• Clinical Research •

A novel analysis of Scheimpflug total corneal refractive power following corneal cross-linking in mild to moderate keratoconus

Chao Pan[1,2], Wei-Na Tan[1,2], Dan Chen[2], Yu Liu[3], Hao-Yu Wang[2], Deng-Feng Liang[2], Yan-Jun Hua[4], Xiao-Hua Lei[2], Qing-Yan Zeng[2], Shao-Zhen Zhao[1]

[1]Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Branch of National Clinical Research Center for Ocular Disease, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin 300384, China

[2]Hankou Aier Eye Hospital, Wuhan 430000, Hubei Province, China

[3]Aier School of Ophthalmology, Central South University, Changsha 410083, Hunan Province, China

[4]Department of Ophthalmology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

Co-first authors: Chao Pan and Wei-Na Tan

Correspondence to: Qing-Yan Zeng. Hankou Aier Eye Hospital, Wuhan 430000, Hubei Province, China. zengqingyan1972@163.com; Shao-Zhen Zhao. Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, 251 Fukang Road, Tianjin 300384, China. zhaosz1997@sina.com

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Abstract

● **AIM:** To detect an earlier improvement in mild to moderate keratoconus following corneal cross-linking (CXL) with total corneal refractive power (TCRP) using ray tracing method.

● **METHODS:** A total of 40 eyes of 30 consecutive patients who underwent CXL for progressive keratoconus were retrospectively enrolled. The following keratometric parameters provided by Pentacam HR, including maximum keratometry (Kmax), steepest keratometry (Ksteep), 3 mm zonal TCRP centered over corneal apex ($TCRP_{apex,zone}$ 3 mm), zonal mean keratometry and TCRP centered over corneal cone ($Km_{cone,zone}$ and $TCRP_{cone,zone}$ 1, 2, 3 mm) were evaluated preoperatively and 1, 3, 6, and 12mo postoperatively. Groups 1 and 2 were defined based on Kmax at postoperative 1mo as improved (the initial improvement group) or worsen (the initial deterioration group) compared to the preoperative level.

● **RESULTS:** In the overall group, only keratometric parameters based on ray tracing method displayed significant improvement early at 3mo postoperatively, in which $TCRP_{cone,zone}$ 1 mm and 2 mm exhibited the largest flattening (0.57 D and 0.53 D, respectively). In Group 1, only Kmax, $Km_{cone,zone}$ 2 mm and $TCRP_{cone,zone}$ 2 mm showed significant improvement initially at 1mo postoperatively, in which Kmax exhibited the largest improvement (1.05 D), followed by $TCRP_{cone,zone}$ 2 mm (0.82 D). In Group 2, only keratometric parameters based on ray tracing method and $Km_{cone,zone}$ 3 mm showed slight but not significant improvement early at 3mo, in which $TCRP_{cone,zone}$ 3 mm displayed the most improvement (0.19 D), followed by $TCRP_{cone,zone}$ 2 mm (0.15 D).

● **CONCLUSION:** The findings indicate that a 2 mm zonal TCRP centered over Kmax could earlier detect keratometric improvement by CXL compared to other commonly used parameters in mild to moderate keratoconic eyes.

● **KEYWORDS:** keratoconus; corneal cross-linking; keratometry; total corneal refractive power; ray tracing

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INTRODUCTION

Keratoconus is a progressive, mostly bilateral corneal degenerative disorder characterized by apical thinning and local protrusion that can result in irregular astigmatism or even corneal scarring with impaired vision[1]. There exists no treatment therapy to stabilize or slow the progression until the introduction of corneal cross-linking (CXL), which was initially proposed by Wollensak *et al*[2] for treatment of progressive keratoconus by increasing the intrinsic corneal biomechanical stability in 2003. Currently, it has been accepted as the major treatment modality for progressive keratoconus since plenty of studies in the literature have demonstrated its short- and long-term safety and efficacy[3-7].

Meanwhile, there were several prominent challenges in CXL, including no consistent or clear definition of ectasia progression[8], tremendous variability in nomenclature and raw data reported[9], and miscellaneous corneal parameters (topographic, tomographic, pachymetric, biomechanical, *etc*.) in detection of CXL effectiveness. Usually, the maximum K value (Kmax) is the commonly used keratometric parameter to indicate the efficiency of CXL in previous studies[10-15]. Nonetheless, series of studies have proposed that the Kmax is a problematic index for the follow-up of keratoconus in terms of repeatability[16-23]. The Kmax, which neglects the contribution of the posterior corneal surface to progression, assumes the natural anterior-to-posterior curvature ratio and subsequently the arbitrary keratometric index (1.3375), and intends to evaluate the severity of corneal protrusion solely on the central area or a single point other than the keratectasia area, has been doubted as a reliable parameter for both progression detection and crosslinking efficacy evaluation[24].

