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ORIGINAL RESEARCH

Comparison of Placido disc and Scheimpflug image-derived topography-guided excimer laser surface normalization combined with higher fluence CXL: the Athens Protocol, in progressive keratoconus

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Video abstract

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Background: The purpose of this study was to compare the safety and efficacy of two alternative corneal topography data sources used in topography-guided excimer laser normalization, combined with corneal collagen cross-linking in the management of keratoconus using the Athens protocol, ie, a Placido disc imaging device and a Scheimpflug imaging device.

Methods: A total of 181 consecutive patients with keratoconus who underwent the Athens protocol between 2008 and 2011 were studied preoperatively and at months 1, 3, 6, and 12 postoperatively for visual acuity, keratometry, and anterior surface corneal irregularity indices. Two groups were formed, depending on the primary source used for topoguided photoablation, ie, group A (Placido disc) and group B (Scheimpflug rotating camera). One-year changes in visual acuity, keratometry, and seven anterior surface corneal irregularity indices were studied in each group.

Results: Changes in visual acuity, expressed as the difference between postoperative and preoperative corrected distance visual acuity were +0.12 ± 0.20 (range +0.60 to −0.45) for group A and +0.19 ± 0.20 (range +0.75 to −0.30) for group B. In group A, K1 (flat keratometry) changed from 45.202 ± 3.782 D to 43.022 ± 3.819 D, indicating a flattening of −2.18 D, and K2 (steep keratometry) changed from 48.670 ± 4.066 D to 45.865 ± 4.794 D, indicating a flattening of −2.805 D. In group B, K1 (flat keratometry) changed from 46.213 ± 4.082 D to 43.190 ± 4.398 D, indicating a flattening of −3.023 D, and K2 (steep keratometry) changed from 50.774 ± 5.210 D to 46.380 ± 5.006 D, indicating a flattening of −4.394 D. For group A, the index of surface variance decreased to −5.07% and the index of height decentration to −26.81%. In group B, the index of surface variance decreased to −18.35% and the index of height decentration to −39.03%. These reductions indicate that the corneal surface became less irregular (index of surface variance) and the "cone" flatter and more central (index of height decentration) postoperatively.

Conclusion: Of the two sources of primary corneal data, the Scheimpflug rotating camera (Oculyzer™) for topography-guided normalization treatment with the WaveLight excimer laser platform appeared to provide more statistically significant improvement than the Placido disc topographer (Topolyzer™). Overall, the Athens protocol, aiming both to halt progression of keratoconic ectasia and to improve corneal topometry and refractive status, produced safe and satisfactory refractive, keratometric, and topometric results. The observed changes in visual acuity, along with keratometric flattening and topometric improvement, are suggestive of overall postoperative improvement.

Keywords: Athens protocol, anterior Pentacam indices, keratoconus, cross-linking, WaveLight/Alcon excimer laser, EX500 excimer laser, higher fluence collagen cross-linking

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Introduction

Keratoconus is a degenerative bilateral, progressive, noninflammatory disorder characterized by ectasia, thinning, and irregular topography.[1,2] It is associated with loss of visual acuity particularly in relation to corneal irregularity,[3,4] and usually manifests asymmetrically between two eyes in the same patient.[5,6]

Corneal collagen cross-linking (CXL) using riboflavin and ultraviolet A irradiation is an acceptable treatment option for eyes with progressive keratoconus.[7] Laboratory data suggest that CXL using riboflavin and ultraviolet A irradiation increases stromal collagen fibril diameter, resulting in increased corneal biomechanical strength.[8] Several clinical reports indicate that CXL halts progression of ectasia,[7,9] improves corneal keratometry, refraction and reduces higher-order aberrations. Postoperative complications are infrequent.[7] Our team has introduced several variations and applications of CXL.[10,11]

We have also reported on sequential partial topography-guided photorefractive keratectomy in conjunction with the CXL treatment,[12] which is a promising approach to improve topometric and refractive outcomes,[13] with good long-term stability.[14,15] Furthermore, we have introduced and extensively reported[16–20] the combination of excimer-laser debridement of the top 50 μm of the epithelium, partial topography-guided excimer ablation limited to removal of a maximum of 50 μm stromal tissue, followed in the same session by immediate high-fluence ultraviolet A radiation (5, 6, and 10 mW/cm²) and short-duration (18, 15, and 10 seconds) CXL in a procedure known as the Athens protocol.[21,22] This technique has already been described in detail.[23]

This study compared the efficacy of two alternative corneal topography data sources used in the topography-guided part of this procedure with the WaveLight®/Alcon excimer laser platform (Alcon, Fort Worth, TX, USA), specifically, a Placido disc imaging device and a Scheimpflug imaging device, by analysis of long-term refractive, topometric, and visual rehabilitation changes.

