Long-term evaluation of posterior corneal surface parameters after accelerated corneal cross-linking with a comparison with uncross-linked keratoconic eyes

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Abstract

Purpose To evaluate the 36 months changes in posterior corneal surface parameters in keratoconic eyes after accelerated corneal cross-linking and to compare the data with uncross-linked progressive and non-progressive keratoconic eyes.

Methods Thirty five cross-linked, 30 uncross-linked progressive, and 30 uncross-linked non-progressive keratoconic eyes were included. Maximum keratometry (K_max), thinnest pachymetry, minimum radius of curvature back (R_min, back), asphericity back, posterior elevation and corneal densitometry, back corneal higher order aberrations (HOAs), back surface deviation (Db), final D, posterior radius of curvature (PRC) and ‘B’ unit values were recorded at baseline and at the 12, 24, 36 months follow-up. Data were analyzed with repeated measures ANOVA and paired t-tests.

Results K_max and thinnest pachymetry were significantly changed in the cross-linked and progressive uncross-linked groups. R_min, back, asphericity back, and HOAs did not change in either group. Total posterior corneal densitometry improved; posterior elevation, Db and B unit worsened in the cross-linked group and did not change in the uncross-linked groups. PRC and final D worsened in the cross-linked and progressive uncross-linked groups, and did not change in the non-progressive group.

Conclusion Despite a decreased K_max, the posterior corneal surface parameters, posterior elevation values were determined to have significantly worsened in the cross-linked group and this increase was higher than in progressive uncross-linked eyes.

Keywords Accelerated corneal cross-linking · Back corneal elevation · Higher order aberration · Keratoconus · Posterior corneal surface

Introduction

Keratoconus is a bilateral progressive degenerative corneal ectatic disease with stromal collagen matrix alterations that lead to stromal thinning and irregular protrusion of the cornea [1]. This irregular cornea creates an irregular astigmatism deteriorating visual acuity to counting fingers in advanced cases.

Corneal cross-linking (CXL) is the only promising method that can halt the progression of keratoconus [2]. Corneal cross-linking is a technique that uses a combination of riboflavin and ultraviolet-A (UVA) radiation to create covalent bonds within and between both collagen molecules and proteoglycan core proteins. These cross-links aim to restore the biomechanical strength and stability of the cornea [3].
Wollensak et al. developed a standard CXL protocol in 2003 [3], while accelerated protocols have been introduced since 2010 to achieve some advantages such as shortened operation time and reduced rate of complications [4]. Accelerated protocols are carried out in 3, 5, and 10 min using 30, 18, and 9 mW/cm² irradiance, respectively, without changing the cumulative irradiation dose of 5.4 J/cm². In the last meta-analysis of randomized controlled trials by Kobashi et al. [5] accelerated CXL showed a comparable efficacy and safety profile and both methods similarly stopped the disease progression.

There are many studies in the literature investigating the outcomes of CXL. The parameters most evaluated are maximum keratometry, central corneal thickness, visual acuity, spherical equivalent, and corneal biomechanical properties. Few studies have examined posterior corneal parameters and they have mainly investigated the effects of standard CXL [6–8]. As far as the authors are aware, there is no study in the literature evaluating the long-term effects of accelerated CXL on all posterior corneal surface parameters.

The aim of this study was to evaluate the long-term effects of accelerated CXL (10 min, 9 mW/cm²) on posterior corneal surface parameters and to compare the posterior corneal surface Scheimpflug tomography measurement changes between cross-linked and uncross-linked keratoconic eyes.

Materials and methods

Patients

This retrospective observational study was conducted in compliance with the institutional and government review board regulations and informed consent regulations. The study protocol was approved by the Ankara Research and Training Hospital Local Ethics Committee with the number E-2572, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before performing CXL.

From the large database in the corneal unit, keratoconus patients were reviewed individually. Keratoconus diagnosis was based on the characteristic keratoconus signs in the anterior sagittal curvature, maps in the anterior sagittal curvature, elevation, and pachymetry maps (e.g., an asymmetric bowtie pattern with or without skewed axes or inferior or central steeping, anterior and posterior elevation, decreased pachymetry) and supported by at least one biomicroscopic sign (e.g., an asymmetric bowtie pattern with or without skewed axes or inferior or central steeping). Patients were excluded from the study if they were aged < 18 years, had anterior segment surgery history, corneal scarring, corneal haze > grade 1 (focal areas of corneal clouding or reticulation), ocular surface problems, or if they had undergone repeated CXL. Progression was defined as a consistent change in at least three of the following three parameters where the magnitude of the change was above the normal noise of the testing system: (1) progressive steepening of the anterior corneal surface, (2) progressive steepening of the posterior corneal surface, and (3) progressive thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point [9].

First, 35 eyes of 35 progressive keratoconus patients who underwent CXL treatment and were followed up for at least 36 months after CXL were included as the cross-linked group. To make a comparison, the data of 30 eyes of 30 progressive keratoconus patients who showed progression in the 12th month of follow-up and underwent CXL after 12th month examinations constituted the progressive uncross-linked group, and 30 eyes of 30 patients who did not show progression in the 12th month formed the non-progressive uncross-linked group.

CXL procedure

All CXL procedures were performed in an operating room under topical anesthesia with 0.5% proparacaine hydrochloride eye drops. The corneal epithelium was mechanically removed from the 8.0 mm treatment zone and then ultrasound pachymetry was applied (Sonomed 300P PacScan Pachymeter; Escalon Medical Corp., USA). If the corneal thickness was < 400 µm, hypoosmolar riboflavin was instilled until the cornea had swollen to a thickness exceeding 400 µm. When the corneal thickness exceeds 400 µm, iso-osmolar riboflavin solution (0.1% riboflavin in 20% dextran T500 solution, Meran Medicine, BNM Inc., Turkey) was instilled to the cornea every 2 min, for a total of 30 min. The cornea was exposed to 370 nm UVA light with a 5.4 J/cm² surface dosage.
using a commercially available UVA system (UV-X System, Peschke Meditrade GmbH, Huenenberg, Switzerland). The intended 9 mW/cm² surface irradiance was applied for 10 min while the riboflavin solution continued to be instilled. The cornea was irrigated with cold water at the end of the procedure, and a silicon-hydrogel bandage contact lens (Acuvue Oasys, Johnson&Johnson, base curve 8.4 mm) was applied. Postoperative treatment included moxifloxacin hydrochloride 0.5% four times a day for 1 week, fluorometholone 5% eye drops four times a day on a tapering schedule for 2 weeks, and artificial tears four times a day for 1 month. The bandage contact lens was removed on the fifth postoperative day.