Ray tracing method, which takes in account of the anterior and posterior corneal surface and calculates corneal power with the actual refractive index without relying on any assumptions, could overcome the aforementioned limitations and evaluate corneal power more accurately. Besides, Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany), the most widely used corneal tomographer, has provided a customized ray traced corneal power-total corneal refractive power (TCRP), which could calculate certain area centered over certain point. Continued efforts to establish reliable metrics which can accurately assess the effect of CXL is a fundamental requirement for clinical management. To the best of our knowledge, limited information in the literature could prove our conjecture that could TCRP be regarded as a more reliable indicator. Thus, the current study intends to compare TCRP with other commonly used keratometric parameters during 12-month follow-up after CXL and assess the performance of TCRP in evaluating the efficacy of CXL treatment.

SUBJECTS AND METHODS

Ethical Approval The study was performed in accordance with the tenets of the Declaration of Helsinki and approved by the Ethics Committee and Institutional Review Board of Hankou Aier Eye Hospital. Progressive keratoconus patients who had received CXL treatment between August 2017 and September 2018 in Hankou Aier Eye Hospital were retrospectively enrolled into the current study. All participants were provided with written informed consent before participation.

Subjects The severity of keratoconus was graded according to the Amsler-Krumeich classification system which depends on corneal power, corneal thickness, astigmatism, and corneal transparency. Progression was defined as one or more of the following changes over a period of 12mo: an increase of at least 1 diopter (D) in the Kmax measurement, an increase of at least 1.0 D in manifest cylinder[24]. Exclusion criteria included thinnest corneal thickness (TCT) less than 400 μm, central or paracentral opacities, any previous ocular surgery, a history of chemical burns, severe infections, and other corneal or ocular surface disorders. Also among the excluded criteria were patients with incomplete data, poor compliance, pregnant/nursing women, and patients wearing rigid gas-permeable lenses during the last 4wk. Patients were further divided into two subgroups for analysis based on Kmax at postoperative 1mo had improved (Group 1, the initial improvement group) or worsen (Group 2, the initial deterioration group) compared to the preoperative level.

Table 1 CXL methods

Parameters	Variables
Fluence (total) (J/cm^2)	5.4
Soak time and interval (min)	30 (q2)
Intensity (mW)	3
Treatment time (min)	30
Epithelium status	Off
Chromophore	Riboflavin (Avedro, Waltham, MA, USA)
Chromophore carrier	Dextran
Chromophore osmolarity	Iso-osmolar
Chromophore concentration	0.1%
Light source	Avedro (Waltham, MA, USA)
Irradiation mode (interval)	Continuous
Protocol modifications	None

CXL: Corneal cross-linking.

Surgical Technique CXL procedures were performed by one experienced surgeon (Chen D) using the epithelium-off CXL as described in previous study[2] (Table 1).

Measurements and Parameters At baseline and each time point of the postoperative follow-up examinations (1, 3, 6, and 12mo), all patients underwent uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) assessment, non-contact intraocular pressure tonometry, slit-lamp biomicroscopy, Pentacam HR corneal tomography (Version 1.21r41). The coordinates of Kmax values (surrogate for center of the cone) were automatically determined by the Pentacam HR software and recorded for each eye at each time point after measurements performed under dim light. In the "Power Distribution" display, a 3 mm zone centered over the corresponding coordinate was manually defined on the sagittal curvature map and the TCRP map at each time point (Figure 1). This procedure was repeated for a 2-mm and 1-mm diameter zone. Two software custom keratometric parameters, including TCRP within the zone centered over Kmax ($TCRP_{cone,zone}$) and mean keratometry within the zone centered over Kmax ($Km_{cone,zone}$) were recorded for analysis, accompanied with keratometric value at the steepest meridian (Ksteep), Kmax, TCRP centered over the apex within a diameter of 3 mm zone ($TCRP_{apex,zone}$ 3 mm). Only a measurement with quality specification of "OK" was accepted for analysis.

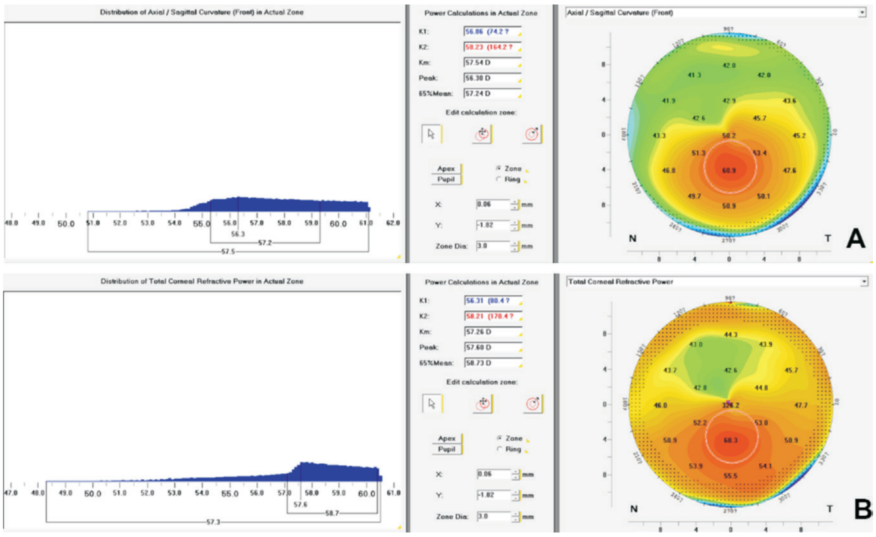

Figure 1 Representative corneal power distribution maps obtained with Pentacam HR A: A 3 mm zonal simulated keratometry centered over the coordinate of maximum keratometry (Kmax) in the anterior sagittal curvature map; B: A 3 mm zonal ray-traced corneal power centered over the coordinate of Kmax in the total corneal refractive power map of the same eye.

