The effect of corneal crosslinking on the rigidity of the cornea estimated using a modified algorithm for the Schiøtz tonometer

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Purpose: The aim of this study was to test a method for estimating corneal rigidity before and after cross-linking (CXL) using a Schiøtz tonometer. **Methods:** The study was performed in the Kyiv City Clinical Ophthalmological Hospital "Eye Microsurgical Center", Ukraine. This was a prospective, consecutive, randomized, masked, case-by-case, clinical study. Corneal rigidity, indicated by the gradient (G) between lg applied weight and corresponding lg scale reading during Schiøtz tonometry, were obtained by increasing (A-mode) then reducing (D-mode) weights by two operators [A] in keratoconus, post-CXL and control subjects for estimation of (i) interoperator and (ii) intersessional errors, (iii) intergroup differences; [B] before and after CXL. Central corneal thickness CCT was measured by scanning slit pachymetry. ANOVA, *t* tests, linear regression were the statistical tools used. **Results:** Average interoperator difference (ΔG) was –0.120 (SD = ±0.294, 95%CI = –0.175 to –0.066). A significant correlation between ΔG and the mean of each pair of G values was found ($r = -0.196$, $n = 112$, $P = 0.038$). Intersessional differences in mean G values were insignificant ($P > 0.05$). There was a significant correlation between G at first session (X_1) and difference between sessions (ΔG) [Operator 1, $\Delta G = 0.598x_1 - 0.461$, $r = 0.601$, $n = 27$, $P = 0.009$]. Significant intergroup differences in G were found (Operator 1, one-way ANOVA, F = 4.489, $P = 0.014$). The difference (Δ) between the pre-(X_2) and post-CXL treatment G values was significantly associated with the pre-CXL treatment value (Operator 1, $\Delta = 1.970x_2 - 1.622$, $r = 0.642$, $n = 18$, $P = <.001$). G values were correlated with CCT in keratoconus and post-CXL. **Conclusion:** Corneal rigidity (G) estimated using the Schiøtz tonometer can be useful for detecting changes after CXL. However, G values are linked to CCT, can vary from time-to-time and the procedure is operator dependent.

Key words: Cornea, CXL, rigidity, Schiøtz tonometer

Access this article online
Website: www.ijo.in
DOI: 10.4103/ijo.IJO_1820_20
Quick Response Code:

Corneal cross-linking (CXL) improves the biomechanical properties of the ectatic cornea and enhances corneal resistance to deformation.[1-8] The currently available non-invasive clinical instruments for the assessment of corneal deformation are complex and deliver results that can be difficult to interpret.[9-21] Furthermore, the corneal resistance to deformation is related to corneal thickness and viscosity.[14,19,22-26] The use of non-invasive systems for monitoring the cornea after CXL has met with mixed results. Some claim that CXL has a negligible effect on corneal resistance to deformation or any improvement is short-lived.[5-8,15,27] The clinical efficacy of these instruments for monitoring pre- and post-CXL cases is questionable when the cost of purchase and maintenance is considered.

Can a low-tech, inexpensive, contact procedure for assessing corneal resistance to deformation be useful for assessing the cornea after CXL? Friedenwald's procedure for the Schiøtz tonometer was probably the first technique for estimating ocular rigidity in vivo.[28] The Schiøtz tonometer weights (stress) and the corresponding indentation that occurs as indicated by the scale reading (strain) are used to estimate ocular rigidity (Ko, units mmHg/μL). The procedure was useful for evaluating change in Ko over the cornea following LASIK and LASEK.[29,30] A preliminary investigation in our clinic did not reveal any significant differences in Ko between keratoconic, post-CXL and normal corneas. The gradient (G) of the linear relationship between the logarithm of the tonometer weights and logarithm of the corresponding scale readings varied between keratoconic, post-CXL and normal corneas. This gradient is representative of corneal rigidity. Could it be useful for differentiating between keratoconic, post-CXL and normal corneas in a clinical setting? The aim of this study was to answer this question and to determine if the gradient

i. is prone to interoperator error,
ii. varies from session-to-session,
iii. in keratoconus changes after routine CXL treatment,
iv. is affected by central corneal thickness.

