL (n = 18)

Variable	Mean ± SD (95% CI) Pre-CXL	Post-CXL	Mean Difference ± SD (95% CI)	P
Corvis ST parameters				
AL1 (mm)	1.72 ± 0.33 (1.56, 1.89)	2.08 ± 0.33 (1.91, 2.25)	0.35 ± 0.38 (0.16, 0.55)	.001
AL2 (mm)	1.63 ± 0.51 (1.38, 1.89)	1.29 ± 0.44 (1.07, 1.51)	-0.34 ± 0.55 (-0.61, -0.06)	.019
AV1 (m/s)	0.13 ± 0.03 (0.11, 0.15)	0.14 ± 0.02 (0.13, 0.16)	0.01 ± 0.03 (-0.00, 0.03)	.143[a]
AV2 (m/s)	-0.41 ± 0.13 (-0.48, -0.34)	-0.36 ± 0.05 (-0.39, -0.33)	0.04 ± 0.11 (-0.01, 0.10)	.110
HC, PD (mm)	4.79 ± 0.61 (4.48, 5.10)	5.12 ± 0.30 (4.97, 5.27)	0.33 ± 0.63 (0.02, 0.64)	.007[a]
HC, R (mm)	5.59 ± 0.93 (5.12, 6.05)	6.22 ± 1.13 (5.65, 6.78)	0.63 ± 0.76 (0.25, 1.01)	.003
HC, DA (mm)	1.08 ± 0.15 (1.00, 1.16)	1.15 ± 0.15 (1.07, 1.22)	0.06 ± 0.11 (0.01, 0.12)	.021
CCT (μm)	471.11 ± 38.66 (451.88, 490.33)	467.05 ± 47.20 (443.58, 490.52)	-4.05 ± 26.86 (-17.41, 9.30)	.530
IOPnct (mm Hg)	13.66 ± 1.29 (13.02, 14.31)	14.44 ± 2.33 (13.28, 15.60)	0.77 ± 2.08 (-0.26, 1.81)	.132
ORA parameters				
CH (mm Hg)	8.77 ± 1.27 (8.14, 9.40)	8.31 ± 1.15 (7.74, 8.89)	-0.46 ± 1.19 (-1.05, 0.13)	.144[a]
CRF (mm Hg)	7.71 ± 1.57 (6.92, 8.49)	7.28 ± 1.40 (6.59, 7.98)	-0.42 ± 1.15 (-0.99, 0.15)	.141
IOPcc (mm Hg)	14.05 ± 3.28 (12.41, 15.68)	14.42 ± 2.42 (13.21, 15.62)	0.37 ± 2.24 (-0.74, 1.48)	.647[a]
IOPg (mm Hg)	11.21 ± 3.44 (9.50, 12.92)	11.10 ± 2.64 (9.78, 12.41)	-0.11 ± 1.97 (-1.09, 0.87)	.814

SD = standard deviation; CXL = corneal cross-linking; CI = confidence interval; AL = applanation length; AV = applanation velocity; HC = highest concavity; PD = peak distance; R = radius; DA = deformation amplitude; CCT = central corneal thickness; IOPnct = uncorrected intraocular pressure; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = corneal compensated IOP; IOPg = Goldmann correlated IOP

[a]*Non-parametric.*

The Corvis ST is manufactured by OCULUS Optikgeräte GmbH, Wetzlar, Germany, and the ORA is manufactured by Reichert Ophthalmic Instruments, Buffalo, NY.

croscopy before and 4 years following CXL are presented in **Table A** (available in the online version of this article).

The mean postoperative changes in refractive components (sphere, cylinder), simulated keratometry and corneal astigmatism were limited to approximately 0.50 diopters (D). Statistical analysis was performed using the paired-samples *t* test or its non-parametric equivalent (Wilcoxon signed-rank test), and did not show significant differences in the mean values ($P > .05$).

Percent change for each parameter in **Table A** was calculated as the post-CXL value minus the pre-CXL value divided by the pre-CXL value. The highest percent changes were related to refractive cylinder axis and UDVA and the lowest ones were related to the corneal volume of endothelial cells and simulated keratometry in the flat meridian.

The mean and standard deviation of some indices obtained from Pentacam in the evaluations before and after CXL are shown in **Table B** (available in the online version of this article).

