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ORIGINAL PAPER

Correlation of central and peripheral keratometric parameters after corneal collagen cross-linking in keratoconus patients

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Abstract

Purpose To evaluate the difference in the central and peripheral keratometric parameters in patients with keratoconus after corneal collagen cross-linking (CXL).

Methods Forty-eight eyes of 32 patients (18 males, 16–28 years) affected by progressive keratoconus in different stages of evolution underwent CXL using the standard epithelium-off protocol. Corneal thickness and corneal curvature before CXL and after 6 and 12 months using the Sirius tomographer were analyzed. The values of the mean corneal thickness at the corneal apex (CAT), center of the pupil (PCT), thinnest point (CTTL) and along concentric circles of 2, 4, 6, 8, 8.5, 9, 9.5 and 10 mm diameter were evaluated; the values of the mean curvature at the corneal apex and at the points in which the inferior, superior, nasal and temporal meridians crossed the above-mentioned concentric circles were also evaluated.

Results The mean preoperative values for CAT, PCT and CTTL were 461.4 ± 30.3, 475.3 ± 30.5 and 441 ± 32.0, respectively. The values after 12 months of CXL were 444.6 ± 36.2, 451.6 ± 36.7 and 418.2 ± 41.4. The peripheral corneal thickness at the eight points ranged from 479 to 733 preoperatively. At 12-month post-CXL, the values ranged from 444.6 to 734.1. The mean posterior curvature from apex to periphery ranged from − 4.5 to − 9.1 days preoperatively and from − 4.5 to − 9.2 days at 12 months. These were not statistically significant (ANOVA and unpaired T test).

Conclusions Our data suggest that CXL over an 8-mm zone can stabilize the peripheral cornea. Longer-term follow-up studies on the peripheral cornea after CXL will provide useful information.

Keywords Keratoconus · Cross-linking · Cornea periphery · Curvature · Thickness

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Introduction

Keratoconus (KC) is a non-inflammatory disease of the cornea which results in progressive thinning and conical ectasia of the cornea. It usually affects both eyes but in an asymmetric manner. KC may cause

myopia, myopic astigmatism and irregular astigmatism with apical corneal scarring that affect vision profoundly [1].

A wide variety of interventions ranging from glasses and contact lenses to complex surgical procedures have been used to treat the condition and improve vision. The latter include intrastromal corneal ring segments (ICRS), thermal keratoplasty, fine corneal shape adjustment—PRK, refractive correction with toric phakic IOLs and more complex procedures such as penetrating keratoplasty and deep anterior lamellar keratoplasty [2–7]. None of these procedures arrest the progression of KC. Even after keratoplasty, KC is known to recur in the graft or continue to progress in the host corneal rim that was retained at keratoplasty [8]. Acute hydrops related to progressive thinning is known to occur in the host rim after corneal transplantation for KC [9, 10].

Collagen cross-linking (CXL) of the corneal stroma is currently the only effective treatment modality to arrest the progression of KC [11]. It is widely recognized that the standard epithelium-off CXL protocol originally described by Wollensak et al. [12] is effective in stopping the progression of KC. After CXL, the main keratometric indices do not undergo any significant change though in some cases a flattening of the cornea is induced [2–7]. CXL is commonly administered to the central 8-mm zone of the cornea, which is similar to the 7–8 mm diameter of the host trephination carried out in corneal transplantation for KC [13]. This study was designed to ascertain whether the peripheral untreated rim of cornea following CXL shows signs of KC progression as have been noted in the rim after keratoplasty for KC.