Methods

This was a prospective, consecutive, randomized, partially masked, observational study conducted between October 2017 and November 2018 at Kyiv City Clinical Ophthalmological

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Received: 07-Jun-2020 Revision: 13-Oct-2020
Accepted: 24-Jan-2021 Published: 21-May-2021

Cite this article as: Tutchenko L, Patel S, Skovron M, Horak O, Voytsekhivskyy O. The effect of corneal crosslinking on the rigidity of the cornea estimated using a modified algorithm for the Schiøtz tonometer. Indian J Ophthalmol 2021;69:1531-6.

Hospital "Eye Microsurgical Center", Ukraine. The study was approved by the local Ethics Board and followed the tenets of the Declaration of Helsinki. All subjects signed informed consent forms after the aims and procedures of the investigation were fully explained. All subjects gave permissions to use their anonymized data. Data were harvested from three groups, keratoconus, normal subjects (controls) and those that had undergone crosslinking (post-CXL) without complication. The subjects designated as controls were volunteers with no history of contact lens wear and free of any ocular or systemic health disorders known to affect the cornea. The keratoconus and post-CXL subjects consisted of patients attending for routine follow up checks. Measurements were taken from each subject on a consecutive, case-by-case, basis. All subjects underwent a full ophthalmological examination that included slit biomicroscopy, applanation tonometry, and pachymetry.

Description of crosslinking procedure and postoperative management

The patients that underwent crosslinking comprised of individuals ≥15 years of age (range 15–47) with a corrected distance vision worse than 20/20, topographical data consistent with keratoconus, a maximum keratometry (K) value in the range 48.8–58.2D, and thinnest corneal thickness value between 301 μm and 498 μm (mean was 417 ± 60.6 μm). All cases were classified as progressive keratoconus having signs of an increase of ≥1D over last 12 months in at least one of the following: steepest K, or manifest astigmatism or manifest refraction spherical equivalent.

Corneal crosslinking (epi-off, 3.0 mW/cm^2, 30 min) was performed by one surgeon (LT). Topical anesthesia was achieved with proparacaine hydrochloride 0.5% drops. The corneal epithelium was debrided over the central 8 mm zone after soaking with 20% alcohol for 30 sec followed by instillation of riboflavin 0.1%, with 20% dextran onto the cornea every 2 min for a total of 30 min and corneal thickness was monitored by ultrasound pachymetry (AxisII PR Ultrasound A mode & Pachymeter, Quantel Medical). When corneal thickness was 400 μm, or more, the cornea was exposed to UV-A radiation (at a wavelength of near 370 nm and an irradiance of 3.0 mW/cm^2) with continuous instillation of riboflavin 0.1% and 20% dextran on the cornea every 2 min for upto 30 min. If the corneal thickness before irradiation was thinner than 400 μm, the cornea was hydrated with hypotonic riboflavin until the pachymetry measured a minimum of 400 μm. A soft bandage contact lens was placed over the cornea at the end of procedure and remained on the patient's eye until re-epithelization had been completed. Postoperative treatment included drops of levofloxacin, dexamethasone and dexpanthenol gel 5 times a day each with a gradual tapering off and a preservative-free combination of trehalose and hyaluronic acid 3 times a day.

Application of Schiøtz tonometer and measurement of central corneal thickness (CCT)

One, brand new factory calibrated, Schiøtz tonometer (Gulden Ophthalmics Elkins Park, PA) was used during this study. The tonometer was cleaned and sterilized by immersing in 3% hydrogen peroxide for 5 min, rinsing thoroughly with sterile saline, soaking in 70% ethanol for 5 min, rinsing in sterile saline, and dried before use on a subject.

With subject in the supine position, the cornea was anaesthetized with proparacaine hydrochloride 0.5% drops, the Schiøtz tonometer was placed at the center of the cornea and the scale reading was recorded immediately (5.5 g plunger weight). With the tonometer remaining steady on the cornea, the scale readings were recorded after sequentially increasing the plunger weights to 7.5, 10.0, and 15.0 g (ascending mode). The tonometer was removed, the subject was asked to relax, remain in the supine position for 5 min and the tonometer, this time loaded with the 15.0 g plunger weight, was placed back onto the cornea, and scale readings were then recorded as the plunger weight was reduced to 10.0, 7.5, and finally 5.5 g (descending mode). Scale readings were recorded within 5 seconds after placing a weight on the tonometer. The total time for taking a series of readings (ascending or descending) was about 20 s.

