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ORIGINAL ARTICLE

The Effects of Epithelium-off Corneal Collagen Crosslinking on Peripheral Corneal Keratometry, Pachymetry as well as Scheimpflug Imaging Calculated Corneal Indices in Keratoconus

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ABSTRACT

Purpose: To utilize Scheimpflug imaging to describe corneal changes in keratoconic patients undergoing collagen crosslinking.

Study type: Case series.

Study design: Retrospective chart review at two sites: Calgary, Alberta and Brandon, Manitoba, Canada. All patients were diagnosed with keratoconus and had undergone corneal collagen crosslinking. All patients had pre- and post-procedure imaging done with Oculus Pentacam.

Results: Sixty-one eyes of 48 patients with 6 months follow-up and 36 eyes of 27 patients with one year follow-up were included. Average age was 27 ± 12 years (15-48 years). Fifty-one males and 10 females were studied. At 1 year follow-up, all Pentacam indices were found to improve: ISV –4.44 ± 18.6 (p = 0.16), IVA –0.07 ± 0.27 (p = 0.12), KI –0.009 ± 0.082 (p = 0.49), CKI –0.012 ± 0.027 (p = 0.01), IHA –3.87 ± 23.3 (p = 0.33) and IDH –0.062 ± 0.308 (p = 0.24). Keratometry measurements were flatter at the pupil centre by 0.87 ± 2.53 D (p = 0.05). K_{max} and K_{min} were flatter by 0.58 ± 1.37 D (p = 0.02) and 0.33 ± 1.70 D (p = 0.25) respectively. Pupil center pachymetry was thinner by 12.9 ± 21.1 µm (p = 0.0006) at 6 months, as were the corneal apex and thinnest local by 12.9 ± 22.3 µm (p = 0.001) and 21.8 ± 54.6 µm (p = 0.05) respectively. However, all central pachymetry readings were not statistically different from baseline at the one year measurements. Peripheral corneal measurements at 6 mm diameter were no different from baseline at 6 months, however, were significantly thicker at the 1 year follow-up.

Conclusion: The data, in this study, points to a more uniform cornea post corneal collagen crosslinking. The inferior cornea becomes flatter and superior cornea steeper with less variation when comparing the corneal curvatures. The peripheral cornea becomes thicker at 1 year post-procedure. Collagen crosslinking stabilizes the cornea.

Keywords: Corneal collagen crosslinking, Keratoconus, Ectasia, Corneal thickness, Pachymetry, Keratometry, Scheimpflug imaging, Oculus pentacam.

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INTRODUCTION

Corneal collagen crosslinking is a procedure that was initially investigated in Europe in 1998, for the treatment of ectatic corneal disease. Diseases, such as keratoconus or post-LASIK ectasia, in which there is a progressive thinning of the cornea are amenable to treatment using corneal collagen crosslinking. The procedure utilizes ultraviolet A irradiation (UVA irradiation), along with photosensitizing agent to induce a responsive change in keratocyte apoptosis along with an improvement in collagen fiber interweave of the anterior corneal stroma. Further, there has been an observed increase of stromal collagen fiber diameters in traditional crosslinking procedures, with a normalization of collagen fiber diameter in transepithelial crosslinking.[1] Crosslinking results in an increased rigidity and stability of the cornea.[2] The photosensitizing agent is riboflavin or vitamin B2, and there is an approximately 300% increase in biochemical rigidity of the cornea. The maximal effect is observed in the anterior 300 microns of the cornea.[2-5]

The purpose of this study was to utilize Scheimpflug imaging to describe corneal changes in keratoconic patients undergoing collagen crosslinking. In particular, the study aimed to describe peripheral corneal keratometric and pachmetric changes. The Oculus Pentacam (Oculus, Wetzlar, Germany) was used to analyze patients in this study as it has been demonstrated to be a reliable instrument in corneal imaging.[6-10]

Table 1: Description of the different Pentacam indices recorded[20]

Index of surface variance (ISV)	Gives the deviation of individual corneal radii from mean values. Raised in all types of corneal irregularities
Index of vertical asymmetry (IVA)	Gives degree of symmetry of corneal radii with respect to horizontal meridian as axis of reflection. Increased in astigmatism of oblique axis, keratoconus, PMD
Keratoconus index (KI)	A calculated ratio of peripheral corneal thickness to the thinnest corneal thickness
Central keratoconus index (CKI)	Similar to the keratoconus index but only in the central cornea
Index of height asymmetry (IHA)	Degree of symmetry of height data across horizontal meridian. Analogous to IVA
Index of height decentration (IHD)	Gives degree of decentration of height data in vertical direction. Increased in keratoconus