There were no significant changes in steepening in the corneal curvature and corneal astigmatism, separately in both corneal surfaces. Preoperative and postoperative differences in the maximum keratometry as one of the criteria for defining progression was approximately 0.25 D. The mean difference in the corneal thickness at the apical and thinnest points was not significantly different between before and 4 years after CXL statistically. Also, the thickness profile indices and the corneal volume did not show statistically significant changes. The only significant difference was related to Q-value in the front corneal surface ($P = .004$).

The results of corneal biomechanical assessment using the ORA and Corvis ST are illustrated in **Table 2**. The standard corneal resistance parameters showed statistically significant differences, except for inward ($P = .143$) and outward ($P = .110$) velocities. The mean difference in the highest concavity parameters including peak distance, radius, and deformation amplitude were 0.33, 0.63, and 0.06 mm between before and 4 years after CXL, respectively, so that the postoperative values were higher compared to the preoperative ones. Also, there were no significant differences in the mean pachymetry and non-contact IOP provided by the Corvis ST ($P > .05$). The classic ORA parameters including corneal hysteresis, CRF, IOPg, and IOPcc were not statistically different between before and 4 years after CXL.

The new parameters using the Corvis ST and Pentacam are shown in **Table 3**.

TABLE 3

Mean ± SD New Parameters Using Corvis ST and Pentacam Before and After CXL (n = 15)

Variable	Mean ± SD (95% CI)		Mean Difference ± SD (95% CI)	*P*
	Pre-CXL	4 Years Post-CXL		
SP-A1 (mm Hg/mm)	74.90 ± 18.05 (64.90, 84.90)	78.28 ± 1 (69.24, 87.33)	3.38 ± 15.18 (-5.02, 11.79)	.402
ARTh	183.82 ± 87.94 (135.11, 232.52)	207.51 ± 123.78 (138.96, 276.06)	23.68 ± 65.51 (-12.59, 59.96)	.183
IR (mm^{-1})	11.42 ± 2.35 (10.11, 12.72)	10.34 ± 1.97 (9.25, 11.44)	-1.07 ± 0.93 (-1.58, -0.55)	.001
DAR	5.32 ± 1.00 (4.76, 5.87)	5.28 ± 0.71 (4.89, 5.68)	-0.03 ± 0.46 (-0.29, 0.22)	.865[a]
CBI	0.99 ± 0.01 (0.98, 1.00)	0.91 ± 0.24 (0.77, 1.05)	-0.07 ± 0.23 (-0.20, 0.05)	.553[a]

SD = standard deviation; CXL = cross-linking; CI = confidence interval; SP-A1 = stiffness parameter at first applanation; ARTh = Ambrósio's Relational Thickness to the horizontal profile; IR = integrated radius; DAR = deformation amplitude ratio; CBI = Corvis Biomechanical Index

[a]*Non-parametric.*

The Corvis ST and Pentacam are manufactured by OCULUS Optikgeräte GmbH, Wetzlar, Germany.

A total of 3 eyes were excluded due to unacceptable quality in the Corvis ST examinations. SP-A1, deformation amplitude 2 mm, and CBI as a combined biomechanical parameter did not show significant changes compared to the pre-treatment state, whereas integrated radius decreased significantly, indicating stiffer corneal behavior ($P = .001$).

DISCUSSION

CXL provides the new covalent bindings in the stromal components that include collagen fibers and proteoglycan main proteins (mimecan and decorin) to improve the corneal mechanical strength.[4,5] There are reports that indicate increased corneal stiffness in laboratory conditions, with a factor of 1.05, 1.510, and 4.511 immediately following CXL in the human cornea. The current study included a longer follow-up time (4 years) of corneal biomechanical changes following CXL than similar studies reported to date. In general, this long-term study illustrated that CXL is an option for progressive keratoconus treatment that shows visual stabilization in comparison of the preoperative and postoperative data 4 years after CXL.

The obtained results showed a stable status with no statistically significant changes in refraction (sphere and cylinder), visual acuity (uncorrected and corrected), corneal geometrical status (curvature and thickness), and corneal endothelial cells (density and variations) 4 years after CXL compared to the preoperative assessments.

The front and back surface postoperative keratometry readings in the 3-mm zone and in both corneal principal meridians and front maximum keratometry value were not significantly different from preoperative values. These findings contradict studies that reported a flattening effect following CXL,[25-29] although the flattening effect may be seen in the short-term assessments, but this effect was not confirmed with the current long-term study. Assessing the change of curvature in the central 5-mm zone (mean keratometry = 5 mm) showed a non-significant change comparing the values before and after CXL.

