Flattening of the cornea after collagen crosslinking for keratoconus

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PURPOSE: To identify preoperative parameters that may predict flattening of the keratoconic cornea after collagen crosslinking (CXL).

SETTING: Institut für Refraktive und Ophthalmo-Chirurgie (IROC), Zurich, Switzerland.

OESIGN: Cohort study.

METHODS: Patients with verified progressive primary keratectasia received standard corneal CXL. Factors such as corrected distance visual acuity (CDVA) and Scheimpflug tomography (Pentacam) were used to follow the evolution from preoperatively to 12 months after CXL. Statistical analysis included *U* tests and Spearman rank correlation tests to detect risk factors for flattening of the keratoconus.

RESULTS: The study enrolled 151 eyes of 151 patients; more than 80% completed the 12-month follow-up. The flattening rate (flattening of the maximum curvature >1.00 diopter [D]) was 37.7%. A preoperative maximum keratometry (K) reading of more than 54.00 D was identified as the only significant risk factor for this effect (odds ratio, 1.88; 95% confidence interval, 1.01-3.51). A restriction to corneas with a maximum K value greater than 54.00 D would have resulted in a significant flattening in 51% of the cases.

CONCLUSIONS: Statistically significant flattening occurred during 1 year after CXL in more than 50% of cases when the preoperative maximum K reading was more than 54.00 D. None of the other preoperative parameters evaluated (eg, age, sex, diagnosis, CDVA, corneal shape factors) had a statistically significant impact on corneal flattening after CXL.

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More than 10 years ago, corneal collagen crosslinking (CXL) by means of riboflavin and ultraviolet light was proposed as a therapeutic approach to improve the biomechanical and biochemical properties of the cornea.[1,A] Meanwhile, there is clinical evidence that CXL is a clinically useful procedure that halts the progression of primary and secondary keratectasia with a failure rate of approximately 3% and a complication rate of 1% or less.[2–7] As a positive side effect, in a certain percentage of the eyes treated with CXL, regression of the keratectasia, documented by significant flattening of the cornea, may occur.[3,7] In rare cases, the regression is more than 10.00 diopters (D).[8] It would be of interest for patients and physicians to identify preoperative parameters that predict such flattening.

In this cohort study, we analyzed the 1-year results of CXL in eyes with primary keratectasia to identify preoperative factors that might predict substantial flattening of the keratectasia.

PATIENTS AND METHODS

Study Group and Protocol

Patients with progressive keratectasia were enrolled in this study. Diagnoses were differentiated as pellucid

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marginal degeneration (PMD) or keratoconus based on the claw pattern in the corneal topography. Progression of the keratectasia was verified by repeated Scheimpflug tomography (Pentacam 70700, Oculus Optikgeräte GmbH) over at least 6 months. Progression was accepted if the increase in the maximum keratometry (K) reading exceeded 1.00 D, which equals 3 standard deviations.[7] Second eyes were treated not earlier than 6 months after the first eye and were not included in the study group. The study protocol was approved by the Ethikkommittee des Kantons Zürich.

Eyes with a maximum K reading less than 76.00 D with contact lens tolerance and a minimum corneal thickness greater than 350 μm were included in the study. Eyes with preoperative corneal opacities were not accepted because Scheimpflug photography may give false results. Additional exclusion criteria were ocular pathology other than keratectasia (eg, cornea guttata or other endothelial irregularities), history of recurrent erosions, actual or intended pregnancy, not available for follow-up examinations for 1 year, and connective tissue disease.

Patients were examined preoperatively, in the early postoperative period (1 to 3 days, until epithelial healing), and 1, 6, and 12 months after CXL. At every follow-up except the early postoperative visit, a standard examination was performed consisting of autorefractometry and autokeratometry (Humphrey Model 599, Carl Zeiss Meditec AG), corneal topography (Keratograph C, Oculus Optikgeräte GmbH), Scheimpflug imaging (Pentacam 70700), manifest refraction using the fogging technique, uncorrected distance visual acuity, corrected distance visual acuity (CDVA), applanation tonometry, and slitlamp inspection of the anterior and posterior segments of the eyes. At the 1-month follow-up examination, the depth of the demarcation line was determined at the slitlamp[9] or by optical coherence tomography.[10]

Patients using rigid contact lenses were asked not to use the lenses for at least 3 weeks before the preoperative examination and for 1 month after treatment. The lenses had to be removed at least 3 weeks before each follow-up examination.