Table 2 Baseline characteristics of the patients

Characteristics	Overall (*n*=40 eyes)	Group 1 (*n*=15 eyes)	Group 2 (*n*=25 eyes)	[b]*P*
Gender (M/F)	23/7	10/3	14/5	0.84
Age (y)	21.05±5.16	21 (17.5, 26)[a]	22 (17, 24)[a]	0.32
AK stage (I/II)	28/12	9/6	19/6	0.285
UDVA (logMAR)	0.85±0.36	1.10±0.32	0.72±0.33	0.005
CDVA (logMAR)	0.22 (0.05, 0.30)[a]	0.30 (0.1, 0.40)[a]	0.10 (0, 0.22)[a]	0.047
MRSE (D)	-5.67±3.11	-6.25 (-9.5, -4.75)[a]	-4.38 (-6.31, -2.81)[a]	0.012
Astigmatism (D)	2 (0.63, 3.38)[a]	-2 (-2.25, -0.25)	-2 (-3.5, -0.75)[a]	0.319
Ksteep (D)	48.74±3.39	49.73±3.63	48.15±3.16	0.16
Km (D)	47.02±2.64	48.01±2.87	46.43±2.36	0.07
Kmax (D)	53.69±5.84	55.48±6.86	52.61±4.97	0.13
TCT (µm)	478 (467, 500)[a]	469 (460.3, 503.8)[a]	482 (472, 498)[a]	0.31
BAD (D)	6.66±2.96	7.36±3.70	6.24±2.40	0.25

AK: Amsler-Krumeich; UDVA: Uncorrected distance visual acuity; logMAR: Logarithm of the minimal angle of resolution; CDVA: Corrected distance visual acuity; MRSE: Manifest refraction spherical equivalent; D: Diopter; Km: Mean keratometry; Kmax: Maximum keratometric value; Ksteep: Keratometric value at the steepest meridian; TCT: Thinnest corneal thickness; BAD: Belin/Ambrósio enhanced ectasia display. [a]Median (25th and 75th percentile); [b]Group 1 *vs* Group 2.

Statistical Analysis All the data were analyzed using SPSS software version 25 (IBM Corp., USA) for Windows. Data were expressed as mean±standard deviation (SD) if fulfilled normality test using the Kolmogorov-Smirnov test. Otherwise, the results were expressed as the median (25th and 75th percentile). One-way analysis of variance (ANOVA) for repeated measures with Bonferroni multiple comparisons was used to assess the time course of changes following CXL treatment in series of keratometric parameters for normally distributed data. For two-sample comparison, statistical analysis was conducted by the Mann-Whitney *U* test for nonparametric data (refraction, UDVA, and CDVA) and by the unpaired *t*-test for parametric data (Kmax, Ksteep, *etc*.). A level of $P<0.05$ was chosen as the criterion for significance.

RESULTS

Demographics A total of 40 eyes of 30 patients, with 23.3% (7/30) of female were enrolled. UDVA were 0.85±0.36 (range: 0.22 to 1.70) and 0.82 (0.40, 0.96) logMAR pre- and 12mo postoperatively (P=0.11); CDVA were 0.22 (0.05, 0.30) and 0.10 (0, 0.30) logMAR (P=0.24); TCT were 478 (467, 500) µm and 473.5 (457.5, 486.5) µm (P<0.001). Based on the Amsler-Krumeich classification, 28 eyes were defined as stage I, 12 eyes were defined as stage II. Detailed baseline characteristics were in Table 2.

Changes of Keratometric Parameters Overall Kmax showed the most improvement at 12mo postoperatively (1.00 D), followed by $TCRP_{cone,zone}$ 1 mm/2 mm (0.96 D and 0.92 D, respectively). All keratometric parameters exhibited

Table 3 Changes of keratometric parameters overall after corneal cross-linking mean±SD (range), D