Grewal et al.[30] reported that the corneal curvature at both surfaces remained without significant changes after CXL at 1 year, which is in agreement with the results of the current study, although the timing of the postoperative assessment was different between these two studies (1 vs 4 years in the current study).

In assessing the CXL 4-year outcomes in 13 examined eyes, Raiskup-Wolf et al.[31] reported improvement in the CDVA, astigmatism, and maximum keratometry reading with mean changes of 0.18 logMAR (1.49 and 2.66 D, respectively) at 4 years after CXL. These findings are not consistent with the current results, which showed no significant changes in the CDVA, astigmatism, and maximum keratometry readings postoperatively. Nevertheless, observing relatively constant refractive and corneal conditions are in general agreement with their study.

Similar significant improvements in CDVA and keratometry readings were reported by Caporossi et al.[32] in a 4-year follow-up and Raiskup et al.[33] 10 years after CXL. This 1.70 D reduction in the corneal astigmatism and 0.14 logMAR improvement in the CDVA in Raiskup et al.'s study versus no change in these parameters in the current study may be partially attributed to the difference in patient age in the two studies. The postoperative age range in their study was 24 to 52 versus 19 to 29 years in the current study. The higher age range is associated with more corneal stiffness secondary to the additive effects of CXL and senile or age-related non-enzymatic CXL[34] and it may be responsible for the higher flattening rate seen in their study.

CXL is safe for the corneal endothelium in the long term because no significant changes in endothelial cell count and their variation were seen that are in line with previous studies.[22,35]

Consistent with previous studies, there were no considerable decreases in CCT and CTP 4 years after

treatment.[19,30] A marginal increase (0.05) in the average progression index resulted in a subtle decrease in CCT similar to Vinciguerra et al.'s study.[36] This finding is justifiable because the central cornea is more affected by CXL than its periphery.

In vitro evaluations reported an increase in corneal stiffness following CXL, so it is theoretically expected to see improvement in the corneal biomechanical parameters. The ORA analysis was limited on the pressure-derived metrics and it was not possible to assess waveform parameters. The current results showed that corneal hysteresis and CRF had no significant change after CXL, which is consistent with the findings of Goldich et al.[19] in the assessment of 10 eyes of 10 patients 6 months after CXL (n = 10 eyes), Sedaghat et al.[22] in a 1-year follow-up study (n = 97 eyes), Gkika et al.[37] in a 12-month follow-up study (n = 50 eyes), Greenstein et al.[38] in 46 eyes of keratoconic patients at 12 months after CXL, and Vinciguerra et al.[20] in 24 eyes 12 months after CXL. However, Vinciguerra et al.[20] showed significant increases in the amplitudes of the infrared signal peaks associated with both inward and outward applanation events that were consistent with stiffening. These outcomes highlight the difference between in vivo and in vitro studies. It can also be attributed to the inability of corneal hysteresis to detect purely elastic changes in the biomechanical characteristics of the cornea when changes in viscosity also occur. In other words, the changes in the elastic properties may be masked by the changes in the viscous properties with CXL, which provides covalent bonds between the collagen chains' terminal and the extracellular matrix.[39]

The 4-year postoperative values of corneal hysteresis and CRF in our study are similar to those reported by Sedaghat et al.[22] after 12 months following CXL and De Bernardo et al.[21] in the follow-up of 57 eyes for 24 months postoperatively. One reason for not finding a difference is probably related to keratoconogenic factors because CXL does not eliminate these factors and only increases corneal resistance against proteolytic and lysosomal enzymes.[40]

Our study showed a significant difference in the standard DCR parameters between before and 4 years following CXL, except for velocity during the first and second applanations. Other studies showed the changes in several parameters obtained from the Corvis ST at different follow-up times after CXL. Bak-Nielsen et al.[41] reported significant changes in the highest concavity time, deformation amplitude, and second applanation time at 97 days after CXL compared to the preoperative values in 27 eyes of 27 patients with keratoconus. Assessment of the peak distance, highest concavity radius and deformation amplitude 1 year after conventional CXL by Tomita et al.[42] showed considerable change in the peak distance compared to others. Also, static and dynamic analysis of the Scheimpflug images to assess the effect of CXL on biomechanical properties in 24 eyes with progressive keratoconus 6 months after treatment showed a significant change 0.5 mm in the peak distance and the corneal radius at the highest concavity phase.[43] Our results indicated a significant increase in these parameters with the mean changes 0.33 mm in peak distance and 0.63 mm in the corneal radius at the highest concavity phase, similar to Steinberg et al.'s study,[43] although the significant changes were not just limited to these two parameters but were also seen in other parameters. Regarding the new Corvis ST parameters, integrated radius changed significantly toward a smaller value (P = .001) after CXL, indicating a stiffer behavior after CXL.