Materials and methods

Forty-eight eyes of 32 patients (18 males and 14 females) aged from 16 to 28 years who were treated by CXL for progressive KC were retrospectively analyzed. KC grade was from I to II by the modified Krumeich classification [14], which is based on values of induced myopia, maximum keratometry reading and corneal thickness. In stage I, the induced myopia is < 5 days and maximum K is ≤ 48 days with minimal thinning. In stage II, the induced myopia ranges from > 5 to < 8 days and the maximum K is ≤ 53 days and corneal thickness ≥ 400 microns. Workup of patients and CXL treatment and follow-up were carried out in accordance with a standardized protocol which included follow-up at 1 week, 1 month and 3, 6 and 12 months. CXL was carried out by the standard epithelium-off protocol (8 mm diameter) with riboflavin (RICROLIN®TE, Sooft, Fermo, Italy) and by the same surgeon (FR) using the VEGA CBM-X-Linker (CSO, Florence, Italy). The epithelium was removed by mechanical brushing after marking the 8 mm zone. Thereafter, the riboflavin was soaked 30 min before irradiation and at 5-min intervals during the course of a 30-min exposure to 370 nm UVA with an irradiance of 3 mW $cm^{2.}$

Data related to corneal thickness and keratometry (Sirius topographer CSO, Florence, Italy), from center to the periphery of the cornea, before and after CXL at the 6- and 12-month points, were gathered and analyzed. The Sirius topographer is a comparatively recent tool and is based on the simultaneous use of a Scheimpflug rotating camera with a Placido disk keratoscope. Sirius is able to obtain an accurate measurement of corneal surfaces by combining Placido's typical arc-step reconstruction data with those derived from the Scheimpflug image analysis, captured at the same instant by two different cameras. This combination generates a high-precision system for the three-dimensional analysis of the cornea and the anterior chamber. As is well known, the reconstruction of Scheimpflug images can provide accurate altimetry and thickness data but is insufficient to calculate curvatures and dioptric powers with high precision.

Values of the mean thickness at the corneal apex (CAT) and at the center of the pupil (PCT), the corneal thickness at the thinnest point (CTTL) and the mean corneal thickness along concentric circles of 2, 4, 6, 8, 8.5, 9, 9.5 and 10 mm diameter centered on the corneal apex were extracted. The thickness along each concentric circle was calculated using the arithmetic average of the corneal thickness in the four points highlighted in Fig. 1a. We also analyzed the curvature at the corneal apex (CAC) and the corneal curvature at the points in which the inferior, superior, nasal and temporal meridians crossed the above-mentioned concentric circles (Fig. 1b). For the curvature analysis, we did not calculate the mean of the four values obtained from each circle but analyzed the data from each of the four points individually.