Parameters	Preop.	Postop. 1mo	Postop. 3mo	Postop. 6mo	Postop. 12mo	*P*
Kmax	53.69±5.84 (44.4-68.2)	54.06±5.68[a] (44.1-66)	53.25±5.58 (43.84-66.5)	53.07±5.74[a] (44.2-66.06)	52.69±5.56[a] (44.26-65.3)	<0.001
Ksteep	48.74±3.39 (43.3-56.5)	49.16±3.49 (43.6-56.7)	48.65±3.40 (43.1-56.9)	48.46±3.46[a] (42.6-57.1)	48.27±3.57[a] (41.4-57.4)	<0.001
TCRP$_{apex,zone}$ 3 mm	46.83±3.25 (41.7-54.35)	47.03±3.34 (42.05-54.65)	46.48±3.22[a] (41.35-54.8)	46.35±3.37[a] (40.25-55.57)	46.12±3.33[a] (39.4-55.59)	<0.001
Km$_{cone,zone}$ 1 mm	52.07±4.87 (44.3-61.92)	52.41±5.06 (44.11-65.17)	51.72±4.7 (43.96-62.19)	51.58±4.77[a] (44.17-61.86)	51.28±4.62[a] (44.25-61.55)	<0.001
Km$_{cone,zone}$ 2 mm	50.83±4.25 (44.11-60.37)	51.12±4.42 (44.01-63.03)	50.54±4.17 (43.86-60.47)	50.36±4.16[a] (44.02-59.68)	50.07±4.05[a] (44.03-60.17)	<0.001
Km$_{cone,zone}$ 3 mm	49.68±3.66 (43.88-58.12)	49.94±3.80 (43.83-59.94)	49.41±3.64 (43.7-58.05)	49.23±3.64[a] (43.23-57.69)	48.99±3.99[a] (43.31-58.06)	<0.001
TCRP$_{cone,zone}$ 1 mm	50.43±4.50 (43.32-61.79)	50.63±4.77 (43.29-65.24)	49.86±4.41[a] (42.97-61.76)	49.71±4.37[a] (43.26-60.89)	49.47±4.21[a] (43.43-60.43)	<0.001
TCRP$_{cone,zone}$ 2 mm	49.47±3.97 (43.25-60.36)	49.65±4.22 (42.8-63.35)	48.94±3.96[a] (43.27-60.2)	48.78±3.85[a] (43.22-59.2)	48.55±3.73[a] (43.31-58.5)	<0.001
TCRP$_{cone,zone}$ 3 mm	48.55±3.48 (43.18-58.44)	48.77±3.69 (42.74-60.75)	48.12±3.52[a] (42.79-58.11)	48.00±3.44[a] (42.72-57.05)	47.77±3.28[a] (42.69-56.07)	<0.001

Kmax: Maximum keratometric value; Ksteep: Keratometric value at the steepest meridian; Km: Mean keratometry; TCRP: Total corneal refractive power; TCRP$_{apex,zone}$/TCRP$_{cone,zone}$: TCRP within a diameter of zone centered at corneal apex or cone location; Km$_{cone,zone}$: Km within a diameter of zone centered at cone location. [a]*P*<0.05 compared to baseline by ANOVA following Bonferroni multiple comparisons.

Table 4 Changes of keratometric parameters after corneal cross-linking in Groups 1 and 2 mean±SD (range), D