Materials and methods

This study was approved by the ethics committee at our institution, adhered with the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject at the time of intervention using the Athens protocol or at the first clinical visit. The study was conducted in patients visiting our clinical practice before the procedure and attending scheduled post-operative visits.

Patient inclusion criteria

The study group consisted of 181 consecutive patients with keratoconus who underwent the Athens protocol between 2008 and 2011. In all procedures, performed by the same surgeon (AJK), epithelial excimer-laser debridement and topography-guided excimer-laser ablation was performed employing the Alcon/WaveLight 400 Hz Eye-Q laser[24] or the 500 Hz EX500 excimer laser.[25,26]

To be considered for the Athens protocol, the patient had to meet the following criteria: clinical diagnosis of progressive keratoconus, minimum age 18 years, and minimum corneal thickness of 300 μm. Patients with systemic disease, previous corneal surgery, history of chemical injury or delayed epithelial healing, pregnancy, or lactation were not considered for the procedure. All patients included in the study underwent an uneventful Athens protocol using the KXL CXL device (Avedro Inc, Waltham, MA, USA), with higher fluence of 6 mW/cm² for 15 minutes after a five-minute soak in 0.1% riboflavin solution (Avedro) and were able to attend our institution for at least one-year of follow-up monitoring.

The consecutive cases were assigned randomly to receive one or the other treatment. Depending on the imaging source used for topography-guided partial photoablation, the following two groups were formed: group A (n = 54 eyes), in which the primary topography data were provided by the Placido disc imaging device, and group B (n = 127 eyes) in which the primary topography data were provided by a Scheimpflug imaging device.

Imaging and measurement

The diagnostic Placido disc device used was the Alcon/WaveLight Allegro Topolyzer™ (WaveLight AG, Erlangen, Germany). The Topolyzer is a wide-cone corneal topographic Placido system with 22 concentric rings for detection of up to 22,000 elevation points. The Placido ring image is referenced to the corneal apex and locates the pupil center and the limbus. Automatic measuring release ensures that the image centration has a peripheral standard deviation of ±4 μm. The embedded pupil recognition software can measure pupil centroid shift, allowing centration of subsequent laser ablation according to the patient's visual needs. The Athens protocol based on topographic data from the Topolyzer (group A) is thus referred to as Placido disc-guided, or simply as "Placido", in which eight acquisitions averaged for consistency are used for each eye.

The Scheimpflug diagnostic device used was the Alcon/WaveLight Oculyzer™ II. The Oculyzer is a high-resolution Pentacam camera (Oculus Optikgeräte

GmbH, Wetzlar, Germany)[27] which is incorporated into the Alcon/WaveLight Refractive Suite.[25] The integrated rotating Scheimpflug camera acquires up to 50 images in real-time measurement. The Athens protocol was based on data from the Oculyzer (group B), so is referred to as Scheimpflug-guided, or simply "Scheimpflug", in which four acquisitions averaged for consistency are used for each eye.

Postoperative follow-up assessment was performed by subjective refraction, best spectacle-corrected distance visual acuity measurement with this refraction, and slit-lamp biomicroscopy, as well as anterior segment optical coherence tomography imaging for clinical signs of corneal CXL.[15]

Anterior surface topographic indices

To measure and monitor topographic changes in keratometric refraction and topographic geometry, quantitative postoperative assessment (measured preoperatively and at months 1, 3, 6, and 12 postoperatively) was performed using the Oculyzer II, obtained and processed via the Oculyzer examination software (Version 1.17 release 47). For each eye, four consecutive measurements were obtained and processed to test for data repeatability (including topographic, tomographic, and pachymetric mapping).[21]

To this end, in addition to keratometric measurements, specific anterior surface indices were studied when used in conjunction with Pentacam camera analysis, developed for grading and classification based on the Amsler–Krumeich stages of keratoconus,[29] as well as the postoperative assessment.[30–36]

These indices include the following: index of surface variance (ISV), an expression of corneal surface curvature irregularity; the index of vertical asymmetry, a measure of the difference between superior and inferior corneal curvature; the keratoconus index; the central keratoconus index; the index of height asymmetry, a measurement similar to the index of vertical asymmetry but based on corneal elevation; the index of height decentration (IHD), calculated with Fourier analysis of corneal height to quantify the degree of vertical decentration; and the minimum radius of curvature, a measurement of the smallest radius of curvature of the cornea (ie, the maximum corneal steepness).[37] In the present work, 12-month postoperative data were compared with the respective preoperative data.