Table 2: Change from baseline in Pentacam indices at 6 months and 12 months post-crosslinking. Positive is an increasing value, negative represents a decrease in the calculated index

	6 months (n = 61)	*12 months (n = 36)*
ISV	2.47 ± 19.9 (p = 0.29)	–4.44 ± 18.6 (p = 0.16)
IVA	0.01 ± 0.27 (p = 0.70)	–0.07 ± 0.27 (p = 0.12)
KI	–0.01 ± 0.09 (p = 0.48)	–0.009 ± 0.082 (p = 0.49)
CKI	–0.004 ± 0.036 (p = 0.43)	–0.012 ± 0.027 (p = 0.01)
IHA	–6.17 ± 21.2 (p = 0.13)	–3.87 ± 23.3 (p = 0.33)
IDH	–0.002 ± 0.031 (p = 0.56)	–0.062 ± 0.308 (p = 0.24)

Table 3: Change from baseline in anterior keratometry measurements (Diopters). Positive values represent a steepening in curvature whereas negative values indicate flattening

	6 months (n = 61)	*12 months (n = 36)*
K anterior center	–0.22 ± 2.42 (p = 0.57)	–0.87 ± 2.53 (p = 0.05)
K anterior superior 2 mm	–0.22 ± 1.81 (p = 0.47)	0.24 ± 2.29 (p = 0.53)
K anterior inferior 2 mm	–0.36 ± 2.64 (p = 0.40)	–0.65 ± 2.57 (p = 0.14)
K anterior nasal 2 mm	0.63 ± 2.15 (p = 0.08)	0.23 ± 1.94 (p = 0.47)
K anterior temporal 2 mm	–0.60 ± 2.06 (p = 0.08)	–0.38 ± 1.41 (p = 0.11)

METHODS

The study is a case series of two corneal surgeons based in Calgary, Alberta and Brandon, Manitoba, Canada. Ethics approval was obtained through the University of Manitoba in accordance with the Declaration of Helsinki. Procedures were performed between February 2009 and July 2011. Inclusion criteria were pre- and postoperative Scheimpflug analysis, clinical diagnosis of progressive keratoconus, corneal thickness greater than or equal to 400 microns centrally at its thinnest point, and keratometry readings less than or equal to 55 D. Patients were excluded if they had concurrent procedures affecting or modifying topographical measurements purely due to crosslinking, such as with intracorneal ring segments and/or phototherapeutic keratectomy.

The procedure was performed as originally described by Wollensak in 2003.[11] In brief, a 7 mm central corneal epithelial debridement was performed with an Amoils epithelial brush (Innovative Excimer Solutions Inc., Toronto, ON) and riboflavin 0.1% solution was applied every 2 minutes for 30 minutes. The debrided area was then exposed to 370 nm wavelength UVA irradiation for 30 minutes (3 mW/cm^2, total UVA dose of 5.4 J/cm^2) while q^2 min riboflavin instillation continued. Following the procedure, a bandage contact lens was placed and patients were followed up as per standard photorefractive keratectomy (PRK) protocol. Where necessary, hypotonic riboflavin solution was used to ensure a corneal thickness of 400 um prior to the crosslinking procedure. Statistical analysis was performed with a student's t-test.

RESULTS

This study included 61 eyes of 48 patients at 6 months and 36 eyes of 27 patients at one year. Average age was 27 ± 12 years (range 15-48 years; 51 M:10 F). Uncorrected visual acuity improved at one year post-procedure from 0.48 to 0.42 logMAR (0.06 ± 0.19, p = 0.04), with best corrected visual acuity improving from 0.18 to 0.15 logMAR (0.03 ± 0.2, p = 0.4). The safety index (mean preoperative CDVA/mean postoperative CDVA in logMAR) was 1.2.

Oculus Pentacam indices that were included in the study where: index of surface variants (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central keratoconus index (CKI), index of height asymmetry (IHA) and index of height decentration (IHD). There was a decrease in all values at 6 and 12 months with a statistically significant decrease only in the central keratoconus index at 12 months (Table 1).

Anterior keratometry was no different from baseline at 12 months, except for the central cornea which flattened by 0.87 ± 2.53 D (p = 0.05) (Table 2). The K_{max}, or steep meridian of the simulated keratometry, was also significantly flatter at 12 months by 0.58 ± 1.37 D (p = 0.02) (Table 3). The peripheral measurements found the inferior and temporal cornea becoming flatter, with the superior and nasal cornea becoming steeper (Table 2). None of these changes were statistically significant at 1 year. The posterior surface curvature (Table 4), was found to be steeper at 12 months; however, only the posterior temporal cornea was significantly steeper by 0.21 ± 0.29 D (p = 0.009).