No significant changes in the IOP (IOPnct [Topcon], IOPcc, IOPg, and IOPnct using Corvis ST) and corneal volume 4 years after treatment were similar to the findings of Grewal et al.[30] It is expected to achieve this pressure outcome in the presence of an almost similar corneal hysteresis, CRF, and corneal thickness preoperatively and postoperatively. Steinberg et al.[44] reported a significant difference in IOPnct using the Corvis ST before and 3 months after treatment, which is in contrast to the results of the current study. This difference is somewhat expected by observing the significant difference in CCT in their study, but no difference in the current study after 4 years.

SP-A1 is a novel stiffness parameter that better reflects the cornea's overall resistance to deformity. The novelty of this parameter is related to the use of a specific (resultant) pressure at A1, which compensates for IOP as a major contributor to corneal biomechanics. Corneas with higher SP-A1 are stiffer biomechanically.[45,46] No significant change in SP-A1 4 years after CXL means that this index does not detect subtle changes 4 years after treatment compared to the preoperative status. On the other hand, the topographic/tomographic indices revealed no evidence of progression during the follow-up. One possible explanation for these findings is that CXL does not eliminate pathogenic factors of the disease but only improves the corneal resistance against proteolytic and lysosomal enzymes over an unknown time period.

Based on ARTh's definition, a higher value refers to a thicker cornea at the thinnest point and/or a lower average pachymetric progression index along the horizontal meridian.[47,48] In the current study, the postoperative ARTh showed no significant difference compared to the preoperative value, which is expected due to insignificant changes in the corneal thickness and thickness profiles.

Postoperative DAR did not show significant change statistically. Vinciguerra et al.[47] reported a lower DAR associated with a stiffer cornea and vice versa. There-

fore, DAR is also not sensitive enough to detect subtle changes after CXL.

Integrated radius or integrated inverse concave radius reduced significantly after CXL. The preoperative and postoperative difference was 1.07 mm^{-1}. Integrated radius is calculated based on the integrated area under the curve of the inverse radius of curvature at highest concavity. A lower integrated radius value is associated with a stiffer cornea[45]; therefore, with attention to this parameter, CXL improves the mechanical strength of cornea compared to the pretreatment status. The integrated radius changes after CXL were related to changes in the curvature after CXL as determined by the mean keratometry in a 5-mm zone around the steepest point.

The CBI is a new index based on the regression analysis of deformation parameters and corneal thickness profile, which varies from 0 to 1 and has a cut-off point of 0.5. The values less than 0.5 are normal and higher values are suspicious biomechanically.[48] The CBI showed a non-significant change following CXL, which is expected because this is a screening parameter, not one designed to detect changes in corneal biomechanics.

One limitation of this study was the relatively small number of eyes (n = 18). Another weakness was the failure to investigate the effect of cone location on the long-term outcome of CXL. Also, we did not include the additional parameters extracted from signal analysis of ORA that describe the waveform of the ORA's response curve. We also had no complete data for analysis during the intervening years. In fact, including 1- or 2-year follow-up imaging data would provide a pattern for longitudinal changes and this should be considered for future prospective studies.

CXL is a minimally invasive treatment option to prevent keratoconus progression over 4 years. Refractive status, visual acuity, corneal curvature, corneal thickness, and corneal endothelial cells were stable during this long-term 4-year follow-up. Corneal biomechanical parameters obtained using ORA did not change following CXL between preoperatively and 4 years of follow-up, whereas Corvis ST parameters were more sensitive than corneal hysteresis or CRF to highlight the changes in the corneal mechanical strength. Further studies with a large sample size and longer time are required to better represent changes in the corneal biomechanics using the Corvis ST after CXL.