Surgical Technique

Topical anesthesia of the cornea was obtained using oxybuprocaine and tetracaine, alternating every 3 minutes for 15 minutes. After insertion of a lid speculum, a corneal abrasion with a diameter of 9.0 mm was created. This was followed by instillation of riboflavin 0.1% drops every 3 minutes for 30 minutes. The riboflavin drops were prepared immediately before the treatment mixing aqueous riboflavin 0.5% solution (Streuli & Co.) with dextran T-500 20.0% solution. During the imbibition with riboflavin drops, the thickness of the central cornea was measured using ultrasound. In cases with a central thickness (without epithelium) of less than 400 μm, additional riboflavin 0.1% drops without dextran were applied until the thickness exceeded 400 μm. The eyes were then inspected at the slitlamp to ensure that the riboflavin had arrived in the aqueous (blue light). After this, the eye was irradiated for 30 minutes with ultraviolet A (UVA) at an irradiance of 3 mW/cm^2 (UV-X, Peschkemed Meditrade). During irradiation, the cornea was moistened every 3 minutes with riboflavin 0.1% drops and oxybuprocaine drops at the patient's discretion. At the end of the procedure, ofloxacin 0.3% was applied and the eye was patched. The patient was asked to use the antibiotic ointment 5 times a day for 3 days. After epithelial healing, the patients used topical fluorometholone twice a day for 1 week.

Numerical Evaluation

Significant corneal flattening 1 year after CXL was defined by a decrease in the maximum K reading of more than 1.00 diopter compared with the preoperative value. Thus, the main variable was

$$\Delta K_{max} = K_{max,preop} - K_{max,1\ year}$$

where ΔK_{max} is the change in the maximum K value, $K_{max,preop}$ is the maximum preoperative K value, and $K_{max,1\ year}$ is the maximum 12-month postoperative K value. Secondary outcomes were preoperative parameters that have been shown to influence the outcomes of CXL, such as age, the maximum K value, CDVA, minimum thickness of the cornea, eccentricity of the cone (radial distance between apex and point of highest curvature), asphericity of the anterior corneal shape, index of surface variance, and the keratoconus index.[7] The correlation of these variables with the change in the maximum K value and its 1-sided significance was calculated using the Spearman rank correlation test. The influence of the digital variables sex (female to male), side (right eye to left eye), and diagnosis (PMD or keratoconus) was studied using the Mann-Whitney *U* test. A subgroup of patients with significant corneal flattening (change in maximum K >1.00 D) was compared with the total study group using the odds ratio (OR) algorithm. The OR of a potential risk factor for regression and its confidence interval (CI) were calculated using the standard algorithm for a 2 × 2 table. All calculations were performed using Winstat for Excel software (R. Finch Software, 2002). A *P* value less than 0.05 was considered statistically significant.

RESULTS

Of the 192 patients (192 eyes) enrolled in the study, 155 completed the 1-year follow-up (dropout rate, 19.3%). The diagnosis was PMD in 32 cases and keratoconus in 103 cases. In 20 cases, the differentiation between the 2 diagnoses was not possible. Four additional eyes were excluded because of massive remodeling resulting from stromal scars after CXL, leaving 151 eyes of 151 patients in the evaluation. Table 1 shows the demographic data of the patients.

Of the 151 eyes, 57 (37.7%) had significant corneal flattening (change in maximum K >1.00 D) (Table 2). Twenty eyes (13.0%) had corneal flattening greater than 2.00 D, 91 eyes (60.3%) remained stable, and 3 eyes (2.0%) had progression of the keratectasia. The maximum flattening was 7.20 D and occurred in a 34-year-old man. The demographic data in Table 1 show a skew toward male patients, left eyes, and keratoconus. There was no statistically significant difference in age ($P=.49$) side (left or right eye) ($P=.976$), sex ($P=.811$), or diagnoses ($P=.24$) between the study group and the flattening subgroup.