Ophthalmological examination

Patients underwent a complete ophthalmological examination, including corrected distance visual acuity (CDVA), slit-lamp biomicroscopy, fundus evaluation and tomographic analysis with a rotating Scheimpflug corneal tomography device (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany). The CDVA was measured with a Snellen chart by a cornea specialist and converted to Logarithm of the Minimum Angle of Resolution (logMAR) for statistical analysis. The examination and measurement data of all the patients were recorded according to the study design.

The Pentacam HR is a noninvasive tomography device with a single rotating Scheimpflug camera. This device uses a 1.45-megapixel camera to maximally capture 138,000 data points of true elevation and a 475-nm ultraviolet-free blue light-emitting diode light for corneal illumination. All measurements were taken by an expert examiner under scotopic conditions with the natural pupil. Each participant was asked to fixate on an internal target after a complete blink, and the joystick was adjusted until perfect alignment was shown. Acceptable maps had at least 10 mm of corneal coverage without any extrapolated data in the central 8.0 mm zone. Scans not meeting acceptable criteria were repeated, so at least three measurements were performed for each eye. Only examinations with quality specification ‘OK’ were noted.

The most commonly used CXL efficacy indicators of maximum keratometry ($K_{\text{max}}$) and thinnest corneal thickness (TCT) were noted. Anterior radius of curvature (ARC) was also noted. Minimum radius of curvature ($R_{\text{min,back}}$) was noted as the point of maximum posterior corneal curvature. Asphericity ($Q_{\text{back}}$) and the most commonly used higher order aberrations of spherical aberration, vertical and horizontal coma, vertical and oblique trefoil, which pertain to the corneal back surface, were noted. The topographic keratoconus classification (TKC) was recorded for all participants.

Corneal light backscatter measurements were recorded via the densitometry software. This software automatically locates the corneal apex and analyzes a surrounding area of 12 mm in diameter. This area is divided into four concentric zones which are 0–2 mm circular zone and 2–6 mm, 6–10 mm, and 10–12 mm annular zones. The analyses also provide densitometric values at three different depths. The anterior layer is the superficial 120 µm region, the posterior layer is the innermost 60 µm region, and the central corneal layer lies between these two layers. For this study, the posterior corneal layer values in all concentric zones were noted. Corneal densitometry values are expressed as the pixel luminance per unit volume in grayscale units. Measurements range from 0 (maximum transparency) to 100 (totally opaque) with regard to the backscattering light degree.

The Belin-Ambrósio Enhanced Ectasia Display (BAD-III) software evaluates the pachymetric progression and the anterior and posterior elevation values of the cornea. The maximum posterior elevation value at the 5.0 mm central cornea ($\text{MaxPost}_{elev}$) and at the thinnest point ($\text{ThinnestPost}_{elev}$) were examined according to the best fit sphere (BFS) reference and to the enhanced BFS reference surface. The deviation of normality of the back elevation (Db) and overall deviation of normality (final $D$) were also noted from the BAD-III software.

The Belin ABCD keratoconus grading system is incorporated in the Pentacam software as part of the topometric/keratoconus grading display. This system uses the anterior and posterior radius of curvature (ARC and PRC) taken from the 3.0 mm zone centered on the thinnest point. The classification parameters are ‘A’ for ARC, ‘B’ for PRC, ‘C’ for thinnest pachymetry, and ‘D’ for distance visual acuity. The PRC and ‘B’ parameters were recorded from this grading system.
Statistical analysis

An a priori power analysis was performed using G*Power 3.1 and revealed that 34 participants for matched pairs and 28 participants for independent groups with an $\alpha$ value of 0.05 and statistical power of 0.80.

Statistical analysis was performed using SPSS for Windows software (version 22.0, IBM Corp.). Conformity of the data to normal distribution was analyzed with the Kolmogorov–Smirnov test. Descriptive statistics were recorded as mean ± standard deviation (SD) values. Longitudinal analyses were performed with repeated-measures analysis of variance (ANOVA) and the Bonferroni post hoc test. The assumption of sphericity was tested with Mauchly’s test of sphericity. When the significance level was greater than the a priori $\alpha$ level ($p > 0.05$), sphericity was assumed and the value from the univariate test table was used. When the significance level was less than or equal to the a priori $\alpha$ level ($p \leq 0.05$), sphericity could not be assumed and Wilk’s $\lambda$ test value from the multivariate test table was used. Paired $t$-tests were performed to determine whether the difference between two measurements of the same eye was significant. Between-group comparisons of the three groups were performed using the one-way ANOVA test. When the overall ANOVA model was significant, the Bonferroni post hoc test was conducted to determine the pairwise comparison of the means that were significantly different. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline demographic characteristics in all the groups are shown in Table 1. Age, TKC, Kmax, and ARC values were significantly different between groups. The bonferroni post hoc test revealed that cross-linked and progressive uncross-linked groups included similar grades of keratoconus in similar age range while non-progressive uncross-linked group included milder keratoconus in older age. Gender and PRC values were similar between groups at baseline examination.