AUTHOR CONTRIBUTIONS

Study concept and design (M-RS, HM-M, RA); data collection (HM-M, ZD, SR, H-RH); analysis and interpretation of data (HM-M, CJR, A-AY, MK, JS); writing the manuscript (HM-M, RA, A-AY, ZD, H-RH); critical revision of the manuscript (M-RS, HM-M, JS, RA, A-AY, CJR, SR, MK); statistical expertise (RA, JS, CJR, A-AY, ZD, SR, MK); administrative, technical, or material support (M-RS, H-RH); supervision (M-RS)

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TABLE A

Mean ± SD of Visual Acuity, Refraction, Intraocular Pressure, Corneal Topography, and Specular Microscopy in the Preoperative and Postoperative Assessments (n = 18)

Variable	Mean ± SD (95% CI) Pre-CXL	Mean ± SD (95% CI) 4 Years Post-CXL	Mean Difference ± SD (95% CI)	Change (%)	*P*
UDVA	0.45 ± 0.48 (0.21, 0.69)	0.42 ± 0.27 (0.29, 0.56)	-0.02 ± 0.40 (-0.22, 0.17)	26.33	.508[a]
CDVA	0.08 ± 0.13 (0.01, 0.15)	0.10 ± 0.11 (0.05, 0.16)	0.02 ± 0.13 (-0.04, 0.09)	22.92	.235[a]
Sphere (D)	-2.86 ± 4.39 (-5.04, -0.67)	-2.73 ± 4.03 (-4.74, -0.73)	0.12 ± 1.15 (-0.44, 0.69)	25.66	.977[a]
Cylinder (D)	-4.00 ± 2.19 (-5.09, -2.90)	-4.25 ± 2.36 (-5.42, -3.07)	-0.25 ± 0.66 (-0.58, 0.08)	10.38	.129
Axis (º)	71.22 ± 58.55 (42.10, 100.34)	77.27 ± 61.43 (46.72, 107.82)	6.05 ± 63.08 (-25.31, 37.42)	84.95	.327[a]
IOP (mm Hg)	15.36 ± 2.81 (13.86, 16.86)	14.70 ± 3.00 (13.21, 16.19)	-0.76 ± 3.20 (-2.47, 0.94)	-3.81	.353
Tomey Kf (D)	45.61 ± 2.79 (44.22, 47.00)	46.04 ± 3.14 (44.47, 47.61)	0.43 ± 1.78 (-0.45, 1.31)	0.01	.446*
Tomey Ks (D)	51.72 ± 4.50 (49.48, 53.96)	52.29 ± 4.92 (49.84, 54.74)	0.57 ± 2.43 (-0.63, 1.78)	1.14	.332
Tomey Axis (º)	82.83 ± 60.34 (52.82, 112.84)	78.11 ± 60.16 (48.19, 108.03)	-4.72 ± 9.77 (-9.58, 0.13)	-4.99	.056[a]
Tomey Km (D)	48.66 ± 3.45 (46.94, 50.38)	49.16 ± 3.77 (47.29, 51.04)	0.50 ± 2.03 (-0.50, 1.51)	1.07	.309
Tomey CA (D)	6.11 ± 2.87 (4.68, 7.54)	6.25 ± 3.36 (4.57, 7.92)	0.13 ± 1.29 (-0.50, 0.78)	2.31	.647[a]
SpecMic CD (cell/mm^2)	3,021.83 ± 299.26 (2,873.01, 3,170.65)	3,110.70 ± 381.13 (2,914.74, 3,306.66)	106.35 ± 276.45 (-35.78, 248.49)	3.74	.132
SpecMic CV	33.77 ± 7.67 (29.96, 37.59)	35.23 ± 3.96 (33.19, 37.27)	2.47 ± 5.79 (-0.51, 5.45)	0.00	.098

SD = standard deviation; CXL = corneal cross-linking; CI = confidence interval; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; IOP = intraocular pressure; Kf = keratometry in flat meridian; Ks = keratometry in steep meridian; Km = mean keratometry; CA = corneal astigmatism; SpecMic = specular microscopy; CD = cell density; CV = coefficient of variation
[a]*Non-parametric.*

TABLE B

Mean ± SD Keratometry and Q-value in Front and Back Corneal Surfaces, Corneal Volume, Corneal Thickness, and Thickness Profile Indices Using Pentacam Before and After CXL (n = 18)