Linear regression analysis was done to seek possible correlations between changes in these indices and visual rehabilitation. Descriptive and comparative statistics, analysis of variance between keratoconus stage subgroups, and linear regression were performed with statistics tools provided by Minitab version 1.6.1 (MiniTab Ltd, Coventry, UK) and Origin Lab version 9 (OriginLab Corp, Northampton, MA, USA). Paired analysis P values < 0.05 were considered to be statistically significant.

Results

The mean ± standard deviation subject age in group A at the time of the Athens protocol was 31.5 ± 7.9 (19–57) years and for group B was 33.3 ± 7.3 (21–57) years. Group A included 16 women and 38 men and group B included 42 women and 85 men. There was a preponderance of males, which is consistent with our clinical experience[15] and keratoconus incidence studies.[38] In group A, 25 eyes were right (OD) and 29 left (OS), while in group B, 69 eyes were right (OD) and 58 were left.

Changes in visual acuity

Mean preoperative corrected distance visual acuity in group A was 0.65 ± 0.23 (1.00–0.10) and for group B was 0.63 ± 0.24 (1.00–0.10, Table 1). Changes in visual acuity, expressed as the difference between postoperative and preoperative corrected distance visual acuity, for group A were +0.12 ± 0.20 (+0.60 to −0.45) and for group B were +0.19 ± 0.20 (+0.75 to −0.30).

Figure 1 shows the above data in the form of box plots, showing median and mean values with 95% confidence

Table 1 Preoperative, 12-month postoperative, and change (gain/loss) in best spectacle-corrected distance visual acuity data, expressed as the difference between postoperative and preoperative corrected distance visual acuity

	Preoperative		Postoperative		Change (gain/loss)	
	Group A (Placido)	Group B (Scheimpflug)	Group A (Placido)	Group B (Scheimpflug)	Group A (Placido)	Group B (Scheimpflug)
Mean	0.65	0.63	0.77	0.82	0.12	0.19
Standard deviation	±0.23	±0.24	±0.19	±0.19	±0.20	±0.20
Maximum	1.00	1.00	1.10	1.20	0.60	0.75
Minimum	0.01	0.01	0.30	0.30	0.45	0.30
Shapiro–Wilk normality test P value	>0.100	0.049	>0.100	<0.010	>0.100	0.054

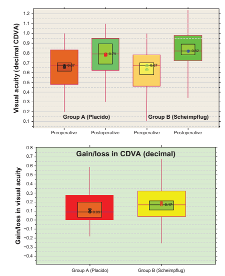

Figure 1 Box plots of corrected distance visual acuity, expressed as decimals. Top, preoperative and postoperative values for both groups. Bottom, gain/loss expressed as difference between postoperative minus preoperative corrected distance visual acuity.
Notes: Box plots are showing median level indicated by ⊞, average symbol ⊡, 95% median confidence range box (black borderline boxes), and interquartile intervals range box (red borderline boxes).
Abbreviation: CDVA, corrected distance visual acuity.

intervals and interquartile ranges. As shown in Figure 1B, the 95% median confidence interval indicates that 95% of eyes in each group had a positive change (stable or better) in visual acuity.

Distribution of keratometric and topographic indices

Average, standard deviation, maximum, and minimum anterior and posterior corneal surface keratometric and topometric indices, as measured preoperatively and 12 months postoperatively in the 8 mm zone, are presented for both groups in Table 2. Box plots of changes (preoperative versus postoperative values) induced for anterior K1 flat (top) and steep K2 (bottom) keratometry (in diopters, D) for groups A and B are shown in Figure 2A and B, respectively. The changes induced for the anterior surface indices are reported for the two groups in Table 3.

Anterior surface keratometry showed the following main changes (defined as mean postoperative versus respective preoperative values from the data in Table 2). In group A, K1 (flat) changed from 45.202 ± 3.782 D to 43.022 ± 3.819 D, indicating a change of −2.18 D, and K2 (steep) changed from 48.670 ± 4.066 D to 45.865 ± 4.794 D, indicating a change of −2.805 D. In group B, K1 (flat) changed from 46.213 ± 4.082 D to 43.190 ± 4.398 D, indicating a change of −3.023 D, and K2 (steep) changed from 50.774 ± 5.210 D to 46.380 ± 5.006 D, indicating a change of −4.394 D.

Correlation between anterior surface topographic index and stages of keratoconus

All eyes in each group were classified preoperatively according to the Amsler–Krumeich keratoconus severity index (nil, KC1, KC1–2, KC2, KC2–3, KC3, KC3–4, and KC4) using the Oculus software. We sought correlations between all of the seven anterior surface topographic images with the above grading stages. The correlation between the derived keratoconus severity index and the seven anterior surface topographic indices is shown as box plots in Figure 3. The best correlates with the keratoconus stage classification were the index of surface variance (with the exception of the highest stage, KC4, all other P values < 0.001, as seen in Table 4) and index of height decentration (with the exception of the lowest stage, KC1, all other P values < 0.001).