### Table 1  Baseline demographic characteristics in all the groups

| Variables       | Cross-linked group mean ± SD | Progressive uncross-linked group mean ± SD | Non-progressive uncross-linked group mean ± SD | $p$ value | $p$ value** (group 1 and 2 group 1 and 3 group 2 and 3) |
|-----------------|-----------------------------|-------------------------------------------|-----------------------------------------------|-----------|---------------------------------------------------|
| Age (years)     | 22.0 ± 3.55                 | 23.29 ± 7.36                             | 32.02 ± 7.55                                 | <0.001*   | 1.00                                              |
| Gender (F/M)    | 22/13                       | 18/12                                     | 19/11                                        | 0.90†     | <0.001                                           |
| TKC             | 2.32 ± 0.78                 | 2.23 ± 0.69                              | 1.45 ± 0.94                                  | <0.001*   | 1.00                                              |
| $K_{\text{max}}$ (Diopters) | 56.63 ± 4.96               | 54.14 ± 4.90                             | 52.80 ± 5.24                                 | 0.007*    | 1.40                                              |
| ARC (mm)        | 6.68 ± 0.52                 | 6.73 ± 0.52                              | 7.03 ± 0.46                                  | 0.01*     | 1.00                                              |
| PRC (mm)        | 4.98 ± 0.42                 | 5.06 ± 0.48                              | 5.22 ± 0.47                                  | 0.07*     | 0.07                                              |

*One-way ANOVA test, †Pearson Chi-Square test **Bonferroni post hoc test
Visual acuity, topography, and aberrometry changes after CXL

Table 2 shows the visual and corneal topographic and aberrometric parameters at baseline and 12, 24, and 36 months after CXL. CDVA significantly improved at 36 months after CXL. CDVA at post-CXL 12 months was significantly better than at baseline in all post-CXL measurements. $K_{\text{max}}$ and TCT were significantly decreased at 36 months after CXL. The Bonferroni post hoc test revealed that all postoperative values were significantly lower than baseline values. ARC value was significantly increased at 36 months after CXL. The Bonferroni post hoc test revealed that anterior curvature was flatter at 36 months compared to baseline values. The $R_{\text{min}}$ and $Q$ values of the back cornea did not significantly change after CXL. None of the higher-order aberrations of the corneal back surface changed at 36 months after CXL.

Corneal densitometry changes after CXL

Table 3 shows the posterior corneal densitometric parameters at baseline and at 12, 24, and 36 months after CXL. Densitometric values in all the zones and total posterior layer significantly improved at 36 months after CXL. The Bonferroni post hoc test revealed that the densitometric values were significantly different between baseline and post-CXL 12th month in the 0–2 and 10–12 mm zones, and significantly different between baseline and post-CXL 24th month in the 6–10 mm zone.

Table 2 Visual and topographic and aberrometric parameters over time in the cross-linked group

| Variables                          | Preoperative Postoperative 12 months | Postoperative 24 months | Postoperative 36 months | p value* | p value** |
|------------------------------------|-------------------------------------|-------------------------|-------------------------|----------|----------|
| CDVA (logMAR)                      | 0.51 ± 0.31                         | 0.22 ± 0.14             | 0.44 ± 0.50             | <0.001   | <0.001   |
| $K_{\text{max}}$ (D)               | 56.63 ± 4.96                        | 54.66 ± 5.12            | 53.82 ± 4.64            | <0.001   | <0.001   |
| TCT (µm)                           | 463.33 ± 41.48                      | 427.93 ± 47.84          | 427.06 ± 51.37          | <0.001   | <0.001   |
| ARC                               | 6.68 ± 0.52                         | 6.94 ± 0.55             | 6.98 ± 0.53             | 0.01     | 0.06     |
| $R_{\text{min}}$ back (mm)         | 4.33 ± 0.45                         | 4.23 ± 0.45             | 4.27 ± 0.44             | 0.14     | 0.91     |
| $Q_{\text{back}}$                   | −0.99 ± 0.27                        | −1.06 ± 0.30            | −1.02 ± 0.26            | 0.49     | 0.02     |
| Spherical aberration (µm)          | 0.09 ± 0.12                         | 0.12 ± 0.15             | 0.11 ± 0.13             | 0.29     |          |
| Vertical coma (µm)                 | −0.08 ± 0.07                        | −0.09 ± 0.07            | −0.07 ± 0.06            | 0.28     |          |
| Horizontal coma (µm)                | −0.008 ± 0.05                       | 0.012 ± 0.06            | 0.013 ± 0.06            | 0.73     |          |
| Vertical trefoil (µm)              | −0.0004 ± 0.02                      | −0.006 ± 0.05           | 0.007 ± 0.04            | 0.12     |          |
| Oblique trefoil (µm)               | 0.03 ± 0.03                         | 0.03 ± 0.06             | 0.02 ± 0.05             | 0.47     |          |

CDVA corrected distance visual acuity, $K_{\text{max}}$ maximum keratometry, TCT thinnest corneal thickness, ARC anterior radius of curvature, $R_{\text{min}}$ back smallest radius of curvature at the back of the cornea, $Q_{\text{back}}$ asphericity value at the back of the cornea

Boldface, significant values, *$p$

*Repeated-measures analysis of variance

**Bonferroni post-test analysis between baseline and 12, 24, and 36 months, respectively, after cross-linking
Posterior surface elevation changes after CXL

Table 4 shows the posterior corneal surface elevation and ectasia indices at baseline and at 12, 24, and 36 months after CXL. The maximum and thinnest point posterior elevation values, Db, and final D parameters significantly increased after CXL. The Bonferroni post hoc test analysis revealed that Db value was significantly higher than baseline at post-CXL 24 and 36 months, and the final D value was higher than baseline at the 12th and 24th months. The PRC value significantly decreased and its Belin unit ‘B’ significantly increased after CXL. Bonferroni post hoc test analysis revealed significantly lower PRC and higher ‘B’ at the postoperative 24th month compared to baseline values.

Comparison of visual acuity, topography and aberrometry changes in the three groups

Table 5 shows the visual acuity and topography and aberrometry changes at the 12 months follow-up examination of the three groups. CDVA did not significantly change in the uncross-linked group and improved in the cross-linked group ($p < 0.001$). $K_{\text{max}}$ significantly decreased in the cross-linked group and significantly increased in the progressive uncross-linked group ($p < 0.001$). TCT significantly decreased in both the cross-linked and progressive uncross-linked groups ($p < 0.001$) and the decrease was greater in the cross-linked group ($p < 0.001$). ARC significantly increased in the cross-linked group and significantly decreased in the progressive uncross-linked group ($p = 0.01$ and $p < 0.001$) while did not significantly change in the non-progressive uncross-linked group. $R_{\text{min}}$ and $Q$ back value changes were similar in all the groups. Table 6 shows the wavefront cornea back aberrometric parameter changes at the 12 months follow-up examination in all three groups. The aberrometry values did not change at 12 months in all the groups and the change values did not differ between the groups ($p > 0.05$ for all values).