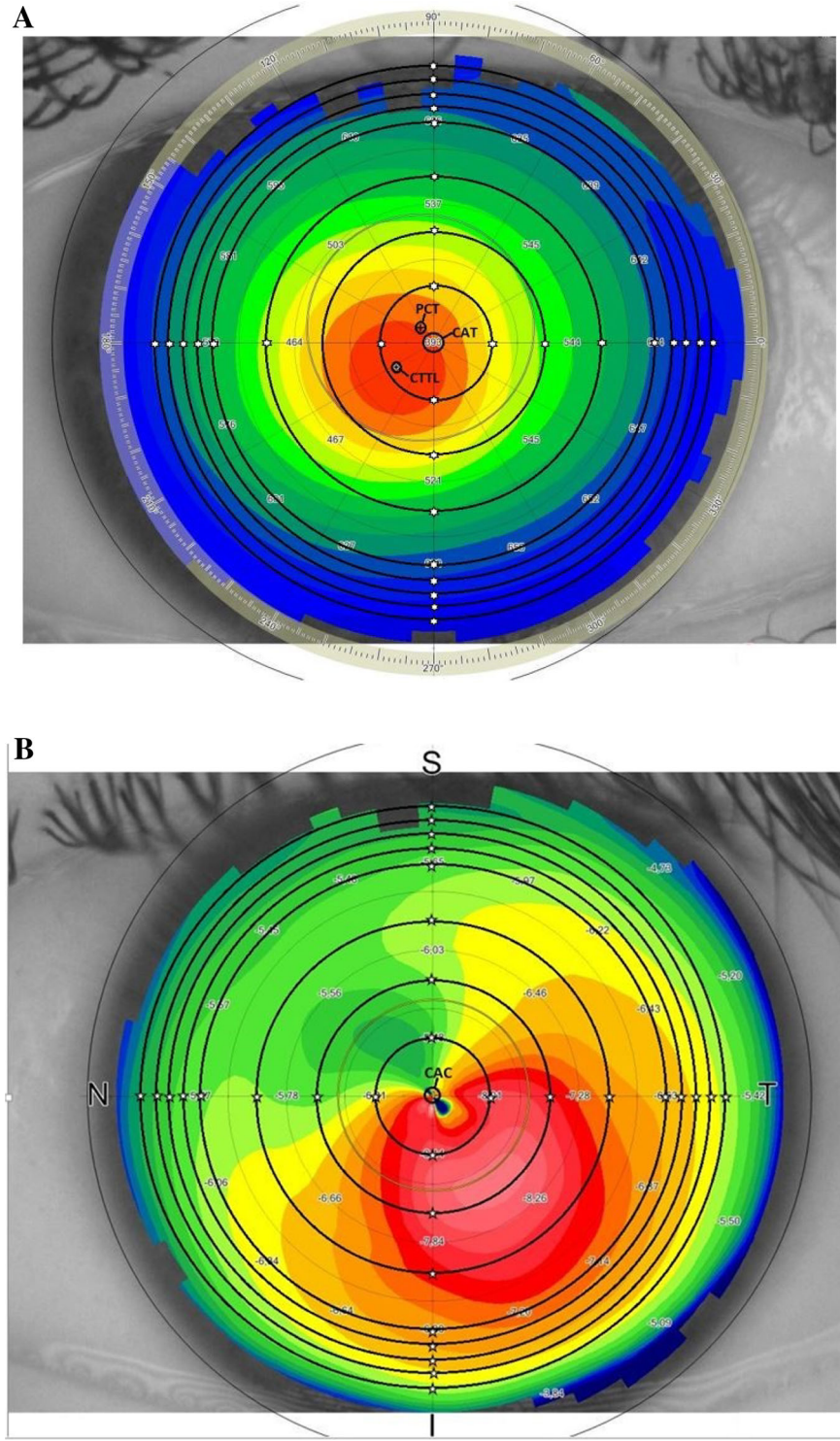

Fig. 1 Sirius topography images of the thickness map (**a**) and of the curvature map (posterior sagittal) (**b**). Eight black circles, from inner to outer, representing the 2, 4, 6, 8, 8.5, 9, 9.5 and 10 mm diameter of the analyzed part of the cornea are shown. For the thickness evaluation, each circle has been studied calculating the arithmetic average of the corneal thickness in the four points highlighted at the superior, inferior, nasal and temporal meridians of each black circle (white dots). The corneal apex thickness (CAT), the corneal thickness at the center of the pupil (PCT) and the corneal thickness at the thinnest point (CTTL) were also studied (**a**). For the curvature evaluation, the data have been analyzed for each circle in the four points individually. The corneal apex curvature (CAC) is also highlighted (**b**)

Statistics

The ANOVA statistical technique (analysis of variance) and an unpaired *T* test (with a Bonferroni correction) were used to analyze all the data obtained.

Results

Details of the thickness and curvature measurements at each point tested for the corneal center and periphery are given in Tables 1 and 2. The mean values for preoperative CCT, PCT and CTTL were 461.4 ± 30.3 μ, 475.3 ± 30.5 μ and 442.3 ± 32 μ, respectively. At 12 months, the mean values for postoperative CCT, PCT and CTTL were 444.6 ± 36.2 μ, 451.6 ± 36.7 μ and 418.2 ± 41.4 μ, respectively. The difference in pre- and postoperative values was not statistically significant. Differences in pre- and postoperative central corneal keratometry values at the 2, 4 and 6 mm from the apex in all four quadrants were not statistically significant, too. The peripheral corneal thickness and keratometric values measured from 8 to 10 mm at 0.5-mm intervals too were not statistically significantly different at any of the time points measured.