Parameters	Group 1 (*n*=15)					Group 2 (*n*=25)				
	Preop.	Postop. 1mo	Postop. 3mo	Postop. 6mo	Postop. 12mo	Preop.	Postop. 1mo	Postop. 3mo	Postop. 6mo	Postop. 12mo
Kmax	55.48±6.86 (44.4-68.2)	54.43±6.43[a] (44.1-66)	54.03±6.48[a] (43.84-66.5)	54.36±6.77[a] (44.2-66.06)	54.35±6.37[a] (44.26-65.3)	52.61±4.97 (46.5-63.9)	53.83±5.31[a] (47.1-65.9)	52.78±5.05 (46-64.4)	52.30±5.01 (44.9-63)	51.69±4.88[a] (45.2-62.6)
Ksteep	49.73±3.63 (43.7-56.5)	49.63±3.76 (43.6-56.7)	49.29±3.80[a] (43.54-56.9)	49.35±3.79[a] (43.8-57.1)	49.35±3.87[a] (43.84-57.4)	48.15±3.16 (43.3-54.3)	48.88±3.36[a] (44.3-55.9)	48.26±3.15 (43.1-54.2)	47.93±3.21 (42.6-53.6)	47.62±3.30[a] (41.4-53.3)
TCRP$_{apex,zone}$ 3 mm	47.99±3.59 (42.35-54.35)	47.59±3.63 (42.05-54.65)	47.25±3.74[a] (41.93-54.8)	47.32±3.83[a] (42.35-55.57)	47.32±3.73[a] (42.58-55.59)	46.14±2.87 (41.7-52.25)	46.69±3.19[a] (42.4-53.4)	46.01±2.86 (41.35-52.05)	45.77±2.99 (40.25-51.6)	45.40±2.92[a] (39.4-50.5)
Km$_{cone,zone}$ 1 mm	53.61±5.33 (44.3-61.79)	53.08±5.55 (44.11-62.01)	52.50±5.19[a] (43.96-60.89)	52.71±5.01[a] (44.17-61.76)	52.68±5.01[a] (44.25-61.55)	51.14±4.43 (44.95-61.92)	52.01±4.81[a] (45.27-65.17)	51.24±4.42 (45.82-62.19)	50.91±4.44 (44.72-61.86)	50.45±4.26 (44.61-61.49)
Km$_{cone,zone}$ 2 mm	52.11±4.61 (44.11-59.48)	51.68±4.68[a] (44.01-59.14)	51.21±4.56[a] (43.86-59.32)	51.31±4.52[a] (44.02-59.68)	51.35±4.36[a] (44.05-60.17)	50.08±3.92 (44.55-60.37)	50.78±4.32[a] (44.25-63.03)	50.14±3.95 (44.5-60.47)	49.79±3.91 (44.14-59.63)	49.29±3.73[a] (44.03-58.68)
Km$_{cone,zone}$ 3 mm	50.65±3.97 (43.88-56.87)	50.45±3.99 (43.83-57.37)	50.05±3.99[a] (43.7-57.58)	50.07±3.92[a] (43.79-57.69)	50.08±3.76[a] (43.84-58.06)	49.10±3.41 (44.25-58.12)	49.63±3.73[a] (44.0-59.94)	49.03±3.45 (43.84-58.05)	48.73±3.44 (43.23-56.71)	48.34±3.21[a] (43.31-56)
TCRP$_{cone,zone}$ 1 mm	51.87±4.76 (43.32-58.99)	51.05±5.12 (43.29-59.38)	50.46±4.78[a] (42.97-57.31)	50.70±4.67[a] (43.26-58.34)	50.77±4.48[a] (43.43-58.41)	49.56±4.20 (44.2-61.79)	50.38±4.64[a] (43.61-65.24)	49.50±4.23 (43.64-61.76)	49.12±4.17 (43.6-60.89)	48.68±3.92[a] (43.68-60.43)
TCRP$_{cone,zone}$ 2 mm	50.66±4.12 (43.25-57.03)	50.00±4.26[a] (43.31-56.05)	49.49±4.23 (43.27-56.23)	49.61±4.03[a] (43.22-56.55)	49.71±3.90[a] (43.34-57.13)	48.76±3.79 (43.83-60.36)	49.44±4.26[a] (42.8-63.35)	48.61±3.84 (43.29-60.2)	48.28±3.73 (43.23-59.2)	47.85±3.51[a] (43.31-58.5)
TCRP$_{cone,zone}$ 3mm	49.49±3.62 (43.18-54.89)	49.10±3.69 (43.32-54.84)	48.64±3.77[a] (43.28-55.03)	48.76±3.63[a] (43.17-55.57)	48.79±3.45[a] (43.10-55.45)	48.00±3.34 (43.41-58.44)	48.57±3.75[a] (42.74-60.75)	47.81±3.41 (42.79-58.11)	47.54±3.30 (42.72-57.05)	47.15±3.07[a] (42.69-56.07)

Kmax: Maximum keratometric value; Ksteep: Keratometric value at the steepest meridian; Km: Mean keratometry; TCRP: Total corneal refractive power; TCRP$_{apex,zone}$/TCRP$_{cone,zone}$: TCRP within a diameter of zone centered at corneal apex or cone location; Km$_{cone,zone}$: Km within a diameter of zone centered at cone location. [a]*P*<0.05 compared to baseline by ANOVA following Bonferroni multiple comparisons.

slight increase from preoperative to 1mo postoperative, then decreased gradually to 12mo (Table 3). Most keratometric parameters displayed significant reduction as early as 6mo postoperatively, while only TCRP$_{apex,zone}$ 3 mm and TCRP$_{cone,zone}$ 1/2/3 mm achieved significant improvement at 3mo postoperatively (*P*<0.05). TCRP$_{cone,zone}$ 1 mm obtained the most improvement (0.57 D), followed by TCRP$_{cone,zone}$ 2 mm (0.54 D) and TCRP$_{cone,zone}$ 3 mm (0.43 D).

The percentage of change of Kmax at 12mo less than -0.50 D, within ±0.50 D and more than 0.50 D were 60% (24/40), 30% (12/40), and 10% (4/40), respectively. While there were 57.5% (23/40), 35% (14/40), and 7.5% (3/40) change of TCRP$_{cone,zone}$ 2mm at 12mo less than -0.50 D, within ±0.50 D, and more than 0.50 D, respectively.

Changes of Keratometric Parameters in Group 1 Unlike the overall, all keratometric parameters in Group 1 exhibited flattening initially at 1mo, achieved the most flattening effect at 3mo, and subsequently reduced gradually till 12mo. At 12mo, all keratometric parameters showed significant improvement compared to baseline except for Ksteep, in which Kmax displayed the most improvement (1.13 D), followed by TCRP$_{cone,zone}$ 1 mm (1.10 D) and 2 mm (0.95 D; Figure 2). Most keratometric parameters displayed significant reduction at 3mo, while only Kmax, Km$_{cone,zone}$ 2 mm, and TCRP$_{cone,zone}$ 2 mm achieved significant improvement early at 1mo postoperatively (*P*<0.05; Table 4).