CCT was measured with a recently serviced Orbscan II corneal topography system (Bausch & Lomb, Rochester, NY, version 3.2) at an acoustic equivalent correction of 0.92. Pachymetry was performed by one investigator (OV), to avoid any interoperator error and bias, just before measurement with the Schiøtz tonometer. Where applicable, subjects were asked to discontinue wearing any rigid contact lenses for at least three weeks (one week for soft lenses) before assessment of corneal topography and pachymetry.

Interoperator error

After a period of training, two operators (1 and 2) were asked to use the Schiøtz tonometer and obtain results from a randomized group consisting of keratoconus, controls and post-CXL subjects. An operator took measurements from a subject's right eye, then the left after an interval of 5 mins. The whole process on the subject was repeated by the other operator after a break of 15 mins.

Intersessional variation

The operators obtained repeat measurements from the subjects they had checked previously when the subjects returned for routine clinic checks. There was no change in the clinical management during the intervening period. The operators were unaware of the results from the first session at the time of the second.

Effect of corneal crosslinking on Schiøtz tonometer measurements

Each operator was asked to obtain measurements from keratoconus subjects, that s/he had previously checked, after they had undergone CXL. The operators were kept unaware of their previous findings during the postop session.

CCT and Schiøtz tonometer measurements in keratoconus and post-CXL

The CCT measurements obtained the first time the Schiøtz tonometer was used on a subject were recorded for analysis.

Statistical analysis

The data were stored on an Excel spreadsheet (Microsoft, Redmond, WA). After calculating all the G values (the gradient of the linear relationship between the logarithm of the tonometer weights and the logarithm of the corresponding scale readings) the data were analyzed in three stages as follows.

Firstly, to determine the significance of any

i. differences between the mean results obtained in the ascending (A-mode) and descending (D-mode) modes by each operator (paired *t* test),
ii. interoperator differences in mean results (paired *t* test) and according to the method of Bland and Altman,[31]
iii. intersessional variations in mean results (paired *t* test),

iv. differences in mean G results, and age, between keratoconus, normal and post-CXL cases (1-way ANOVA) and change in mean result after CXL (paired t-test).

Secondly, to determine the significance of any association between any change in G

v. after CXL and the corresponding value before CXL (Pearson correlation coefficient [r]),

vi. and the time interval following CXL (Pearson correlation coefficient [r]).

Thirdly, to determine the significance of any association between G and central corneal thickness in keratoconus and post-CXL (Pearson correlation coefficient [r]).

Appropriate non-parametric statistical tests were planned if data sets were not normally distributed (Kolmogorov-Smirnov test of normality). The significance level was set at $P < 0.05$.

Results

The estimates of corneal rigidity (G values) are shown in Tables 1 and 2 and Figs. 1-3.

Typical examples of results are shown in Fig. 1. Linear regression revealed highly significant correlations between the logarithms (lg) of the applied weights (x) and corresponding scale readings (y) as follows:

A-mode, $\lg y = 0.558(\lg x)+0.503$ ($r = 0.989$, $n = 4$, $P = 0.011$).

D-mode, $\lg y = 0.405(\lg x)+0.787$ ($r = 0.991$, $n = 4$, $P = 0.009$).

All G values noted in Tables 1 and 2 and Figs. 1-3 are expressed in units of lg scale reading/lg weight (g).

Interoperator error

Both operators took measurements from 112 eyes of 33 keratoconus (51 eyes of 10 females and 23 males, age range 15–47 years), 10 controls (20 eyes of 5 females and 5 males, age range 20–57 years) and 29 post-CXL (41 eyes of 9 females and 20 males, age range 17-43 years) subjects. The mean (±SD, 95% CI) results for A-and D-modes were for: Operator 1 A = 0.954 (±0.310, 0.897-1.010) D = 0.703(±0.205, 0.665-0.741) and operator 2 A = 0.832(±0.259, 0.784-0.880) D = 0.747(±0.288, 0.694-0.800). Differences between the means obtained in the two modes were significant (operator 1 $t = 5.921$, $P < 0.001$ operator 2 $t = 5.823$, $P < 0.001$). Interoperator differences in the means were significant for the A-mode ($t = 4.112$, $P < .001$) but not for the D-mode ($t = 1.939$, $P = 0.054$). Individual values for the interoperator differences in G values (Δ) are shown as Bland and Altman plots in Fig. 2.