We also conducted an index repeatability measurement study, and expressed the measured repeatability as the relative percentage change between four consecutive measurements from the same eye (lower values indicating better repeatability). The results indicate that the indices of surface variance and height decentration were among the best performers, having an average repeatability of 2.77% ± 1.32% for index of surface variance and 4.67% ± 1.62% for index of height decentration index.

Postoperative changes in anterior surface topographic index

Based on the abovementioned results, we followed these two indices, ie, index of surface variance and index of height decentration, as reliable indicators of anterior surface changes induced by the Athens protocol. By their respective definitions, a change towards a lower value (negative change) is indicative of a more regular and more normal corneal keratometry and topography.[31]

The changes induced by the Athens protocol, expressed as the difference between the 12-month postoperative values minus the respective preoperative values are shown in Figure 4 (changes in index of surface variance) and in Figure 5 (changes in index of height decentration). Relative changes in indices of surface variance and height

Table 2 Anterior and posterior corneal keratometry and topometric indices, as measured in the 8 mm zone for both groups, preoperatively and 12 months postoperatively

	Preoperative			Postoperative		
	Mean ± SD	Max	Min	Mean ± SD	Max	Min
Group A (Placido)						
Anterior surface						
K1 flat, D	45.20 ± 3.78	52.1	33.7	43.02 ± 3.82	52.6	31.8
K2 steep, D	48.67 ± 4.07	59.2	42.1	45.86 ± 4.79	59.8	34.6
Km mean, D	46.88 ± 3.60	54.6	41.3	44.37 ± 4.14	54.5	33.1
Posterior surface						
K1 flat, D	−6.44 ± 0.78	−4.6	−8.0	−6.39 ± 0.86	−4.8	−8.5
K2 steep, D	−7.28 ± 0.84	−5.9	−9.4	−7.40 ± 0.91	−5.8	−10.1
Km mean, D	−6.82 ± 0.74	−5.5	−8.6	−6.85 ± 0.82	−5.6	−9.2
Anterior surface indices (in 8 mm zone)						
ISV	91.33 ± 42.59	187	14	86.70 ± 43.91	190	14
IVA	1.06 ± 0.54	2.52	0.09	1.00 ± 0.59	2.69	0.13
KI	1.25 ± 0.15	1.72	1.02	1.21 ± 0.17	1.66	0.93
CKI	1.05 ± 0.05	1.30	0.98	1.04 ± 0.06	1.16	0.86
IHA	26.19 ± 19.80	84	0.60	22.20 ± 18.37	75.1	3.3
IHD	0.087 ± 0.051	0.201	0.007	0.064 ± 0.043	0.163	0.005
Rmin (mm)	6.35 ± 0.70	7.73	5.03	6.69 ± 0.71	7.93	4.96
Group B (Scheimpflug)						
Anterior surface						
K1 flat, D	46.21 ± 4.08	60.7	37.6	43.19 ± 4.40	55.3	30.5
K2 steep, D	50.77 ± 5.21	71.7	42.6	46.38 ± 5.01	59.5	35.7
Km mean, D	48.36 ± 4.44	65.7	40.7	44.71 ± 4.58	57.3	32.9
Posterior surface						
K1 flat, D	−6.58 ± 0.83	−4.6	−9.0	−6.52 ± 0.96	−3.3	−9.8
K2 steep, D	−7.66 ± 1.08	−5.8	−10.9	−7.68 ± 1.13	−5.6	−11
Km mean, D	−7.07 ± 0.90	−5.1	−9.8	−7.04 ± 0.98	−4.6	−10.3
Anterior surface indices (in 8 mm zone)						
ISV	98.14 ± 45.32	208	18	80.13 ± 35.98	169	15
IVA	1.05 ± 0.51	2.45	0.17	0.87 ± 0.46	2.42	0.1
KI	1.27 ± 0.16	1.80	0.97	1.19 ± 0.15	1.56	0.86
CKI	1.05 ± 0.06	1.30	0.90	1.02 ± 0.05	1.16	0.87
IHA	30.95 ± 20.88	88.7	0.3	23.80 ± 17.36	96.3	0.1
IHD	0.09 ± 0.05	0.26	0.01	0.06 ± 0.03	0.172	0.001
Rmin (mm)	6.07 ± 0.79	7.61	4.20	6.65 ± 0.66	7.88	5.12