Changes of Keratometric Parameters in Group 2 In Group 2, all keratometric parameters exhibited steepening at

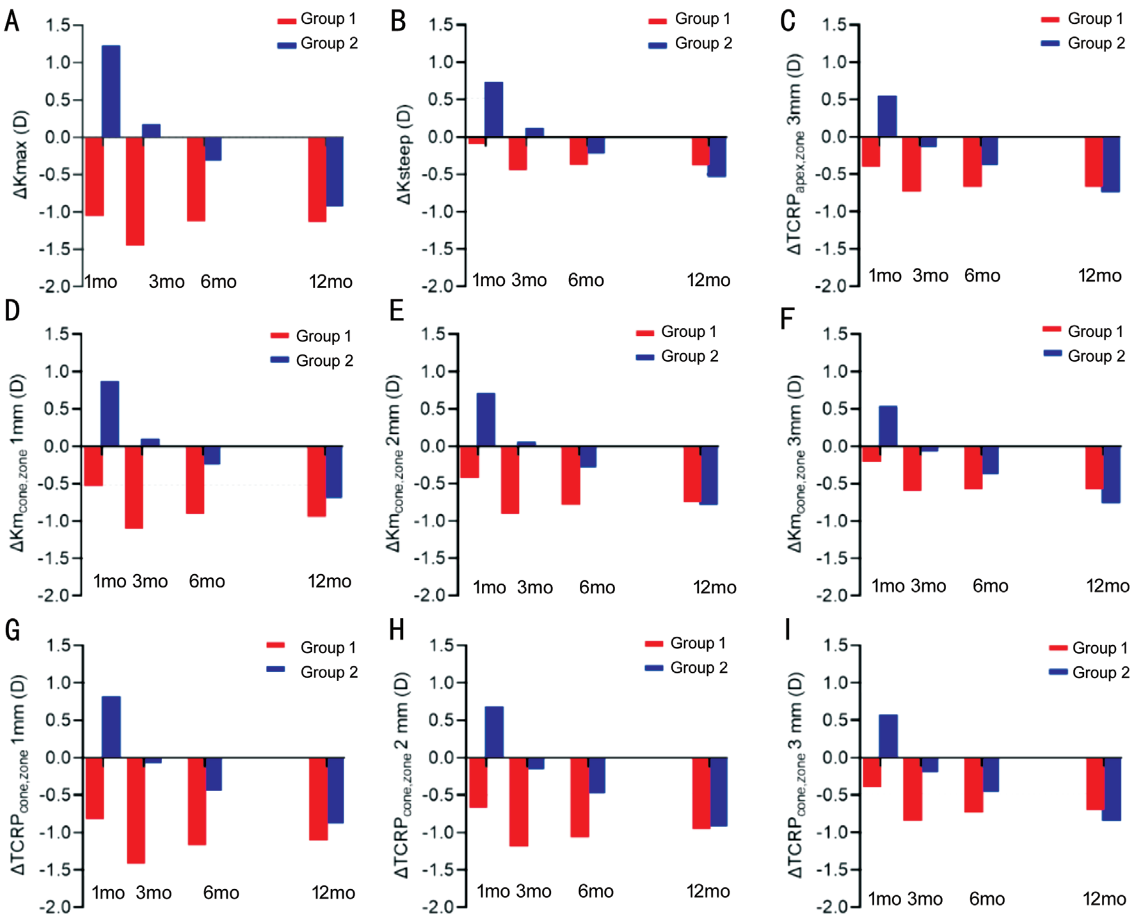

Figure 2 Changes of keratometric parameters after corneal collagen cross-linking during 12mo follow-up.

1mo, subsequently relieved gradually and achieved relatively stable improvement at 12mo except for $Km_{cone,zone}$ 1 mm (mean change -0.69 D, P=0.19). Kmax exhibited the most improvement (0.92 D) at 12mo, followed by $TCRP_{cone,zone}$ 2 mm (0.91 D) and $TCRP_{cone,zone}$ 1 mm (0.87 D; Table 4). Besides, only $TCRP_{cone,zone}$ within diameters of 1 mm to 3 mm and $Km_{cone,zone}$ 3.0 mm became flatter than the preoperative level early at 3mo postoperatively, while other keratometric parameters showed flatter than the preoperative level until 6mo postoperatively. $TCRP_{cone,zone}$ 3 mm showed the most improvement (0.19 D), followed by $TCRP_{cone,zone}$ 2 mm (0.15 D; Figure 2).