Discussion

Most studies on the efficacy of CXL in arresting the progression of KC have demonstrated that this procedure is very effective and has now become the standard intervention in the management of progressive KC. These studies have concentrated on evaluating thickness and curvature of the treated central area of the cornea [12, 14]. In most instances, the authors have used Pentacam Scheimpflug data where the values for K1 (steep meridian keratometry) and K2 (flat meridian keratometry) are obtained from the

Table 1 Keratometric parameters (thickness and curvature) of the central part of the cornea (up to 6 mm diameter) before the CXL and at 6- and 12-month follow-up

Thickness and curvature values	Preoperative		6 months		12 months	
	Mean value	SD	Mean value	SD	Mean value	SD
CAT	461.4	30.3	439.2	37.5	444.6	36.2
PCT	475.3	30.5	443.7	36.7	451.6	36.7
CTTL	441.3	32.0	416.1	37.7	418.2	41.4
Mean corneal thickness 2 mm	479.9	28.7	455.3	36.6	462.5	34.8
Mean corneal thickness 4 mm	523.5	31.5	505.3	37.2	514.0	33.1
Mean corneal thickness 6 mm	577.8	34.3	568.1	36.5	575.5	32.9
CAC	− 8.1	1.47	− 8.23	2.79	− 8.45	1.53
Superior meridian curvature 2 mm	− 6.4	1.1	− 6.6	1.0	− 6.7	1.1
Superior meridian curvature 4 mm	− 5.4	0.6	− 5.6	0.5	− 5.6	0.6
Superior meridian curvature 6 mm	− 5.3	0.3	− 5.4	0.3	− 5.4	0.3
Inferior meridian curvature 2 mm	− 9.1	1	− 9.1	1.4	− 9.2	1
Inferior meridian curvature 4 mm	− 8.5	0.8	− 8.7	0.7	− 8.6	0.7
Inferior meridian curvature 6 mm	− 7.5	0.6	− 7.6	0.5	− 7.5	0.6
Temporal meridian curvature 2 mm	− 8	1.2	− 8.2	1.4	− 8.2	1.3
Temporal meridian curvature 4 mm	− 7.4	0.8	− 7.5	1	− 7.5	0.9
Temporal meridian curvature 6 mm	− 6.6	0.5	− 6.7	0.6	− 6.7	0.6
Nasal meridian curvature 2 mm	− 6.7	0.9	− 6.8	0.9	− 6.9	1
Nasal meridian curvature 4 mm	− 6	0.5	− 6	0.6	− 6	0.5
Nasal meridian curvature 6 mm	− 5.8	0.3	− 5.8	0.4	− 5.8	0.4

CAT corneal apex thickness, *PCT* pupil central thickness, *CTTL* corneal thickness at thinnest location, *CAC* corneal apex curvature, *SD* standard deviation

Table 2 Peripheral keratometric parameters of the peripheral part of the cornea, from 8 to 10 mm diameter before the CXL procedure and at 6- and 12-month follow-up