Comparison of posterior corneal densitometry changes in the three groups

Table 7 shows the posterior corneal densitometry changes at the 12 months follow-up examination in
the three groups. A significant posterior densitometry increase only occurred in the 0–2 mm zone in the cross-linked group ($p = 0.002$) and the amount of change created a significant difference between the groups ($p = 0.01$). The uncross-linked groups did not show significant densitometry changes at 12 months.

Comparison of posterior corneal surface elevation and ectasia indices changes in the three groups

Table 8 shows the posterior corneal surface elevation and ectasia indices changes in the three groups at the 12 months follow-up examination in the three groups. Maximum posterior elevation at the 5.0 mm central cornea and at the thinnest point, and the deviation of normality of the back elevation values significantly increased in the cross-linked group, and did not significantly change in the uncross-linked groups (respectively $p = 0.01, p = 0.01, p = 0.09$, respectively). Overall deviation of normality significantly increased and posterior radius of curvature significantly decreased in the cross-linked and progressive uncross-linked groups, and did not change in the non-progressive uncross-linked group ($p < 0.001$ and $p = 0.008$). The amount of change was higher in the cross-linked group than in the progressive uncross-linked group for both final $D$ and $Db$. The $B$ value significantly increased in the cross-linked group and did not significantly change in the uncross-linked groups ($p = 0.01$).

Discussion

The posterior corneal surface evaluation first began with the measurement of the radius of curvature and central corneal thickness using some techniques such as purkinje image photography and pachymetry [10, 11]. Orbscan scanning slit topography (Bausch&Lomb, Orbtex Inc., Salt Lake City, UT) and later Pentacam Scheimpflug imaging provided more detailed information about the posterior surface than had been previously possible. The

**Table 4** Posterior corneal surface elevation and ectasia indices parameters over time in the cross-linked group

| Variables | Baseline | Postoperative 12 months | Postoperative 24 months | Postoperative 36 months | $p$ value* | $p$ value** |
|-----------|----------|-------------------------|-------------------------|-------------------------|-----------|-----------|
| $\text{MaxPost}_{elev}$ (µm) | $64.10 \pm 18.24$ | $70.36 \pm 18.31$ | $71.13 \pm 19.01$ | $72.10 \pm 20.26$ | $0.01$ | $0.05$ |
| $Db$ | $8.02 \pm 3.70$ | $9.10 \pm 3.62$ | $9.29 \pm 3.39$ | $9.24 \pm 3.74$ | $0.03$ | $0.06$ |
| Final $D$ | $8.33 \pm 2.52$ | $9.44 \pm 2.54$ | $9.44 \pm 2.74$ | $9.11 \pm 3.24$ | $0.005$ | $0.003$ |
| $\text{ThinnestPost}_{elev}$ (µm) | $46.10 \pm 19.36$ | $51.70 \pm 18.47$ | $52.73 \pm 24.79$ | $52.50 \pm 23.49$ | $0.04$ | $0.05$ |
| PRC (mm) | $4.98 \pm 0.42$ | $4.88 \pm 0.43$ | $4.83 \pm 0.40$ | $4.88 \pm 0.48$ | $0.001$ | $0.09$ |
| $B$ value (Belin unit for PRC) | $4.12 \pm 1.71$ | $4.52 \pm 1.83$ | $4.75 \pm 1.71$ | $4.59 \pm 1.94$ | $0.012$ | $0.14$ |

$MaxPost_{elev}$ maximum posterior elevation at the 5.0 mm central cornea, $Db$ deviation of normality of the back elevation, $ThinnestPost_{elev}$ maximum posterior elevation at the thinnest point, $PRC$ Posterior radius of curvature

Boldface, significant values, $p$

*Repeated-measures analysis of variance. **Bonferroni post-test analysis between baseline and 12, 24, and 36 months, respectively, after cross-linking
reliability and the validity of the posterior cornea measurements with Orbscan have been questioned in many cases and it has been concluded that Orbscan posterior cornea results may be an artifact [12, 13]. Scheimpflug imaging is capable of measuring 25,000 true elevation points and may detect posterior corneal elevations with mathematical reconstruction [14]. Scheimpflug-derived posterior

Table 5 Visual and topographic parameters at baseline and at 12 months in all the groups

| Variables         | Group                     | Baseline | 12 months follow-up | Mean change | p value* | p value** | p value† |
|-------------------|----------------------------|----------|---------------------|-------------|----------|----------|----------|
| CDVA (logMAR)     | Cross-linked               | 0.51 ± 0.31 | 0.22 ± 0.14 | −0.28 ± 0.31 | <0.001 | <0.001 | <0.001 |
|                   | Progressive uncross-linked| 0.18 ± 0.19 | 0.18 ± 0.20 | 0.001 ± 0.11 | 0.93    |          |          |
|                   | Non-progressive uncross-linked | 0.17 ± 0.21 | 0.17 ± 0.20 | −0.004 ± 0.02 | 0.32    |          |          |
| K max (D)         | Cross-linked               | 56.63 ± 4.96 | 54.66 ± 5.12 | −1.96 ± 2.19 | <0.001 | <0.001 | <0.001 |
|                   | Progressive uncross-linked| 54.14 ± 4.90 | 55.73 ± 5.17 | 1.54 ± 1.80  | <0.001 | <0.001 | <0.001 |
|                   | Non-progressive uncross-linked | 52.80 ± 5.24 | 52.69 ± 5.01 | −0.11 ± 0.61 | 0.24    |          |          |
| TCT (µm)          | Cross-linked               | 463.33 ± 41.48 | 427.93 ± 47.84 | −35.40 ± 26.40 | <0.001 | <0.001 | <0.001 |
|                   | Progressive uncross-linked| 448.40 ± 91.60 | 439.53 ± 90.97 | −8.96 ± 14.74 | 0.001 |          | 0.05    |
|                   | Non-progressive uncross-linked | 449.55 ± 50.58 | 450.91 ± 50.56 | 1.17 ± 8.46  | 0.30    |          |          |
| ARC (mm)          | Cross-linked               | 6.68 ± 0.52 | 6.94 ± 0.55 | 0.26 ± 0.52  | 0.01    | <0.001 | <0.001 |
|                   | Progressive uncross-linked| 6.73 ± 0.52 | 6.59 ± 0.51 | −0.13 ± 0.11 | <0.001 | 0.003   |          |
|                   | Non-progressive uncross-linked | 7.03 ± 0.46 | 7.02 ± 0.44 | −0.01 ± 0.06 | 0.34    | 0.33    |          |
| R min back        | Cross-linked               | 4.33 ± 0.45 | 4.23 ± 0.45 | −0.10 ± 0.27 | 0.05    | 0.15    |          |
|                   | Progressive uncross-linked| 4.53 ± 0.56 | 4.41 ± 0.50 | −0.11 ± 0.20 | 0.005   |          |          |
|                   | Non-progressive uncross-linked | 4.86 ± 0.58 | 4.84 ± 0.58 | −0.01 ± 0.11 | 0.39    |          |          |
| Q back            | Cross-linked               | −0.99 ± 0.27 | −1.06 ± 0.30 | −0.06 ± 0.21 | 0.12    | 0.19    |          |
|                   | Progressive uncross-linked| −0.85 ± 0.43 | −0.89 ± 0.43 | −0.02 ± 0.11 | 0.09    |          |          |
|                   | Non-progressive uncross-linked | −0.74 ± 0.37 | −0.74 ± 0.38 | 0.02 ± 0.22  | 1.00    |          |          |