Table 3 shows the correlation coefficients of the flattening parameter (change in maximum K value) and the preoperative variables. There was a statistically significant correlation between the flattening

Table 1. Demographic data by group.

Parameter	Study Group (n = 151)	Regression Subroup (n = 57)
Age (y) at treatment		
Mean ± SD	29.3 ± 8.6	28.2 ± 8.4
Range	12, 53	15, 46
Sex (n)		
Female	54	21
Male	97	36
Eye (n)		
Right	66	25
Left	85	32
Diagnosis (n)		
KC	103	43
PMD	32	8

KC = keratoconus; PMD = pellucid marginal degeneration

Table 3. Correlation between preoperative parameters and the flattening parameter ΔK_{max}p-value.

Parameter	*r* Value*	*P* Value*
K_{max}	0.214	.004
Q_{ant}	−0.149	.045
Eccentricity	−0.141	.05
CDVA	−0.136	.048
Age	−0.100	.110
KI	0.079	.170
ISV	0.078	.174
d_{min} (μm)	−0.051	.270

CDVA = corrected distance visual acuity; d_{min}/μm = minimum corneal thickness; ISV = index of surface variance; KI = keratoconus index; K_{max} = maximum keratometry reading; Q_{ant} = asphericity of the anterior corneal shape
*Correlation coefficient

parameter and the maximum K value, asphericity of the anterior corneal shape, eccentricity of the cone, and CDVA.

Table 2 compares the outcomes between the flattening subgroup and the total study group. The only statistically significant differences between the 2 groups were in the preoperative maximum K value and asphericity of the anterior corneal shape. To illustrate the significant difference in the maximum K value in more detail, Figure 1 compares the relative distributions of maximum K in the 2 groups; maximum K readings greater than 54.00 D occurred more frequently in the flattening subgroup than in the total study group. To verify this impression, the OR algorithm was used and found that a maximum K value greater than 54.00 D was a significant risk factor for flattening (OR, 1.88; 95% CI, 1.01-3.51). If the study had included only eyes with a maximum K value greater than 54.00 D, the percentage of eyes with corneal flattening would increase from 38% to 51%. No significant risk limit for asphericity of the anterior corneal shape was found.

Table 2. Comparisons of flattening group and total study group.

Parameter	Mean ± SD Flattening Group	Mean ± SD Total Study Group	Difference *P* Value
ΔK_{max} (D)	2.24 ± 1.42	0.89 ± 1.49	<.001
K_{max} (D)	56.2 ± 6.5	54.3 ± 6.4	.043
Q_{ant}	−0.88 ± 0.53	−0.72 ± 0.64	.052
Δ eccentricity (mm)	−0.08 ± 0.24	−0.07 ± 0.21	.082
CDVA	0.49 ± 0.29	0.55 ± 0.28	.19
KI	1.28 ± 0.13	1.26 ± 0.14	.22
ISV	100 ± 40	95 ± 43	.35
Age (y)	28.2 ± 8.4	29.3 ± 8.6	.50
d_{min} (μm)	447 ± 39	450 ± 37	.64
Diagnosis	—	—	.24

Δ = change; CDVA = corrected distance visual acuity; d_{min} = minimum corneal thickness; ISV = index of surface variance; KI = keratoconus index; K_{max} = maximum keratometry reading; Q_{ant} = asphericity of the anterior corneal shape

DISCUSSION

The major findings in this prospective clinical study are that the maximum curvature regressed significantly in approximately 40% of cases within the first year after CXL and that the only predictive factor for such flattening was a preoperative curvature (maximum K value) greater than 54.00 D. Wollensak et al.[2] and our working group[7] found a reduction in maximum K readings after CXL, a finding that was