The mean (±SD, 95% CI) interoperator difference (Δ) and limits of agreement (±1.96SD) were, in the A-mode -0.120 (±0.294, -0.175 to -0.066) and 0.576, and in the D-mode -0.06 (±0.300, -0.116 to -0.005) and 0.588. There was a significant correlation between Δ and the corresponding average of each pair of G values (A-mode $P = 0.038$, D-mode $P < 0.001$).

Intersessional error

Operator 1 took repeat measurements from 27 eyes (13 keratoconus and 14 post-CXL eyes of 3 females and 19 males, age range 20-33 years). Operator 2 took repeat measurements from 16 eyes (13 keratoconus and 3 post-CXL eyes of 2 females and 13 males, age range 20-31 years).

Differences in mean G values obtained between one session and the next were not significant $P > 0.05$). Linear regression revealed significant associations between the difference (y) in G between sessions 1 and 2 and the G revealed during session 1 (x). The equations of the least squares regression line linking y with x are:

For operator 1, $y = 0.598x-0.461$ (A-mode $r = 0.601$, $n = 27$, $P = 0.009$). eq. 1

$y = 0.954x-0.633$ (D-mode $r = 0.838$, $n = 27$, $P < 0.001$). eq. 2

For operator 2, $y = 0.815x-0.787$ (A-mode $r = 0.628$, $n = 16$, $P = 0.009$). eq. 3

$y = 0.753x-0.494$ (D-mode $r = 0.728$, $n = 16$, $P < 0.001$). eq. 4

Mean estimates of G in keratoconus, post-CXL and controls

The first Operator took measurements from 59 keratoconus (12 females, 28 males, age range 15–47 years), 41 post-CXL (7 females, 12 males, age range 17–43 years)

Table 1: Corneal rigidity (G) in keratoconus, post-CXL and controls.

	Keratoconus	Control	Post-CXL	*P*
Operator 1 (A)	0.774 (59,0.183,0.727-0.821)	0.892 (20,0.288,0.766-1.018)	0.859 (41,0.314,0.763-0.955)	0.069
Operator 1 (D)	0.667 (59,0.208,0.614-0.720)	0.812 (20,0.238,0.708-0.916)	0.708 (41,0.187,0.651-0.765)	0.014
Operator 2 (A)	0.884 (55,0.302,0.804-0.965)	1.027 (20,0.298,0.896-0.157)	0.981 (45,0.315,0.890-1.073)	0.076
Operator 2 (D)	0.577 (55,0.268,0.505-0.649)	0.552 (20,0.143,0.489-0.615)	0.637 (45,0.207,0.577-0.698)	0.226

Values are in units of lg scale reading/lg plunger weight. Corresponding values for n, ±SD and 95% confidence limits are in parenthesis. (A) = results obtained in ascending mode. (D) = results obtained in the descending mode, P=significance of differences between groups (1-way ANOVA)

Table 2: Pre-and post CXL treatment estimation of corneal rigidity (G).

	Before treatment mean (±SD, 95% CI)	After treatment mean (±SD, 95% CI)	*P*
Operator 1 (n=18) A	0.737 (0.168,0.610 to 0.864)	0.908 (0.427,0.696 to 1.120)	0.064
Operator 1 (n=18) D	0.663 (0.237,0.545 to 0.781)	0.780 (0.163, 0.699 to 0.861)	0.081
Operator 2 (n=20) A	0.811 (0.268,0.786 to 0.936)	1.064 (0.450,0.854 to 1.275)	0.038
Operator 2 (n=20) D	0.732 (0.417,0.537 to 0.927)	0.768 (0.256, 0.648 to 0.888)	0.745

Values are in units of lg scale reading/lg plunger weight. Corresponding values for n, ±SD and 95% confidence limits are in parenthesis. (A)=results obtained in ascending mode. (D) = results obtained in the descending mode, P=significance of differences between results obtained before and after crosslinking (paired t test)