CDVA corrected distance visual acuity, K max maximum keratometry, TCT thinnest corneal thickness, ARC anterior radius of curvature, R min back smallest radius of curvature at the back of the cornea, Q back sphericity value at the back of the cornea

Boldface, significant values, p

*Paired t-test analysis for postoperative 12 months and baseline comparison

**One-way ANOVA test analysis for comparison of the mean change values between groups

†Bonferroni posttest analysis between cross-linked and progressive uncross-linked, cross-linked and non-progressive uncross-linked, progressive uncross-linked and non-progressive uncross-linked groups, respectively
elevation measurements have acceptable reproducibility in both keratoconic and cross-linked keratoconic eyes [15].

There are many studies in the literature which have investigated the changes in CDVA, $K_{\text{max}}$, and TCT parameters after CXL. The current study results are consistent with those of recent studies that have reported improved $K_{\text{max}}$, CDVA and decreased TCT values after accelerated CXL [16–18]. Visual acuity changes in the current study were not significant in the uncross-linked groups. $K_{\text{max}}$ increased and TCT decreased in the progressive uncross-linked group as a consequence of progression. Corneal thickness was measured thinner in the cross-linked group than in the progressive uncross-linked group despite a flatter anterior surface. In a recent study by the current authors, the CCT measurement difference between the Pentacam and ultrasound pachymetry was largest in the CXL group, followed by the keratoconus and control groups ($-20.9 \pm 21.5$, $-10.6 \pm 20.3$, and $0.4 \pm 6.8 \mu m$), and it was concluded that pachymetric measurements from Scheimpflug must be interpreted with extreme caution [19].

The decrease in posterior surface asphericity and minimum radius of curvature was not significant in the long term, and the amounts of change were similar in the cross-linked and progressive uncross-linked groups at postoperative 12 months. In a comparative study of changes of corneal curvatures at 1 year post-CXL by Safarzadeh et al., curvatures of the posterior corneal surface were reported to be significantly increased [8]. This study can be considered to add to the literature that CXL does not have a positive or negative effect on back surface curvatures while it significantly improves anterior surface curvatures at a 36 months longitudinal follow-up.

Posterior HOAs are not calculated by extracting the anterior HOAs from the entire corneal aberrations because the incident rays on the posterior surface have a deformed wavefront caused by anterior surface refraction. Therefore, evaluation of both anterior and posterior corneal surface HOAs allows increased understanding of the optical quality of keratoconic eyes [20]. In studies by Hassan and Iselin et al., aberrations of the posterior corneal surface did not change at 7 and 24 months after CXL [6, 21]. In the present study, higher-order aberrations of the posterior corneal surface did not significantly change in a post-CXL follow-up period of 36 months similar to the study by Iselin et al. Greenstein et al. compared HOA changes at 1 year post-CXL between cross-linked and control ectatic eyes, and concluded that there was a

### Table 6 Wavefront cornea back aberrometric parameters at baseline and at 12 months in all the groups

| Variables          | Group                  | Baseline  | 12 months follow-up | Mean change | $p$ value* | $p$ value** |
|--------------------|------------------------|-----------|---------------------|-------------|-----------|-------------|
| Spherical aberration | Cross-linked           | 0.09±0.12 | 0.12±0.15           | 0.02±0.10   | 0.16      | 0.35        |
|                    | Progressive uncross-linked | 0.04±0.16 | 0.06±0.17           | 0.01±0.06   | 0.19      |             |
|                    | Non-progressive uncross-linked | -0.01±0.13 | -0.01±0.12        | 0.0007±0.01 | 0.84      |             |
| Vertical coma      | Cross-linked           | -0.08±0.07 | -0.09±0.07          | -0.05±0.05  | 0.57      | 0.34        |
|                    | Progressive uncross-linked | 0.51±0.23 | 0.53±0.25           | 0.01±0.10   | 0.32      |             |
|                    | Non-progressive uncross-linked | 0.35±0.24 | 0.37±0.25           | 0.01±0.03   | 0.05      |             |
| Horizontal coma    | Cross-linked           | 0.008±0.05 | 0.01±0.06           | 0.003±0.02  | 0.39      | 0.43        |
|                    | Progressive uncross-linked | -0.03±0.24 | -0.06±0.26          | -0.02±0.16  | 0.41      |             |
|                    | Non-progressive uncross-linked | 0.006±0.13 | 0.009±0.13          | 0.003±0.02  | 0.55      |             |
| Vertical trefoil   | Cross-linked           | -0.0004±0.02 | -0.006±0.05         | -0.005±0.04 | 0.49      | 0.15        |
|                    | Progressive uncross-linked | -0.02±0.17 | 0.01±0.18           | 0.04±0.15   | 0.13      |             |
|                    | Non-progressive uncross-linked | 0.03±0.12 | 0.03±0.10           | 0.0009±0.08 | 0.95      |             |
| Oblique trefoil    | Cross-linked           | 0.03±0.03  | 0.03±0.06           | 0.002±0.05  | 0.81      | 0.68        |
|                    | Progressive uncross-linked | -0.14±0.13 | -0.17±0.18          | -0.02±0.14  | 0.41      |             |
|                    | Non-progressive uncross-linked | -0.15±0.12 | -0.15±0.16          | -0.004±0.11 | 0.85      |             |

*Paired $t$-test analysis for postoperative 12 months and baseline comparison

**One-way ANOVA test analysis for comparison of the mean change values between groups
mean decrease in posterior corneal HOAs in the treatment group while there was a mean increase in the control group [22]. In contrast to that study, the current study results showed that CXL did not add additional benefit to posterior corneal HOAs.