Thickness and curvature values	Preoperative		6 months		12 months	
	Mean value	SD	Mean value	SD	Mean value	SD
Mean corneal thickness 8 mm	647.6	37.4	645.4	37.5	647.5	35.1
Mean corneal thickness 8.5 mm	669.4	38.3	667.9	38.8	668.9	36.2
Mean corneal thickness 9 mm	691.1	40.3	688.8	40.2	690.6	38.8
Mean corneal thickness 9.5 mm	712.7	42.5	709.9	42.7	711.9	41.5
Mean corneal thickness 10 mm	733.0	44.2	729.5	42.8	734.1	42.4
Superior meridian curvature 8.5 mm	− 5.2	0.2	− 5.1	0.3	− 5.2	0.2
Superior meridian curvature 9 mm	− 5.0	0.2	− 5.0	0.2	− 5.0	0.2
Superior meridian curvature 9.5 mm	− 4.8	0.2	− 4.7	0.3	− 4.8	0.3
Superior meridian curvature 10 mm	− 4.5	0.2	− 4.4	0.4	− 4.6	0.4
Inferior meridian curvature 8 mm	− 6.6	0.4	− 6.6	0.3	− 6.6	0.4
Inferior meridian curvature 8.5 mm	− 6.4	0.4	− 6.4	0.3	− 6.4	0.3
Inferior meridian curvature 9 mm	− 6.1	0.4	− 6.2	0.3	− 6.0	1.0
Inferior meridian curvature 9.5 mm	− 5.8	0.5	− 5.9	0.3	− 5.9	0.3
Inferior meridian curvature 10 mm	− 5.5	0.4	− 5.6	0.3	− 5.6	0.3
Temporal meridian curvature 8 mm	− 6.2	0.3	− 6.3	0.4	− 6.3	0.4
Temporal meridian curvature 8.5 mm	− 6.2	0.3	− 6.2	0.4	− 6.2	0.3
Temporal meridian curvature 9 mm	− 6.1	0.3	− 6.1	0.3	− 6.1	0.3
Temporal meridian curvature 9.5 mm	− 6.0	0.3	− 6.0	0.3	− 6.0	0.3
Temporal meridian curvature 10 mm	− 5.8	0.2	− 5.8	0.2	− 5.8	0.3
Nasal meridian curvature 8 mm	− 5.6	0.3	− 5.6	0.3	− 5.6	0.3
Nasal meridian curvature 8.5 mm	− 5.5	0.3	− 5.5	0.3	− 5.5	0.3
Nasal meridian curvature 9 mm	− 5.3	0.3	− 5.2	0.3	− 5.2	0.3
Nasal meridian curvature 9.5 mm	− 5	0.4	− 5	0.4	− 4.9	0.4
Nasal meridian curvature 10 mm	− 4.5	0.6	− 4.5	0.6	− 4.5	0.7

SD standard deviation

3-mm optical zone, though it is possible to manually change the region of interest. Reflection technology can only give partial information by not being able to measure the back surface and measuring the front surface with a limited coverage. Sirius exceeds these limitations by combining these data.

CXL is primarily carried out to arrest the progression and stabilize the cornea in KC. However, flattening of the cornea has been reported [15] and is a welcome bonus when it occurs. In our study, we did not notice any significant difference in keratometry values obtained preoperatively and at 6- and 12-month post-CXL. The dioptric value did not increase or decrease. Several studies in the published literature have analyzed and shown that the repeatability and reproducibility of CCT measurements with Pentacam were high [16, 17] and the vast majority of the pachymetry studies with Pentacam have only evaluated the CCT comparing it with the ultrasound pachymetry.

Yam et al. [18] in another study, using anterior segment optical coherence tomography (OCT), have evaluated the depth of the stromal demarcation line both at the center of the cornea and at the periphery after corneal cross-linking, highlighting a gradual peripheral reduction in the depth of the stromal demarcation line. However, their 'peripheral' measurements were also within the treated area. Similar results have also been obtained by Koller et al. [19]. Ng et al. [20] on the other hand have conducted a study

comparing the conventional and the accelerated CXL methods and showed that with the former method the stromal demarcation line was significantly more superficial in both the central and peripheral cornea. The demarcation line is considered to result from the induced difference in refractive index and light reflectivity of untreated and cross-linked stroma. This is related to stromal fiber shrinkage, cell alteration, loss of keratocytes and keratocyte apoptosis. It is taken as a marker of the depth of the effect of cross-linking [21, 22].

Richoz et al. [23] carried out an experimental study on rabbits evaluating whether irradiation with UVA of the corneal periphery and of the sclerocorneal limbus would compromise the replicative ability of limbal stem cells, highlighting the safety of the procedure. These studies indicate that the effect of CXL on the corneal periphery is at best limited in extent and depth.