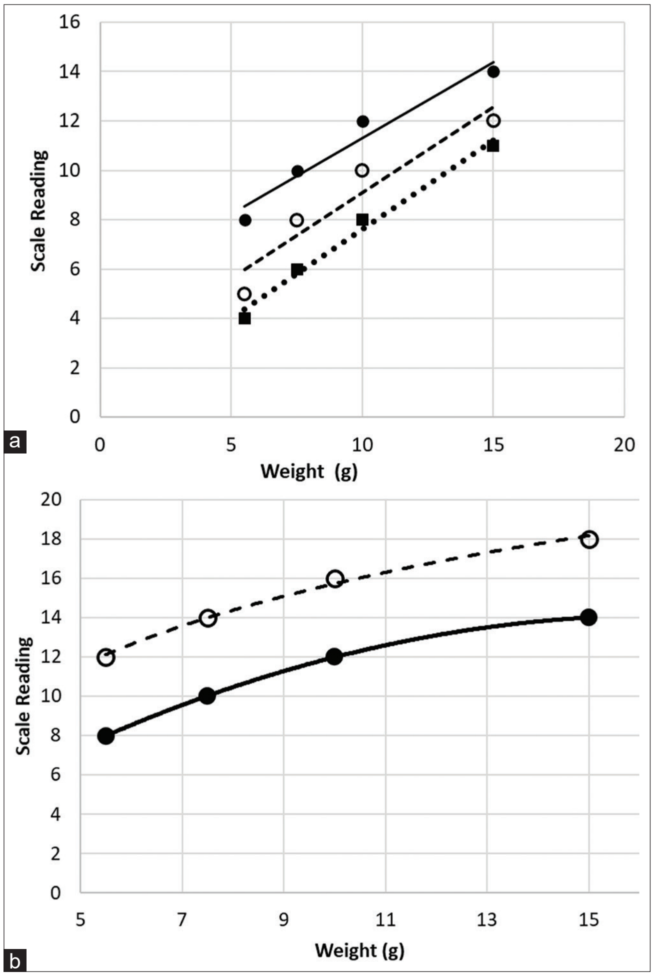

Figure 1:(a) Examples of results obtained in keratoconus (filled circles, solid line), post-CXL (empty circles, broken line) and normal control (filled squares, dotted line). (b) Example of results observed in ascending (filled circles) and descending (empty circles) modes in keratoconus

and 20 control (5 females, 5 males, age range 20-57 years) eyes. The second operator took measurements from 55 keratoconus (9 females, 27 males, age range 15–47 years), 45 post-CXL (10 females, 23 males, age range 17–43 years) and 20 control (5 females, 5 males, age range 20–57 years) eyes.

For results obtained by operator 1. Intergroup differences in age were not significant ($p > 0.05$), but significant intergroup differences in G values were found for results obtained in the D-mode (1-way ANOVA, F = 4.489, $P = 0.014$). Comparing pairs of groups, significant differences were revealed between keratoconus and controls (A-mode $t = 2.137$, $P = 0.036$. D-mode $t = 2.605$, $P = .016$), and post-CXL and controls (A-mode $t = 1.711$, $P = .045$. D-mode $P > 0.05$), but not between keratoconus and post-CXL (A-and D-modes $P > 0.05$).

For results obtained by operator 2. Intergroup differences in age were not significant ($p > 0.05$). Significant differences were revealed between keratoconus and controls (A-mode $t = 2.092$, $P = 0.020$). All other possible comparisons were insignificant ($p > 0.05$).

Change in G value after CXL

Operator 1 took pre-and postop measurements from 18 keratoconus eyes (5 females and 11 males, age range 20-37 years). Operator 2 took pre-and postop measurements from 20 eyes (5 females and 12 males, age range 20-33 years).