Compromised regularity of cells in keratoconic eyes increases the densitometry values of these corneas. With this knowledge, corneal densitometry changes have been investigated as an outcome of CXL. Greenstein et al. reported that the mean densitometry values peak at 1 month after CXL, but decreased throughout 12 months, and did not completely return to the baseline value at the postoperative 12th month [23]. Alnawaiseh et al. found that densitometry values including the posterior 0–2 and 2–6 mm zones were stable at 12 months post-CXL, and decreased below the preoperative values at the post-CXL 24th month [24]. Similarly in the current study, posterior densitometry values in the 0–2 and 2–6 mm zones were higher in the 12th month and lower in the 36th month compared to the baseline values. In the 12th month comparison between the groups, corneal densitometry increased in both the cross-linked and progressive uncross-linked groups. Although the densitometric change at the 12th month resembled ongoing ectatic change, posterior surface backscattering values improved 36 months after CXL.

Table 7  Posterior corneal densitometric parameters at baseline and at 12 months in all the groups

| Variables Group | Group | Baseline | 12. months follow-up | Mean change | p value* | p value** | p value† |
|-----------------|-------|---------|---------------------|-------------|---------|---------|---------|
| 0–2 mm (GSU)    | Cross-linked | 8.48 ± 1.17 | 9.64 ± 1.79 | 1.16 ± 1.89 | 0.002   | 0.01 | 0.46 |
|                 | Progressive uncross-linked | 8.35 ± 1.12 | 8.87 ± 1.59 | 0.51 ± 1.65 | 0.09 |
|                 | Non-progressive uncross-linked | 8.23 ± 1.50 | 8.00 ± 0.98 | −0.23 ± 1.69 | 0.45 |
| 2–6 mm (GSU)    | Cross-linked | 9.09 ± 0.85 | 9.35 ± 1.06 | 0.26 ± 1.41 | 0.31 | 0.16 |
|                 | Progressive uncross-linked | 8.76 ± 0.98 | 9.22 ± 1.21 | 0.45 ± 1.43 | 0.09 |
|                 | Non-progressive uncross-linked | 8.43 ± 1.55 | 8.18 ± 0.93 | −0.24 ± 1.54 | 0.39 |
| 6–10 mm (GSU)   | Cross-linked | 8.79 ± 0.79 | 8.53 ± 0.97 | −0.26 ± 1.41 | 0.21 | 0.40 |
|                 | Progressive uncross-linked | 8.84 ± 1.50 | 9.00 ± 1.45 | 0.15 ± 1.30 | 0.51 |
|                 | Non-progressive uncross-linked | 9.05 ± 1.75 | 8.83 ± 1.39 | −0.22 ± 1.48 | 0.42 |
| 10–12 mm (GSU)  | Cross-linked | 13.37 ± 3.61 | 11.88 ± 2.31 | −1.49 ± 2.86 | 0.008 | 0.04 | 0.05 |
|                 | Progressive uncross-linked | 13.31 ± 4.83 | 13.44 ± 4.24 | 0.13 ± 2.52 | 0.78 |
|                 | Non-progressive uncross-linked | 13.07 ± 3.04 | 12.83 ± 2.06 | −0.24 ± 2.31 | 0.56 |
| Total (GSU)     | Cross-linked | 9.53 ± 0.85 | 9.53 ± 0.98 | 0.003 ± 1.26 | 0.98 | 0.28 |
|                 | Progressive uncross-linked | 9.35 ± 1.22 | 9.69 ± 1.23 | 0.33 ± 1.36 | 0.18 |
|                 | Non-progressive uncross-linked | 9.35 ± 1.69 | 9.12 ± 1.05 | −0.23 ± 1.55 | 0.41 |

Boldface, significant values, p

*Paired t-test analysis for postoperative 12 months and baseline comparison
**One-way ANOVA test analysis for comparison of the mean change values between groups
†Bonferroni posttest analysis between cross-linked and progressive uncross-linked, cross-linked and non-progressive uncross-linked, progressive uncross-linked and non-progressive uncross-linked groups, respectively
Table 8 Posterior corneal surface elevation and ectasia indices parameters at baseline and 12 months follow-up in all groups