DISCUSSION

In the present study, our overall results revealed that all keratometric parameters achieved reduction of approximately 0.50-1.0 D at 12mo following CXL treatment in keratoconic eyes. It is not surprising that Kmax achieved the most improvement (1.0 D), which is consistent with previous studies[5-6], since Kmax represents the most severe protrusion point and naturally exhibits the most dramatic changes following crosslinking. Ksteep achieved the least reduction (0.47 D). Previous studies reported a reduction of Ksteep (the steepest simulated keratometry) varied from 0.49 to 5.16 D[2-6]. It is assumed that the ethnicity difference of the patients, the variety of treatment protocol, the inherent variability in the progression of keratoconus, as well as the limited reproducibility of parameters measurement and the difference of instruments all take responsible for such a large disparity. Besides, it is noteworthy that partial Ksteep in the previous studies may actually represent the Kmax. Ksteep and Kmax represent the two versions of the maximum keratometry, in which the former represents the meridian maximum keratometry within a 3 mm area centered over the corneal apex, while the latter represents the single point maximum keratometry at the anterior surface surrogated for center of the cone. It is reasonable that Kmax captured more prominent changes compared to Ksteep. The apical cornea may exhibit little or mild changes when the conic area protrudes, in decentered cones this phenomenon would be particularly obvious[24]. Bardan *et al*[25] reported a larger percent of peripheral cones (38.4%) and disclosed that Kmax may not be central although cornea thins centrally. In the present study, there were 82.5% central, 15% paracentral and 2.5% peripheral cones.

Furthermore, our study evaluated the performance of the third version of Kmax (zone value)-$Km_{cone,zone}$, which may more globally represent the ectatic region than Kmax as a single point parameter. Interestingly, $Km_{cone,zone}$ 3 mm in Group 2 exhibited a slight improvement early at 3mo while Ksteep and Kmax showed reduction until 6mo postoperatively. Previously, Lytle *et al*[26] reported that the $Km_{cone,zone}$ 3 mm not Kmax showed statistically significant improvement from baseline at 3mo and proposed that the 3 mm zonal Km may allow for earlier detection of the efficacy of CXL than the use of a point Kmax value alone. Meanwhile, a recent study[27] disclosed that the keratectasia area showed in corneal topography was more sensitive than Kmax/Ksteep in describing the early stage morphological changes in keratoconic eyes. Taking all these works together, it seems to be speculated that a zonal Km centered on Kmax taking in account a larger portion of the ectatic region rather than a single point value may more accurately depict changes in the keratoconus remission or deterioration following CXL treatment. Nonetheless, such a mild improvement (0.07 D) presented in the current study failed to achieve a statistical significance and limited its clinical application. Besides, it is unclear why $Km_{cone,zone}$ 3 mm other than 1 mm or 2 mm could exhibit such an earlier mild improvement trend. One possible explanation could be that the peripheral ectatic area may show more prominent topographic changes compared to the more central ectatic area. A larger sample study would be warranted to explore the possible mechanism and to validate if zonal Km centered over the cone could serve as an earlier indicator in detecting the effect of CXL on keratoconus stabilization and improvement.

TCRP represents total corneal power by ray tracing method, which takes in account of anterior and posterior corneal surface using actual corneal refractive index. Its measurement principle determines its superiority in evaluating corneal power in altered corneas, such as post-refractive eyes[28]. Considering local thinning and protrusion in keratoconic eyes disrupted the natural ratio of anterior-to-posterior corneal curvature more seriously, it is reasonable for researchers to begin to shift their interest into TCRP evaluation in eyes with keratoconus. A retrospective study by Takahashhi *et al*[29] disclosed that $TCRP_{apex,ring}$ 3 mm decreased by 1.0 D at 12mo after CXL similar to the simulated keratometry. In the current study, $TCRP_{apex,zone}$ 3 mm instead of $TCRP_{apex,ring}$ 3 mm displayed a smaller reduction of approximately 0.70 D at 12mo after CXL in the overall group analysis. More importantly, $TCRP_{apex,zone}$ 3 mm and $TCRP_{cone,zone}$ 1/2/3 mm displayed statistically significant improvement early at 3mo in the overall group, while other keratometric parameters showed statistically significant improvement until 6mo. Besides, $TCRP_{cone,zone}$ 1 mm/2 mm exhibited an identical improvement compared to Kmax at 12mo. We initially conjectured that $TCRP_{cone,zone}$ 1 mm/2 mm both could serve as an earlier indicator for evaluating the improvement by CXL treatment during 12mo follow-up. To further verify this speculation, we performed the subgroups analysis and disclosed different results. In Group 1, all the other keratometric parameters disclosed significant improvement as early as 3mo, whereas Kmax, $TCRP_{cone,zone}$ 2 mm and $Km_{cone,zone}$ 2 mm detected significant improvement even earlier at 1mo postoperatively. Besides, the improvement exhibited by $TCRP_{cone,zone}$ 2 mm at each follow-up time point showed no statistically significant difference from Kmax. This further indicates that only $TCRP_{cone,zone}$ 2 mm could be accepted as an earlier indicator for evaluating the improvement by CXL treatment. Meanwhile, only the keratometric parameters based on ray tracing method and $Km_{cone,zone}$ 3 mm showed slight improvement as early as 3mo postoperatively in Group 2. $TCRP_{cone,zone}$ 1 mm achieved the least amount of improvement (0.07 D), which was so faint that could be approximately neglectable in the clinical daily practice. As the defined measurement zone centered over cone became larger, the improvement increased gradually. It is speculated that a relatively more peripheral ectatic region or even normal region of cornea incorporated into the TCRP calculation may exhibit more distinct topographic changes and subsequently influence the TCRP changes following CXL treatment. However, a larger diameter of 4 mm was not included in the present study considering that it may incorporate either more normal cornea or far peripheral or extrapolated data. Although improvement of approximately -0.15 D to -0.20 D obtained with $TCRP_{cone,zone}$ 2 mm and 3 mm were neither statistically significant nor clinically relevant, this still represents a trend that keratometric parameters based on ray tracing method may detect an earlier improvement compared to the widely used keratometric parameters. Taking all these analyses together, we speculated that $TCRP_{cone,zone}$ 2 mm could earlier detect the improvement by CXL treatment during 12mo period follow-up. This may represent the most important findings in the current study, that our work firstly explored a newly keratometric parameter which could be used as an early indicator in detecting the effect of CXL on keratoconus stabilization and improvement. The possible mechanisms behind this phenomenon could be that $TCPR_{cone,zone}$ takes in account of the neglected posterior corneal surface, captures a certain area instead of a single point, and centers over the cone instead of the apex.