It is well known that KC in the peripheral cornea can continue to progress after corneal transplantation [8, 24]. Hence, when the central 8 mm of the cornea is cross-linked as in conventional CXL, KC progression in the form of thinning and/or ectasia potentially may manifest in the peripheral cornea over time. However, this was not seen in our study over the 1-year follow-up period. A likely explanation is that a much longer follow-up period is required as the progression is slow. The 1-year duration of follow-up in this study may be a limitation in this regard. On the other hand, it could suggest that the effect of CXL extends in the stroma beyond the area treated. Riboflavin administered to the denuded stroma diffuses posteriorly and also peripherally [25]. Similarly, the UV light beam, which is concentrated on the central cornea during CXL, may suffer some scattering to influence the peripheral cornea by acting on the riboflavin that diffuses into the peripheral cornea.

Long-term follow-up studies after CXL have shown arrest of progression (thinning and ectasia) in keratoconus [26]. Some studies cover a duration of 10 years [27]. This would imply that KC progression in the corneal periphery that is reported after PK is not seen after CXL at least for the duration of the follow-up [28].

Only a few studies describe the changes in the peripheral cornea in normal subjects and in keratoconus [29, 30]. Fares et al. [31] have studied the correlation of central and peripheral corneal thickness in healthy subjects. They obtained the CAT, CCT and CTTL using an ultrasound pachymetry and the Oculus Pentacam, and they compared the data at different points (2, 3, 4, 6, 7, 8 and 10 mm) with each other finding a gradual increase in thickness from the center to the periphery with statistically significant correlation between the CTTL values and the mean thickness at the circles of 2, 3, 6, 8 and 10 mm, suggesting that the CCTL can be a viable guide for predicting peripheral thickness in normal corneas. This may not be applicable to KC corneas where the ectasia can be eccentric and central thinning progresses faster than peripheral thinning [29]. This can be useful in some surgical procedures such as astigmatic surgery and lamellar corneal surgery.

Similar to the thickness data, the curvature data at the untreated peripheral zone too did not show any significant increase over the follow-up period. Some significant changes in thickness values were noted in the central cornea before and after CXL. These changes are to be expected in the area treated with CXL and were not progressive. No such changes were seen in the peripheral untreated cornea, which confounds the explanation that some treatment effect spills into the peripheral cornea.

The most likely explanation for lack of changes seen in the peripheral cornea could be the short follow-up duration. However, as pointed out above, longer-term follow-up of CXL patients has demonstrated a lack of progression in the peripheral cornea. If this fact is substantiated over time, it will be valuable information to surgeons considering surgical interventions on the peripheral cornea such as limbal relaxing incisions (LRIs) or through the peripheral cornea as for phacoemulsification.

The use of intrastromal corneal ring segments (ICRS) in patients affected by KC is also well described [3]. It has been shown that they are effective in flattening the corneal shape and improving the vision in many patients with keratoconus, but the efficacy is highly variable. Some authors believe that they can be implanted in association with CXL, either before, during or after CXL [32]. This peripheral corneal procedure is without any doubt a viable option for those patients who want to improve their quality vision. Recently, it has been shown by Mastropasqua et al. [33] that addition of a negative meniscus-shaped stromal lenticule through an intrastromal pocket produces both a cone flattening and a central corneal thickness increase. The results of this study can help in

establishing the indication for this approach and delay the more complex procedure of DALK.

To the best of our knowledge, this is the first study analyzing peripheral corneal shape variations in patients who underwent CXL with some interesting observation related to stability of the peripheral cornea with implications for peripheral corneal surgery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights statement This article does not contain any studies with animals performed by any of the authors.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Informed consent The study is a retrospective analysis of instrumental examinations carried out previously: For this reason, authors did not ask informed consent.

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