Abbreviations: ISV, index of surface variance; IVA, index of vertical asymmetry; KI, keratoconus index; CKI, central keratoconus index; IHA, index of height asymmetry; IHD, index of height decentration; Rmin, smallest sagittal curvature; SD, standard deviation; D, diopter K1, flat keratometry; K2, steep keratometry; Km, median keratometry.

decentration (defined as percentage change in the parameter with regard to respective preoperative value) are shown in Table 3. In group A, the index of surface variance was reduced to −5.07% and the index of height decentration to −26.81%; in group B, the index of surface variance was reduced to −18.35% and the index of height decentration to −39.03%, respectively. This negative change is indicative of the corneal surface becoming less irregular (index of surface variance) and the "cone" becoming more central (index of height decentration) at the postoperative assessment.

Placido disc versus Scheimpflug camera imaging for topoguided ablation

The above data, ie, changes in visual acuity, keratometry, and anterior surface topometric indices, indicate that there was a difference in outcomes when comparing group A (Placido disc) and group B (Scheimpflug camera).

To expand our investigation further, we formed two subgroups within each group, based on preoperative index of height decentration. The distinction was made by arbitrarily defining this as "low" if IHD ≤ 0.09, referring to a more centered keratoconus cone, and "high" if IHD > 0.09, referring to a more decentered cone. The following subgroups were formed: group A1 (Placido low, n = 30 eyes), group A2 (Placido high, n = 24 eyes), group B1 (Scheimpflug low, n = 65 eyes), and group B2 (Scheimpflug high, n = 64 eyes). We then investigated the changes induced by the Athens protocol in index of height decentration within each subgroup. For group A1, the relative percentage change in index of surface variance was −4.61% and in index of height decentration was −22.10%; for group A2,

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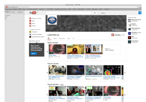

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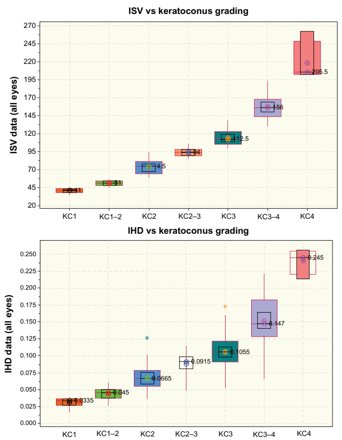

Figure 3 Top, box plot of preoperative ISV, and bottom, preoperative IHD versus keratoconus grading, as produced by the Oculyzer software.
Notes: Median level is indicated by ⊗, average by ⊕, the 95% median confidence range box by the lack borderline, and the interquartile intervals range box by the red borderline.
Abbreviations: IHD, index of height decentration; ISV, index of surface variance.

evaluating keratoconus and the results of treatment has been anterior surface topometry and topography.[42]

It is known that CXL alone results in a change in corneal pachymetry, which may not be accurately depicted by Scheimpflug imaging because of the procedure used, ie, densitometry. In addition, the partial photoablation aspect of the Athens protocol reduces corneal thickness, so any classification scheme which includes corneal pachymetry may be insufficient for postoperative assessment. Particularly after treatment (eg, with CXL), changes in the anterior surface may provide a more pertinent reflection of changes induced by the procedure.[43,44]

Our clinical observation, which is also confirmed by other researchers,[45] has been that postoperatively, the short-term (particularly during the first 6 months) refractive, topometric, and pachymetric results[46] can be described as being "in continuous change", with progressive improvement towards the one-year assessment, and possibly further on. Because of this, we chose to select and analyze the one-year interval results as a common reference to what we subsequently refer to as "postoperative" data. In this study, we evaluated the one-year postoperative changes in visual acuity, keratometry, and seven anterior surface topographic indices induced by

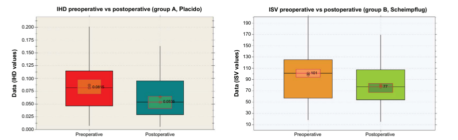

Figure 5 Box plot describing changes (preoperative versus postoperative values) induced for IHD for the two groups: top, group A, Placido; bottom, group B, Scheimpflug.
Notes: ⊗, median level; ⊕, average; red borderline, 95% median confidence range box; black borderline, interquartile intervals range box.
Abbreviations: IHD, the index of height decentration; ISV, index of surface variance.

postoperative changes in CXL using the topometric indices of surface variance and height decentration may prove very helpful in clinical practice.