| Variables             | Group                  | Baseline       | 12. months follow-up | Mean change | p value* | p value** | p value† |
|-----------------------|------------------------|----------------|----------------------|-------------|----------|-----------|----------|
| MaxPost<sub>ele</sub> (µm) | Cross-linked           | 64.10 ± 18.24  | 70.36 ± 18.31        | 6.26 ± 12.15 | 0.008    | 0.01      | 0.06     |
|                       | Progressive uncross-linked | 55.53 ± 21.23 | 56.03 ± 18.94        | 0.50 ± 10.45 | 0.79     |           |          |
|                       | Non-progressive uncross-linked | 42.03 ± 16.33 | 41.50 ± 17.26        | −0.53 ± 3.67 | 0.43     |           |          |
| Db                    | Cross-linked           | 8.02 ± 3.70   | 9.10 ± 3.62          | 1.07 ± 2.18  | 0.01     | 0.09      |          |
|                       | Progressive uncross-linked | 7.42 ± 4.73   | 25.36 ± 7.71         | 0.28 ± 1.72  | 0.37     |           |          |
|                       | Non-progressive uncross-linked | 5.06 ± 3.39   | 5.27 ± 3.36          | 0.20 ± 1.02  | 0.28     |           |          |
| Final D               | Cross-linked           | 8.33 ± 2.52   | 9.44 ± 2.54          | 1.11 ± 1.55  | <0.001   | <0.001    | 0.06     |
|                       | Progressive uncross-linked | 7.77 ± 3.16   | 8.28 ± 3.35          | 0.50 ± 1.00  | 0.004    |           | 0.05     |
|                       | Non-progressive uncross-linked | 6.96 ± 2.86   | 6.91 ± 2.97          | −0.05 ± 0.55 | 0.54     |           |          |
| ThinnestPost<sub>ele</sub> (µm) | Cross-linked           | 46.10 ± 19.36  | 51.70 ± 18.47        | 5.60 ± 10.89 | 0.009    | 0.01      | 0.09     |
|                       | Progressive uncross-linked | 46.76 ± 19.74  | 47.43 ± 21.79        | 0.66 ± 9.59  | 0.70     |           |          |
|                       | Non-progressive uncross-linked | 36.20 ± 13.91 | 35.20 ± 14.84        | −1.00 ± 4.16 | 0.19     |           |          |
| PRC (mm)              | Cross-linked           | 4.98 ± 0.42   | 4.88 ± 0.43          | −0.10 ± 0.21 | 0.01     | 0.008     | 0.66     |
|                       | Progressive uncross-linked | 5.06 ± 0.48   | 4.99 ± 0.49          | −0.05 ± 0.15 | 0.02     |           | 0.30     |
|                       | Non-progressive uncross-linked | 5.22 ± 0.47   | 5.23 ± 0.47          | 0.01 ± 0.08  | 0.35     |           |          |
| B value (Belin unit for PRC) | Cross-linked           | 4.12 ± 1.71   | 4.52 ± 1.83          | 0.40 ± 0.93  | 0.02     | 0.01      | 0.70     |
|                       | Progressive uncross-linked | 3.87 ± 1.93   | 4.10 ± 2.03          | 0.19 ± 0.68  | 0.05     |           | 0.01     |
|                       | Non-progressive uncross-linked | 3.25 ± 1.74   | 3.21 ± 1.75          | −0.04 ± 0.32 | 0.39     |           | 0.41     |

Boldface, significant values, p

*Paired t-test analysis for postoperative 12 months and baseline comparison

**One-way ANOVA test analysis for comparison of the mean change values between groups

†Bonferroni posttest analysis between cross-linked and progressive uncross-linked, cross-linked and non-progressive uncross-linked, progressive uncross-linked and non-progressive uncross-linked groups, respectively
In a study by Kırgız et al. [16] it was found that apical keratoscopy back increased 6 months after CXL and was associated with increased visual acuity. Hashemi et al. [25] reported that the decrease in posterior $R_{\text{min}}$ and the increase in posterior elevation values were significant at 4 years after 5 min accelerated CXL while the changes were not significant after standard CXL. Tian et al. [26] found that posterior elevation values slightly decreased 1 year after accelerated transepithelial CXL, but the parameters were significantly increased at the 3 years follow-up. It has been concluded that the posterior surface of the cornea may not be adequately cross-linked with accelerated CXL. In the current study, posterior surface elevation parameters significantly worsened at 36 months after CXL. In addition, the posterior elevation value changes were higher in the cross-linked group than in the progressive uncross-linked group. This suggested that posterior elevation increases could not be explained solely by ongoing ectatic changes.

There were considered to be three most likely reasons for the worsened posterior surface elevation measurements found after CXL. The first was that ectatic changes were ongoing due to inadequate cross-linking to the posterior cornea but this is unlikely due to the large difference between the cross-linked and progressive uncross-linked groups. The second possible reason was that tissue shrinkage and thinning induced by cross-linking may subsequently rearrange the corneal sequence, so more anterior and more elevated corneal regions may be measured at the post-CXL visits compared to baseline. The third reason could be that it is a result of a technical limitation of topography devices. Corneal topographers that measure the anterior and posterior corneal surface with optical methods depend on the pathway of the reflected waves of light and need a clear cornea structure for precise measurements [27]. For example, thinner corneal thickness values after CXL may be found as a result of a change in the refractive index of the stroma leading to false thinner results with optical ray tracing. Unreliable posterior surface measurements because of refractive index changes and demarcation line artifacts may be another reason for highly elevated posterior surface values.

There were some limitations to this study related to the retrospective design of the study. The primary limitation is the relatively small sample size but a large database was checked to identify patients with regular follow-up of at least 36 months after CXL and the quality of measurements was also checked. A second limitation is that there was no comparison with a standard CXL protocol because heavily accelerated CXL is performed in our busy tertiary care hospital. The third limitation is that corneal changes could not be compared with different topography devices. The fourth limitation is that due to the progressive nature of disease, interindividual comparison of three groups was limited to a follow-up time of 12 months. After 12 months, CXL was performed for progressive keratoconic eyes to halt the progression.

In conclusion, visual acuity improved, anterior corneal surface was flattened and posterior corneal surface was elevated at 36 months after accelerated CXL and the posterior corneal surface elevations were higher than in the progressive uncross-linked eyes. CXL seems to halt the progression of keratoconus by affecting mainly the anterior parts of the cornea and the ectatic progression may persist in posterior cornea. The higher posterior elevation values after CXL may also indicate the affect of wound healing process and device artifact. Further studies are needed to reveal the exact cause of posterior surface elevation 36 months after CXL and to reveal the cutoff values for posterior elevation parameters that may indicate ongoing progression after CXL.

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**Data availability** Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

**Declarations**

**Conflict of interest** The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

**References**

1. Jeyabalan N, Shetty R, Ghosh A, Anandula VR, Ghosh AS, Kumaramanickavel G (2013) Genetic and genomic perspective to understand the molecular pathogenesis of
keratoconus. Indian J Ophthalmol 61(8):384–388. https://doi.org/10.4103/0301-4738.116055

2. Suri K, Hammersmith KM, Nagra PK (2012) Corneal collagen cross-linking: ectasia and beyond. Curr Opin Ophthalmol 23(4):280–287. https://doi.org/10.1097/ICO.0b013e328354865e

3. Wollenhaupt G, Spoerl E, Seiler T (2003) Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 135(5):620–627. https://doi.org/10.1016/s0002-9394(02)02220-1

4. Wen D, Li Q, Song B, Tu R, Wang Q, O’Briart D, McAlinden C, Huang J (2018) Comparison of standard versus accelerated corneal collagen cross-linking for keratoconus: a meta-analysis. Inv Ophthalmol Vis Sci 59(10):3920–3931. https://doi.org/10.1177/1050178418809106