Corneal thickness at 6 months was significantly thinner in the pericentral region as demonstrated by the pupil centre, apex, thinnest local measurements as well as the pachymetry measurements taken at the 2 mm diameter zone (Tables 5 and 6). At 12 months, these same

Table 4: Change from baseline in simulated keratometry values as calculated by the Pentacam (Diopters). Positive values represent an increase in curvature whereas negative values indicate flattening

	6 months (n = 61)	*12 months (n = 36)*
Mean curvature	–0.38 ± 1.32 (p = 0.09)	–1.57 ± 6.98 (p = 0.19)
K_{max}	–0.41 ± 1.32 (p = 0.06)	–0.58 ± 1.37 (p = 0.02)
K_{min}	–0.32 ± 1.47 (p = 0.19)	–0.33 ± 1.70 (p = 0.25)

central corneal measurements were no longer significantly different from baseline (Table 7). The peripheral cornea at a 6 mm diameter was significantly thicker at 12 months post-procedure by an average of 14.25 ± 3.76 µm (Table 5).

DISCUSSION

Crosslinking is an effective new treatment for ectatic corneal disease, such as keratoconus. The procedure has been proven to stabilize the cornea and halt the progressive nature of the disease. Many studies have even found an improvement in visual acuity and a generalized flattening trend of the central cornea.[4,12-17]

The Pentacam indices are designed and calculated to reflect the variability in the curvature of the anterior surface of the cornea. In our study, all indices improved at the 1 year follow-up, with CKI becoming significantly better. Multiple other studies have confirmed improvement in the indices, with variation as to which particular indices become statistically significant in different studies.[18-20] Ultimately, the indices indicate anterior surface does not worsen at 1 year post-procedure, and in some cases there is improvement.

Keratometric data demonstrates, there was no significant change in the curvatures at 6 months. At 12 months, there was a statistically significant flattening of the central cornea by 0.87 ± 2.53 D (p = 0.05). Specifically, K_{max} became flatter by 0.58 ± 1.37 D (p = 0.02), which is similar to multiple other studies.[12,14,16,17,21-27] The trend is for significant flattening of the central steeper curvature.

Table 5: Change from baseline in posterior surface of the cornea (units of Diopters). Positive values represent a steepening in curvature whereas negative values indicate a flattening

	6 months (n = 61)	*12 months (n = 36)*
K posterior center	–0.09 ± 0.85 (p = 0.52)	0.08 ± 0.76 (p = 0.54)
K posterior superior 2 mm	0.14 ± 0.41 (p = 0.03)	0.1 ± 0.38 (p = 0.12)
K posterior inferior 2 mm	0.1 ± 0.43 (p = 0.17)	0.03 ± 0.53 (p = 0.73)
K posterior nasal 2 mm	0.11 ± 0.30 (p = 0.03)	0.09 ± 0.29 (p = 0.06)
K posterior temporal 2 mm	0.14 ± 0.56 (p = 0.13)	0.21 ± 0.47 (p = 0.009)

Of interest, the peripheral keratometry measurements found the inferior and temporal cornea to become flatter, with superior and nasal cornea becoming steeper. These findings were not statistically significant; however, this points to a remodeling of the anterior surface. No other studies have commented on peripheral corneal curvature changes post-crosslinking. With the inferior cone becoming flatter and the superior cornea becoming steeper there is less variability between the two; this suggests crosslinking leads to a more uniform cornea, by means of a possible 'coupling' effect. This explains the improvement in the calculated indices. Many of the indices directly compare points of the cornea reflect in the horizontal axis. In other words, if there is less difference in elevation between the superior and inferior cornea, the indices will improve. With less variation in the peripheral cornea, there should be less distortion and aberrations.