Our study indicates that the outcomes of the Athens protocol used for keratoconus stabilization and visual rehabilitation appear to be better when using Scheimpflug-driven topography data. Based on our analysis, group B, for which primary topographic data were provided by the Oculyzer II, a Scheimpflug rotating camera, when compared with group A, the primary topographic data for which were provided by the Vario Topolyzer, a Placido topographer, showed a greater reduction in keratometry, as well as the two anterior surface

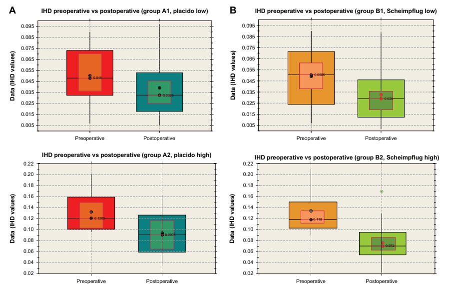

Figure 6 (**A**) Box plot describing preoperative versus postoperative changes in IHD induced for the subgroups. Top, group A1 (Placido low) indicating less affected keratoconic eyes; bottom, group A2 (Placido high) indicating more affected keratoconic eyes. (**B**) Box plot describing preoperative versus postoperative changes in IHD induced for the subgroups. Top, group B1 (Scheimpflug low) indicating less affected keratoconic eyes; bottom, group B2 (Scheimpflug high) indicating more affected keratoconic eyes.
Notes: ⊗, median level; ⊕, average; red borderline, 95% median confidence range box; black borderline, interquartile intervals range box.
Abbreviation: IHD, index of height decentration.

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ORIGINAL RESEARCH

Introduction of quantitative and qualitative cornea optical coherence tomography findings induced by collagen cross-linking for keratoconus: a novel effect measurement benchmark

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Purpose: To introduce a novel, noninvasive technique to determine the depth and extent of anterior corneal stroma changes induced by collagen cross-linking (CXL) using quantitative analysis of high-resolution anterior-segment optical coherence tomography (OCT) post-operative images.
Setting: Private clinical ophthalmology practice.
Patients and methods: Two groups of corneal cross-sectional images obtained with the OptoVue RTVue anterior-segment OCT system were studied: group A (control) consisted of unoperated, healthy corneas, with the exception of possible refractive errors. The second group consisted of keratoconic corneas with CXL that were previously operated on. The two groups were investigated for possible quantitative evidence of changes induced by the CXL, and specifically, the depth, horizontal extent, as well as the cross-sectional area of intrastromal hyper-reflective areas (defined in our study as the area consisting of pixels with luminosity greater than the mean +2 × standard deviation of the entire stromal cross section) within the corneal stroma.
Results: In all images of the second group (keratoconus patients treated with CXL) there was evidence of intrastromal hyper-reflective areas. The hyper-reflective areas ranged from 0.2% to 8.8% of the cross-sectional area (mean ± standard deviation; 3.46% ± 1.92%). The extent of the horizontal hyper-reflective area ranged from 4.42% to 99.2% (56.2% ± 23.35%) of the cornea image, while the axial extent (the vertical extent in the image) ranged from 40.00% to 86.67% (70.98% ± 7.85%). There was significant statistical difference ($P < 0.02$) in these values compared to the control group, in which, by application of the same criteria, the same hyper-reflective area (owing to signal noise) ranged from 0.00% to 2.51% (0.74% ± 0.63%).
Conclusion: Herein, we introduce a novel, noninvasive, quantitative technique utilizing anterior segment OCT images to quantitatively assess the depth and cross-sectional area of CXL in the corneal stroma based on digital image analysis. Mean cross-sectional area showing evidence of CXL was 3.46% ± 1.92% of a 6 mm long segment.
Keywords: Collagen cross-linking, keratoconus, optical coherence tomography, higher fluence cross-linking, cornea ectasia, Athens Protocol

Video abstract

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Introduction

Keratoconus (KCN) is a degenerative bilateral, progressive, noninflammatory disorder characterized by ectasia, thinning, and increased curvature of the cornea, and is associated with loss of visual acuity, particularly in relation to high-order aberrations.[1–4]

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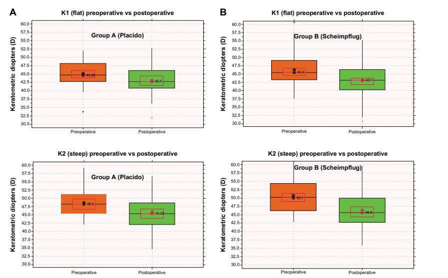

Figure 2 (**A**) Box plot describing induced changes (preoperative versus postoperative values) for anterior flat (top) and steep (bottom) keratometry (in diopters, D) for group A (Placido). (**B**) Box plot describing induced changes (preoperative versus postoperative values) for anterior flat (top) and steep (bottom) keratometry (in diopters, D) for group B (Scheimpflug).
Notes: Median level is indicated by ⊗, average by ⊕, the 95% median confidence range box by the red borderline, and the interquartile intervals range box by the black borderline.

the relative percentage change in index of surface variance was –5.35% and in index of height decentration was –29.05%. For group B1, the relative percentage change in index of surface variance was –13.54% and in index of height decentration was –32.82%; for group B2, the relative percentage change in index of surface variance was –20.36% and in index of height decentration was –41.19%. The results are presented in the form of box plots in Figure 6, and are tabulated in Table 5.