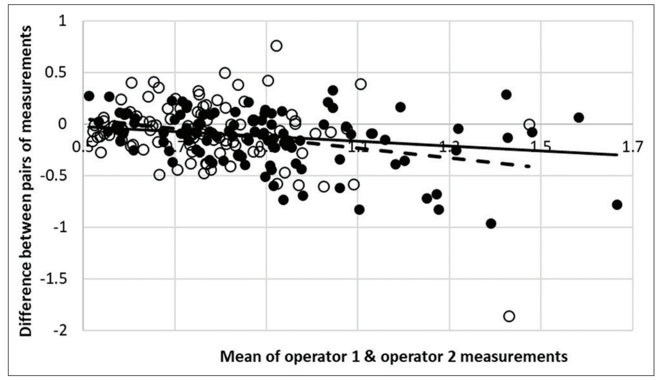

Figure 2: Bland and Altman plots for results obtained by the two operators. The results obtained in ascending (filled circles), descending (empty circles) modes and best fit regression lines shown. Equations of these lines are $y = -0.235x + 0.090$ ($r = 0.196$, $n = 112$, $P = 0.038$, ascending mode, unbroken line) and $y = -0.476x + 0.288$ ($r = -0.309$, $n = 112$, $P < 0.001$ descending mode, broken line)

The change in mean G value after CXL was significant only for the data harvested by operator 2 (A-mode $t = 2.163$, $P = 0.038$). Linear regression revealed some significant associations between the change in G (y = preop – postop values) and preop G (x), and the number of days since CXL procedure was performed (T). The key results are shown in Fig. 3. The equations of the significant least squares regression lines linking y with x or T are:

For operator 1, $y = 1.970x - 1.622$ (A-mode $r = 0.642$, $n = 18$, $P = <.001$). eq. 5

$y = 1.005x - 0.763$ (D-mode $r = 0.826$, $n = 18$, $P < 0.001$). eq. 6

$y = 0.009T - 0.490$ (D-mode $r = 0.675$, $n = 18$, $P = 0.002$). eq. 7

For operator 2, $y = 1.051x - 0.805$ (D-mode $r = 0.864$, $n = 20$, $P = <.001$). eq. 8

All other associations between y, x and T were not significant ($P > 0.05$)

Estimate of G and central corneal thickness (CCT)

Linear regression revealed some significant associations between G (y) and CCT (μm) in keratoconus and post-CXL cases. These were revealed for G values obtained in the A-mode. The equations of the significant least squares regression lines linking y with CCT are:

For operator 1, Keratoconus, $y = 0.001CCT + 0.323$ ($r = 0.335$, $n = 59$, $P = 0.009$). eq. 9

Post-CXL $y = 0.002CCT + 0.203$ ($r = 0.410$, $n = 41$, $P = 0.008$). eq. 10

For operator 2, Keratoconus, $y = 0.002CCT + 0.132$ ($r = 0.373$, $n = 55$, $P = 0.005$). eq. 11

Discussion

The G values in Tables 1 and 2 can be interpreted as either markers of corneal elasticity or corneal rigidity. Traditionally, corneal

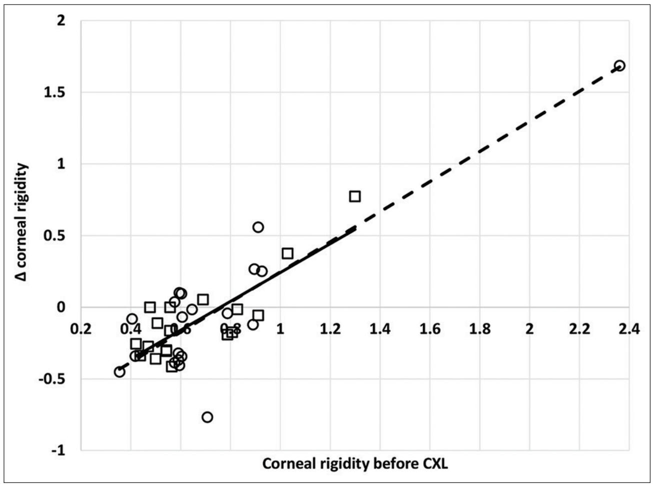

Figure 3: Corneal rigidity before (x-axis) and the change (Δ) observed after cross-linking (CXL). Values are in units of lg scale reading/ lg plunger weight. Results obtained by operator 1 (squares) and 2 (circles) for the descending mode. The associations between the two parameters are represented by, $y = 1.005x - 0.763$ ($r = 0.826$, $n = 18$, $P < 0.001$, operator 1, squares, unbroken line) $y = 1.051x - 0.805$ ($r = 0.864$, $n = 20$, $P = <.001$, operator 2, circles, broken line)

rigidity has been the term to describe of the cornea's resistance to deformation. Hence, the values in the tables and figures are interpreted as indicators of rigidity. Low G values indicate more flexible corneas, high G values indicate more rigid corneas.