Variable	Mean ± SD (95% CI) Pre-CXL	Mean ± SD (95% CI) 4 Years Post-CXL	Mean Difference ± SD (95% CI)	*P*
Kf front (D)	45.84 ± 3.20 (44.25, 47.43)	46.49 ± 3.12 (44.94, 48.04)	0.65 ± 1.44 (-0.06, 1.36)	.061[a]
Ks front (D)	50.54 ± 3.91 (48.59, 52.49)	50.69 ± 3.65 (48.87, 52.51)	0.15 ± 0.99 (-0.34, 0.64)	.531
Axis front (º)	70.12 ± 57.09 (41.72, 98.51)	80.64 ± 61.22 (50.19, 111.08)	10.52 ± 36.63 (-7.69, 28.73)	.248[a]
Front CA (D)	4.70 ± 2.02 (3.69, 5.70)	4.20 ± 1.93 (3.23, 5.16)	-0.50 ± 1.51 (-1.25, 0.25)	.178
Kmax (D)	55.60 ± 5.46 (52.88, 58.31)	55.84 ± 5.35 (53.17, 58.50)	0.24 ± 1.03 (-0.27, 0.75)	.330
Kf back (D)	-6.61 ± 0.60 (-6.91, -6.30)	-6.68 ± 0.63 (-7.00, -6.36)	-0.07 ± 0.18 (-0.16, 0.02)	.120
Ks back (D)	-7.48 ± 0.66 (-7.81, -7.15)	-7.53 ± 0.64 (-7.85, -7.21)	-0.05 ± 0.21 (-0.16, 0.04)	.282
Axis back (º)	90.77 ± 64.94 (58.47, 123.06)	91.60 ± 68.46 (57.55, 125.65)	0.83 ± 18.23 (-8.23, 9.90)	.663[a]
Back CA (D)	-0.87 ± 0.32 (-1.03, -0.70)	-0.85 ± 0.33 (-1.02, -0.69)	0.01 ± 0.21 (-0.09, 0.12)	.936[a]
Q front	-0.81 ± 0.44 (-1.03, -0.59)	-0.94 ± 0.53 (-1.20, -0.67)	-0.12 ± 0.16 (-0.20, -0.04)	.004
Q back	-0.78 ± 0.43 (-0.99, -0.56)	-0.91 ± 0.68 (-1.24, -0.57)	-0.12 ± 0.44 (-0.34, 0.09)	.238
CV (mm^3)	55.76 ± 2.82 (54.35, 57.16)	55.70 ± 2.58 (54.41, 56.98)	-0.06 ± 1.66 (-0.88, 0.76)	.306[a]
CCT (μm)	458.44 ± 40.16 (438.47, 478.41)	453.27 ± 37.33 (434.71, 471.84)	-5.16 ± 10.62 (-10.45, 0.11)	.055
CTP (μm)	452.27 ± 40.83 (431.97, 472.58)	451.05 ± 39.63 (431.34, 470.76)	-1.22 ± 12.79 (-7.58, 5.14)	.690
CTPy (mm)	-0.46 ± 0.20 (-0.56, -0.36)	-0.51 ± 0.21 (-0.62, -0.41)	-0.05 ± 0.28 (-0.19, 0.08)	.444
ART (μm)	186.29 ± 85.65 (142.25, 230.33)	170.22 ± 71.21 (134.80, 205.63)	-16.58 ± 44.20 (-39.31, 6.14)	.141
PPImax	2.99 ± 1.04 (2.46, 3.53)	2.95 ± 0.89 (2.51, 3.40)	-0.01 ± 0.54 (-0.29, 0.26)	.888
PPIave	2.00 ± 0.62 (1.68, 2.32)	2.04 ± 0.55 (1.76, 2.31)	0.05 ± 0.24 (-0.07, 0.17)	.382

SD = standard deviation; Q = asphericity (Q-value); CXL = corneal cross-linking; CI = confidence interval; Kf = keratometry in flat meridian; D = diopters; Ks = keratometry in steep meridian; CA = corneal astigmatism; Kmax = maximum keratometry; CV = corneal volume; CCT = central corneal thickness; CTP = corneal thinnest point; CTPy = displacement of CTP along the y-axis; ART = Ambrósio Relational Thickness; PPImax = Maximum Pachymetric Progression Index; PPIave = Average Pachymetric Progression Index
[a]*Non-parametric.*
The Pentacam is manufactured by OCULUS Optikgeräte GmbH, Wetzlar, Germany.