Discussion

The options available to clinical investigators for clinical assessment and evaluation of keratoconus and monitoring of induced postoperative improvement due to CXL procedures include a multitude of diagnostic devices. Corneal pachymetry[39,40] and analysis of cornea biomechanical properties[41] can also be very significant in the keratoconus assessment, although the long-standing standard for

Table 3 Changes induced in seven anterior surface indices for the two groups

	ISV	IVA(mm)	KI	CKI	IHA(μm)	IHD(μm)	Rmin (mm)
Group A (Placido)							
Relative change	–5.07%	–5.65%	–3.20%	–1.42%	–15.24%	–26.81%	2.18%
Mean change	–4.630	–0.060	–0.040	–0.015	–3.991	–0.023	0.139
SD	±16.617	±0.225	±0.066	±0.055	±21.003	±0.027	±0.263
Maximum	29	0.45	0.07	0.06	40.6	0.023	1.31
Minimum	–50	–0.74	–0.23	–0.27	–57.5	–0.102	–0.28
Group B (Scheimpflug)							
Relative change	–18.36%	–16.64%	–6.24%	–3.24%	–23.10%	–39.03%	9.64%
Mean change	–18.016	–0.175	–0.079	–0.034	–7.150	–0.035	0.585
SD	±20.687	±0.253	±0.073	±0.042	±17.087	±0.036	±0.409
Maximum	38	0.42	0.08	0.06	37.7	0.017	1.93
Minimum	–83	–0.95	–0.43	–0.22	–65.1	–0.213	–0.22

Notes: Average change is defined as the postoperative value minus the preoperative value. Relative change is defined as the percentage mean change in each parameter with regard to the respective preoperative value.
Abbreviations: ISV, index of surface variance; IVA, index of vertical asymmetry; KI, keratoconus index; CKI, central keratoconus index; IHA, index of height asymmetry; IHD, index of height decentration; Rmin, smallest sagittal curvature; SD, standard deviation.

Table 4 Two-sample *t*-test results, not assuming equal variance, between the keratoconus grading subgroups (KC1, KC1–2, KC2, KC2–3, KC3, KC3–4, and KC4) for the topometric indices of ISV and IHD as measured preoperatively

	Estimate for difference	95% CI for difference	*P* value
ISV			
K1 versus K1–2	10.31	(7.35, 13.27)	<0.001
K1–2 versus K2	21.84	(17.87, 25.82)	<0.001
K2 versus K2–3	21.02	(17.02, 25.03)	<0.001
K2–3 versus K3	20.3	(16.88, 23.72)	<0.001
K3 versus K3–4	43.7	(37.79, 49.62)	<0.001
K3–4 versus K4	61	(14.1, 107.8)	0.026
IHD			
K1 versus K1–2	0.01255	(0.00474, 0.02035)	0.003
K1–2 versus K2	0.02411	(0.01522, 0.03300)	<0.001
K2 versus K2–3	0.02012	(0.01038, 0.02985)	<0.001
K2–3 versus K3	0.01856	(0.00836, 0.02876)	0.001
K3 versus K3–4	0.04487	(0.03165, 0.05808)	<0.001
K3–4 versus K4	0.0888	(0.0610, 0.1166)	<0.001

Abbreviations: ISV index of surface variance; IHD, index of height decentration; CI, confidence interval.

the Athens protocol, and investigated for associations with visual acuity outcomes.

Our results indicate that the minimum radius of curvature, defined as the inverse of corneal steepness, was increased postoperatively in agreement with the decrease in anterior surface keratometry[47,48] (Table 2). As such, the improved one-year improvement observed for corrected distance visual acuity (Table 1 and Figure 1) can be justified, because the anterior corneal surface attains a more optically manageable refractive shape. The values of all other six topographic indices were reduced in comparison with the respective preoperative values, indicating corneal surface improvement. The postoperative reduction noted in some of these indices has been reported only recently.[31] These changes are all indicative of improved corneal topography (ie, reduction of irregularity, cone becoming less steep and more central) in agreement with other studies.[31,41] Therefore, it appears that quantitative assessment of

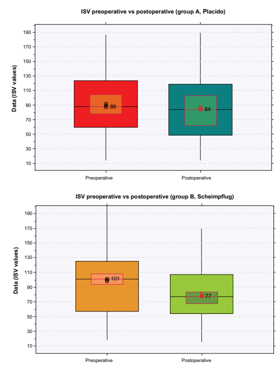

Figure 4 Box plot describing changes (preoperative versus postoperative values) induced for ISV in the two groups: top, group A, Placido; bottom, group B, Scheimpflug.
Notes: ⊗, median level; ⊕, average; red borderline, 95% median confidence range box; black borderline, interquartile intervals range box.
Abbreviation: ISV, index of surface variance.