The interoperator differences in the estimation of corneal rigidity were significant as shown in Fig. 2. At times, the difference between individual pairs of measurements were small, but these were swamped by the magnitude of the limits of agreement. The results are operator dependant and not interchangeable. The difference between values obtained in the A- and D-modes can be explained as a direct consequence of the viscous nature of the cornea.[32-34] Therefore, the procedure used to obtain the G (A- or D-mode) should be recorded because the values are not readily interchangeable. Significant intersessional differences in the means were not found. This is encouraging but should be interpreted with caution. Eqs 1-4 predict the likely change in G from time-to-time. The predictions can be interpreted as the expected natural fluctuation in G. If the intersessional changes in G were purely random then eqs. 1–4 should insignificant. Could the intersessional reliability of the procedure have been affected by the structural integrity of the Schiøtz tonometer? According to Chronister,[35] a newly calibrated Schiøtz tonometer becomes inaccurate by reason of corrosion after 24 h soaking in 3% hydrogen peroxide or 144 h soaking in 70% isopropyl alcohol. For all the occasions the Schiøtz tonometer was soaked in both 3% hydrogen peroxide and 70% ethanol, the total soak time was no more 6 h. Our device was subjected to far less potential damage and this would have a negligible effect on its' precision.

Table 1 shows the G value in keratoconus was generally lower compared with post-CXL and controls. Following on from a literature search, it would appear this is the first report of a Schiøtz tonometer being used to assess G in post-CXL cases.

For the results obtained in the A-mode, both operators found the mean G value in keratoconus was significantly lower compared to controls, but not when compared to post-CXL. Indenting the cornea is expected to change the area of one corneal surface (either the front or back) relative to the other. If the area of one surface increases relative to the other, then it is reasonable to expect this has come about by the sliding of intracorneal layers against to each other. CXL increases the stiffness of the anterior 200 μm of the cornea and this occurs along the tangential plane of the cornea.[14-16,36-39] Wollensak *et al.* claimed CXL does not affect the cohesive forces between stromal lamellae.[39] Thus, neighbouring lamellae would maintain the facility to slide against each other during corneal indentation, and a change in rigidity by indention should not be detected after CXL. This explains why some investigators found no change in corneal biomechanical properties after CXL.[7,8] However, most *in vivo* studies show that CXL does stiffen the cornea along the sagittal direction.[1-6]

Table 2 shows a significant difference in mean G values was detected between post-CXL and keratoconus in one instance. The variance in the data may have obscured any genuine differences in the remaining comparisons. Fig. 3 shows the change in G depended on its' value prior to CXL. In general, cases where preop G values were below 0.70 improved and those above 0.70 became worse. The bulk of data in Fig. 3 are below the y = 0 abscissa and these represent the cases where G increased, the corneas became stiffer. Eqs. 5, 6 and 8 predict, the lower the preop G value (ie the more flexible the cornea) the greater the likely change that can be expected. And eq. 7 shows the change in G is, to some extent, time dependent. Are the changes noted in Fig. 3 genuinely related to the CXL procedure or are they simply intersessional fluctuations? Compared with eqs 5, 6 and 8, the gradients in eqs. 1-4 are generally lower. Therefore, on a case-by-case basis, the changes shown in Fig. 3 result from the CXL procedure over and above the expected changes due to the intersessional variation.

The significance of the postop time must be viewed with caution because this was found in just one of the four comparisons.

Significant associations between G and corneal thickness (CCT) were found (eqs 9-11) and these confirm both expectations and previous findings.[14,19,22] However, the significant correlations were detected for measurements taken during A-mode but not D-mode. This may be associated with corneal viscosity, but further comment here would be speculative.

Conclusion

Corneal rigidity estimated using the Schiøtz tonometer can be useful for detecting alterations following CXL. However, corneal rigidity is linked to CCT, and can vary from time-to-time, and the procedure is operator dependent.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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