Changes to the posterior surface of the cornea were small but generally suggested a steepening of the posterior surface. By comparison, Grewal et al found no change in central posterior curvature at one year.[21] Vinciguerra et al assessed the posterior surface using elevation maps and found no significant difference at one year.[15]

Table 6: Change in corneal pachymetry from baseline in micrometers. Positive values represent a thickening of the cornea whereas negative values indicate a thinning of the cornea

	6 months (n = 61)			*12 months (n = 34)*		
	2 mm	*4 mm*	*6 mm*	*2 mm*	*4 mm*	*6 mm*
Superior	–11.1 (p = 0.002)	–3.9 (p = 0.19)	–4.6 (p = 0.45)	–4.9 (p = 0.69)	14.4 (p = 0.003)	18.3 (p = 0.006)
Inferior	–10.7 (p = 0.003)	–6.3 (p = 0.07)	–1.4 (p = 0.81)	1.7 (p = 0.74)	18.6 (p = 0.22)	13.1 (p = 0.01)
Nasal	–10.8 (p = 0.02)	–9.1 (p = 0.01)	–3.1 (p = 0.44)	6.7 (p = 0.16)	8.8 (p = 0.12)	16 (p = 0.001)
Temporal	–10.2 (p = 0.01)	–8.7 (p = 0.02)	–2.7 (p = 0.47)	–0.4 (p = 0.91)	3.9 (p = 0.27)	9.6 (p = 0.004)

Table 7: Change in central corneal pachymetry from baseline in micrometers. Positive values represent a thickening of the cornea whereas negative values indicate a thinning of the cornea

	6 months (n = 61)	*12 months (n = 36)*
Pach pupil center	–12.9 ± 21.1 (p = 0.0006)	2.8 ± 27.3 (p = 0.55)
Pach apex	–12.9 ± 22.3 (p = 0.001)	1.3 ± 29.5 (p = 0.82)
Pach thinnest local	–21.8 ± 54.6 (p = 0.05)	0.2 ± 28.4 (p = 0.97)

The central corneal pachymetry measurements were significantly thinner at 6 months, with a rebound to be similar readings at the one year mark compared to preoperative levels. This finding was in all central readings including pupil centre, apex, and thinnest local pachymetry values and comparable to other studies.[14,15,18,21,28] There appears to be initial thinning, followed by a return to baseline at 1 year. Greenstein et al summarizes multiple factors that could contribute to this phenomenon.[28] Possibilities include epithelial remodeling, anatomic and structural changes of the corneal collagen fibrils,[29,30] alterations in corneal hydration[31] and edema,[32,33] keratocyte apoptosis,[34-36] and changes in glycosaminoglycans.[37]

The centrifugal measurements of corneal thickness reflect the concept that at 6 months follow-up the more central readings are significantly thinner, but interestingly the 6 mm diameter measurements are no different. At one year, the more central readings are no different from baseline, but the 6 mm readings become significantly thicker. Vinciguerra et al recorded the average corneal thickness in a circle at 2, 4, 6 and 8 mm diameter but their findings were contradictory demonstrating significant thinning of the cornea at 2, 4 and 6 mm at the one year mark.[15] The difference may be in the method used; in this study, we used four peripheral corneal points at each diameter, whereas Vinciguerra et al utilized a calculated average corneal thickness over an entire circle at each diameter. Interestingly, Vinciguerra et al had also found significant thinning of the central cornea at one year, whereas this study demonstrated no difference from baseline at one year. There could also be some fundamental difference that is not apparent from analyzing the published data.

This study is limited in its retrospective design; it was not a randomized prospective study with matched controls. Further, in this clinical setting there was a large portion of patients who were not followed to the one year follow-up. Also, imaging with the Pentacam has inter-user and intrauser variability. There is an inherent error with the Pentacam as the reference points are not defined when measuring the cornea.

CONCLUSION

The natural progression of keratoconus is for the cornea to progressively thin. The data in this study reaffirms that the procedure of corneal collagen crosslinking as a stabilizing one. At the one year follow-up, the anterior curvatures were significantly flatter in the central cornea. In this study, peripheral keratometry points to a steepening of the superior cornea while there is a flattening of the inferior cornea. Although not significant, these changes explain the improvements seen in the Pentacam indices. The indices are an average calculation of corneal curvature, often comparing superior to inferior cornea. There appears to be a shifting of the overall shape of the cornea from a typical keratoconic cornea to one that is more uniform; there is not as large a difference between the superior and inferior cornea, suggesting a type of 'coupling' effect. It would be interesting to follow these changes further into the future to see if they become significant.

The thickness measurements also demonstrate a stabilizing effect of cross-linking. This study confirms the apparent paradoxical thinning of the central cornea at 6 months post procedure. It is, however, reassuring that the central cornea rebounds to be no different from baseline at one year post-procedure. Of interest, the peripheral cornea became significantly thicker at one year post procedure. When comparing to one other study that evaluated average peripheral corneal thickness the results appear contradictory. This is perhaps an area for further evaluation and study considering different methods where used to evaluate these peripheral corneal thicknesses.

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