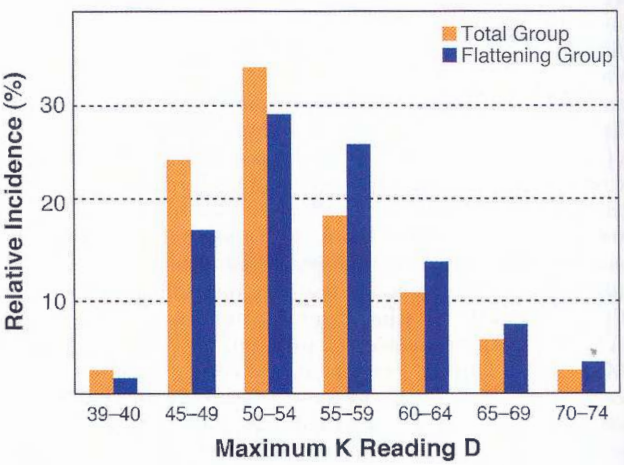
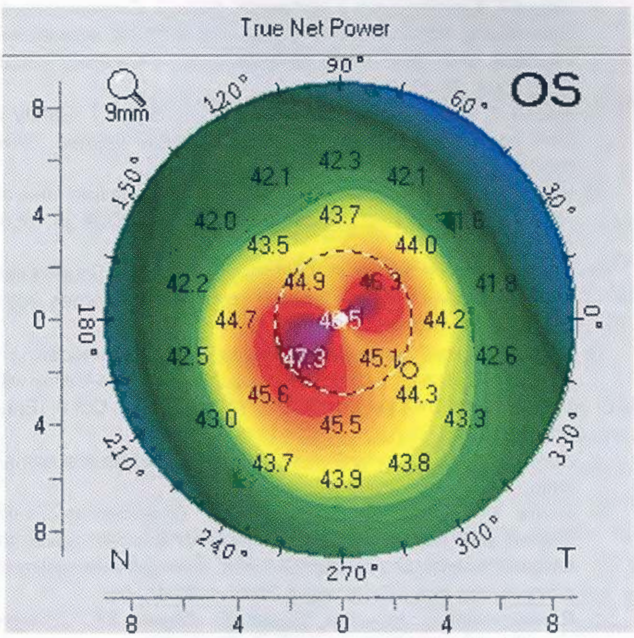


Figure 1. Comparison of the relative incidences of maximum K values between the flattening subgroup and total study group.

confirmed in this study. According to the long-term follow-up presented by the Dresden group,[11] this flattening process can, on average, continue for years. Although a 1.00 or 2.00 D reduction in the maximum K reading may not be enough to rehabilitate visual acuity, the accumulative effect during several years can do so. Moreover, in special cases, the flattening effect is much stronger. Figure 2 shows the evolution of corneal shape during the first year after CXL, with flattening greater than 6.00 D at the central cornea.

The flattening parameter (change in the maximum K value) showed a statistically significant correlation with the preoperative variables of maximum curvature (maximum K value), asphericity of the anterior corneal shape, eccentricity of the cone, and CDVA. However, in a comparison of the subgroup with significant flattening and the total group, the maximum K value remained the only statistically significant factor. Figure 1 shows the relative distributions of maximum K in the 2 groups, and it is obvious that corneas with



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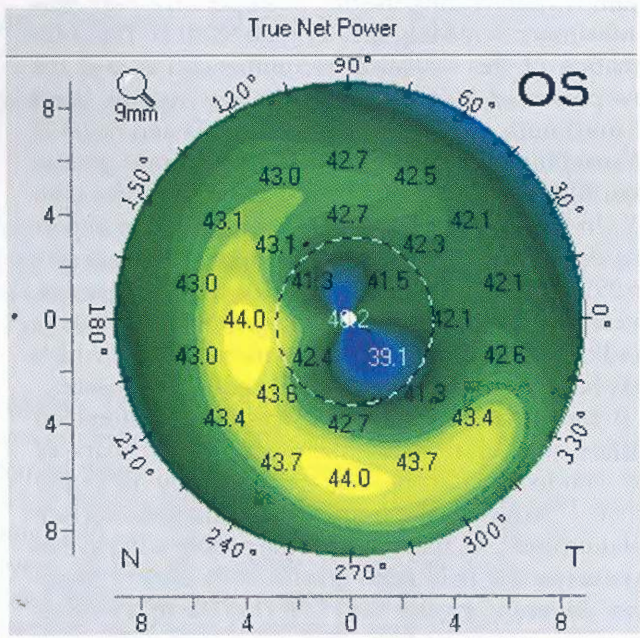