5. Kobashi H, Tsubota K (2020) Accelerated versus standard corneal cross-linking for progressive keratoconus: a meta-analysis of randomized controlled trials. Cornea 39(2):172–180. https://doi.org/10.1097/ICO.0000000000002092

6. Hassan Z, Modis L, Szalai E, Berta A, Nemeth G (2014) Scheimplug imaged corneal changes on anterior and posterior surfaces after collagen cross-linking. Int J Ophthalmol 7(2):313–316. https://doi.org/10.3980/j.issn.2222-3959.2014.02.21

7. Steinberg J, Ahmadiyar M, Rost A, Frings A, Filev F, Katz T, Linke SJ (2014) Anterior and posterior corneal changes after crosslinking for keratoconus. Optom Vis Sci 91(2):178–186. https://doi.org/10.1097/OPX.0000000000000141

8. Safarzadeh M, Nasiri N, Doostdar A, Kamali M (2016) Comparative study of changes of corneal curvatures and uncorrected distance visual acuity prior to and after corneal collagen cross-linking: 1-year results. Taiwan J Ophthalmol 6(3):127–130. https://doi.org/10.1016/j.tjo.2016.06.003

9. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, Maleczafe F, Nishida K, Sangwan VS (2015) Global consensus on keratoconus and ectatic diseases. Cornea 34(4):359–369. https://doi.org/10.1097/ICO.0000000000000408

10. Garner LF, Owens H, Yap MK, Frith MJ, Kinnear RF (1997) Radius of curvature of the posterior surface of the cornea. Optom Vis Sci 74(7):496–498. https://doi.org/10.1097/00006324-199707000-00016

11. Royston JM, Dunne MC, Barnes DA (1990) Measurement of posterior corneal surface toricity. Optom Vis Sci 67(10):757–763. https://doi.org/10.1097/00006324-199010000-00002

12. Maldonado MJ, Nieto JC, Díez-Cuenca M, Piñero DP (2006) Repeatability and reproducibility of posterior corneal curvature measurements by combined scanning-slit and placido-disc topography after LASIK. Ophthalmology 113(11):1918–1926. https://doi.org/10.1016/j.ophtha.2006.05.053

13. Nawa Y, Masuda K, Ueda T, Hara Y, Uozato H (2005) Evaluation of apparent ectasia of the posterior surface of the cornea after keratorefractive surgery. J Cataract Refrac Surg 31(3):571–573. https://doi.org/10.1016/j.jcrs.2004.05.050

14. Ciolino JB, Belin MW (2006) Changes in the posterior cornea after laser in situ keratomileusis and photorefractive keratectomy. J Cataract Refrac Surg 32(9):1426–1431. https://doi.org/10.1016/j.jcrs.2006.03.037

15. Labiris G, Giarmoukakis A, Sideroudi H, Bougatsou P, Lazaridis I, Koizobolis VP (2012) Variability in Scheimpflug image-derived posterior elevation measurements in keratoconus and collagen-crosslinked corneas. J Cataract Refrac Surg 38(9):1616–1625. https://doi.org/10.1016/j.jcrs.2012.04.039

16. Kozakz A, Atalay K, Çubuk KŞ, Kaldırım H, Taşkapılı M (2016) Factors affecting visual acuity after accelerated crosslinking in patients with progressive keratoconus. Arq Bras Oftalmol 79(3):151–154. https://doi.org/10.5935/0004-2749.20160046

17. Badawi AE (2017) Accelerated corneal collagen cross-linking in pediatric keratoconus: one year study. Saudi J Ophthalmol 31(1):11–18. https://doi.org/10.1016/j.sjopty.2017.01.002

18. Omar I, Zein HA (2019) Accelerated epithelium-off corneal collagen cross-linking for Keratoconus: 12-month results. Clin Ophthalmol 13:2385–2394. https://doi.org/10.2147/OPHT.S232118

19. Kosekaya P, Koc M, Yalçınsoy KO, Kocabas DO, Toker MI (2020) Comparative evaluation of central corneal thickness in cross-linked keratoconic eyes. Cornea 39(9):1080–1085. https://doi.org/10.1097/ICO.0000000000002339

20. Nakagawa T, Maeda N, Kosaki R, Hor Y, Inoue T, Saika M, Mihashi T, Fujikado T, Tano Y (2009) Higher-order aberrations due to the posterior corneal surface in patients with keratoconus. Invest Ophthalmol Vis Sci 50(6):2660–2665. https://doi.org/10.1177/1050178409346224

21. Iselin KC, Baenninger PB, Bachmann LM, Bochmann F, Thiel MA, Kaufmann C (2020) Changes in higher order aberrations after central corneal regularization: a comparative two-year analysis of a semi-automated topography-guided photorefractive keratectomy combined with corneal cross-linking. Eye Vis 7:10. https://doi.org/10.1186/s40662-020-00179-2

22. Greenstein SA, Fry KL, Hersh MJ, Hersh PS (2012) Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. J Cataract Refrac Surg 38(2):292–302. https://doi.org/10.1016/j.jcrs.2011.08.041

23. Greenstein SA, Fry KL, Bhatt J, Hersh PS (2010) Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refrac Surg 36(12):2105–2114. https://doi.org/10.1016/j.jcrs.2010.06.067

24. Alnawaiseh M, Rosentreter A, Böhm MR, Eveslage M, Eter N, Zumhagen L (2015) Accelerated (18 mW/cm²) corneal collagen cross-linking for progressive keratoconus. Cornea 34(11):1427–1431. https://doi.org/10.1097/ICO.0000000000000578

25. Hashemi H, Mohabbi M, Asgari S (2020) Standard and accelerated corneal cross-linking long-term results: a randomized clinical trial. Eur J Ophthalmol 30(4):650–657. https://doi.org/10.1177/1120672119839927

26. Tian M, Jian W, Zhang X, Sun L, Zhou X (2020) Three-year follow-up of accelerated transepithelial corneal cross-linking for progressive paediatric keratoconus. Br J Ophthalmol 104(11):1608–1612. https://doi.org/10.1136/bjophthalmol-2019-315260

27. Franko Zeitz P, Kohlhaas M (2012) Einfluss der hornhaut-transparenz auf die Qualität von Topografien [Influence of corneal transparency on the quality of topographies]. Klin
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