Finally, as a second outcome, the changes of keratometric parameters in keratoconic eyes after CXL treatment displayed two distinct trends during 12mo follow-up. Majority of the keratoconic eyes displayed an initial deterioration at 1mo with subsequent improvement up to 12mo postoperatively, which corroborates with previous studies[5-6]. It is speculated that the apparent initial keratoconus progression at 1mo could be attributable to the epithelial debridement and regrowth[5,30-31]. In 2009, Reinstein *et al*[32] described that the corneal epithelium by Artemis very high-frequency digital ultrasound system in keratoconic eyes demonstrated an epithelial doughnut pattern of a localized thinning over the cone surrounded by an annulus of epithelial thickening, which could either partially or totally mask the stromal surface cone. In accordance with the findings of Reinstein *et al*[32], previous studies observed that epithelial debridement increased the magnitude of anterior corneal keratometry in keratoconic eyes[31,33]. In addition, the regrowth of an epithelial layer of more uniform thickness after CXL procedure could paradoxically result in apparent steepening of the keratometric parameters until the halt effect by increased biomechanical stability prevails over the epithelial remodeling effect[31]. There existed a second change trend in the present study that minority keratoconic eyes exhibited a flattening initially at 1mo, achieved the largest flattening effect at 3mo, and subsequently reduced gradually till 12mo, which is in alignment with previous findings of Asri *et al*[3] Previously, Caporossi *et al*[7] conducted a prospective study in evaluation of stability and functional response after CXL in pediatric patients with keratoconus, in which patients in the thinner group (TCT<450 μm) showed a significantly faster functional recovery than the thicker group (TCT>450 μm) at the 3-month follow-up. In the current study, baseline characteristics analysis suggested that higher manifest refraction spherical equivalent, worse visual acuity may take response for an initial improvement process following CXL treatment. Meanwhile, the keratometric readings and pachymetric parameters in Group 1 reflected a slightly serve degree but without statistically significance. It is speculated that the severity degree of disease, the CXL procedure, the respond to the CXL treatment, the corneal epithelium remodel process may play an important role in the change trend and recovery speed. Nonetheless, a prospective study may further disclose the possible explanations for the above phenomenon.

There are some shortcomings in our study. First, the sample we evaluated was relatively small, a greater number of keratoconic eyes would be warranted to corroborate our findings. Second, cone locations and its impact on keratometric parameters have not been further analyzed and would need another investigation in the future. Bardan *et al*[25] disclosed that classifying cone location based on Kmax led to an earlier identification of changes in these parameters (Kmax *etc*.). Thus, TCRP centered over Kmax instead of TCT has been chosen in our analysis. Besides, the unified center ($TCRP_{cone,zone}$, $Km_{cone,zone}$, Kmax) could avoid introducing confounding factors and explore the possible explanation behind the phenomenon accurately. Nonetheless, using TCRP centered over TCT instead of Kmax may disclose a different result and deserve another study in the future. Third, the majority of keratoconic eyes enrolled into the current study were Amsler-Krumeich stage I/II eyes, an observation consisted of more advanced keratoconus would further strength the current conclusions. Nonetheless, our study has comprehensively compared a series of keratometric parameters, especially zonal TCRP centered over cone in evaluating the effectiveness and detecting early improvement of CXL in eyes with keratoconus and provided useful information in the interpretation and selection of suitable parameters. Further studies could explore the sensitivity and availability of $TCRP_{cone,zone}$ in discriminating subclinical keratoconus from normal corneas and detecting early progression in keratoconus.

In conclusion, our findings indicate that a 2 mm zonal TCRP centered over Kmax could earlier detect keratometric improvement by CXL postoperatively compared to other commonly used parameters. Further studies with larger sample size could verify if this new parameter could be used as an early indicator in detecting the effect of CXL on keratoconus stabilization and improvement.

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