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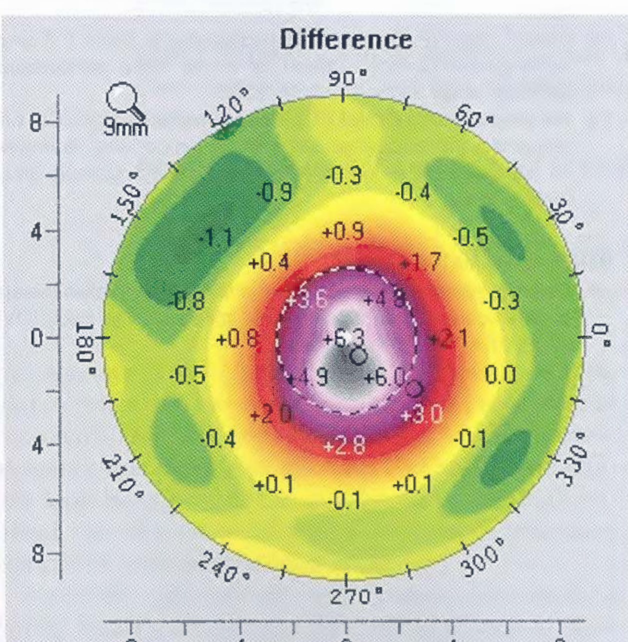

C

Figure 2. Temporal evolution of a cornea after CXL within the first postoperative year shown on true net power maps (*A* and *B*) and the difference map (C); that is, the difference between map *A* and map *B*. Although the difference map shows maximum flattening of more than 6.00 D, the reduction in maximum K is only 3.20 D.

stronger curvature had a greater chance of flattening after CXL. We expected to find other predictive parameters, such as age, diagnosis, and the keratoconus index; however, none of these variables passed the simple significance test. The risk analysis made it even clearer: The only statistically significant risk factor for significant flattening after CXL was maximum K reading greater than 54.00 D, and none of the other factors came close to significance.

In a previous study,[6] the risk factor for failure of CXL, defined as a 1.00 diopter increase in the maximum K value during the first postoperative year, was a maximum K reading greater than 58.00 D. The combination of this statistical recommendation and the one presented here creates a relatively narrow band of maximum success—between 54.00 D and 58.00 D of maximum K—in which a flattening rate greater than 50% is accompanied by a failure rate of less than 1%. In the range of 54.00 D and less, one can expect less flattening; however, there is a good success rate (>99%) in terms of stabilization of the keratoconus. In contrast, a maximum K value greater than 58.00 D predicts more flattening but also more failures, which may have to be emphasized during patient counseling.

A topic that needs to be addressed is customized surface ablation to regularize the multifocal shape of the keratoconus cornea, as proposed by us[12] and others.[13] So far, the reasoning for simultaneous surface ablation and CXL includes that the patient will have to experience the pain from erosion only once.[13] However, flattening greater than 1.00 D in the first year after CXL in more than 50% of cases and more important, flattening of 2.00 D or more in 13% of cases, decreases the predictability of simultaneous surgery. Targeting undercorrection or performing the operations in 2 steps may be a solution.

In summary, we found that statistically significant flattening of the cornea (without scarring) during 1 year after CXL occurred in more than 50% of the cases when the preoperative maximum K reading was greater than 54.00 D. None of the other preoperative parameters investigated (eg, age, sex, diagnosis, CDVA, corneal shape factors) had a statistically significant impact on regression after CXL.

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