Table 5 Changes in ISV and IHD induced in the four subgroups

	ISV	IHD
Group A1 (Placido low)		
Relative	–4.61%	–22.10%
Mean	–2.900	–0.011
SD	±17.010	±0.020
Maximum	29	0.023
Minimum	–50	–0.054
Group A2 (Placido high)		
Relative	–5.35%	–29.05%
Mean	–6.792	–0.038
SD	±16.208	±0.026
Maximum	23	0.013
Minimum	–36	–0.102
Group B1 (Scheimpflug low)		
Relative	–13.54%	–32.82%
Mean	–8.908	–0.016
SD	±18.339	±0.020
Maximum	38	0.014
Minimum	–48	–0.074
Group B2 (Scheimpflug high)		
Relative	–20.36%	–41.19%
Mean	–26.750	–0.054
SD	±18.968	±0.037
Maximum	13	0.017
Minimum	–83	–0.213

Notes: Mean change is derived from the postoperative minus the preoperative value in each case. Relative change is defined as percentage mean change in the parameter with regard to respective preoperative value.
Abbreviations: ISV, index of surface variance; IHD, index of height decentration; SD, standard deviation.

topographic indices having the strongest correlation with keratoconus grading, ie, the indices of surface variance and height decentration.

This study evaluated a very large number of cases over an extended period of time, when compared with the current peer-reviewed literature. The difference in absolute numbers between group A (Placido disc-guided, 54 cases) and group B (Scheimpflug tomography-guided, 127 cases) is due to early results suggesting that the procedure used in group B demonstrated higher efficacy, leading to discontinuation of recruitment for group A. Although different, these numbers and the duration of follow-up are still quite substantial and permit sensitive statistical analysis and a confident conclusion regarding the differential in postoperative efficacy. This change is more pronounced in the more irregular and more decentrated anterior surfaces preoperatively (subgroups A2 and B2), reaching up to a –41% reduction in index of height decentration for group B2.

The above findings may be explained by the procedures used with the corresponding diagnostic devices. The Placido disc imaging devices, despite providing a single, snapshot measurement, are more suitable for measurements at the peripheral cornea, and have lower reliability for information at the corneal center, in addition to being susceptible to error due to abrupt changes in corneal height. Placido disc imaging cannot clearly differentiate between abrupt flattening and abrupt steepening changes, and simply measures changes in curvature. This potential bias of measurement may be one, or the main, reason for the difference in clinical efficacy seen in our study. On the other hand, the rotating measurement process used by the Scheimpflug imaging camera, despite being sequential, captures images with a fine meshed dot matrix in the center, providing high-resolution data for absolute elevation from the large corneal area imaged. The potential bias here is interference of the eyelid and eyelashes with the image quality, as well as potential bias in thickness measurement attributed to arcus senilis in the peripheral cornea. All Scheimpflug images used in our treatments are carefully screened in order to exclude these potential biases.

Conclusion

Topography-guided normalization of extreme cornea irregularity, such as keratoconus, coupled with higher fluence CXL appears to be achieved with significantly greater efficacy when the Scheimpflug rotating camera (Oculyzer) is used with the WaveLight excimer laser platform. It appears to provide significantly better improvement in refractive, topometric, and visual rehabilitation when compared with Placido disc (Topolyzer) topography-driven normalization and CXL treatments. This Athens protocol, aiming to both halt progression of keratoconic ectasia and improve anterior corneal normality, topometry, and visual performance, demonstrates a good safety record with either platform and very effective refractive, keratometric, and topometric results.

Disclosure

AJK is a consultant for Alcon/Wavelight and Avedro. GA is a consultant for Alcon/Wavelight. The authors report no conflicts of interest in this work.

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Table 1 Hyper-reflective area corresponding to meridional corneal cross section, as measured in the two groups

	Group A (control)		Group B (KCN)	
	Hyper-reflective area (pixels)	Cross-sectional area (%)	Hyper-reflective area (pixels)	Cross-sectional area (%)
Mean	427	0.74%	2018	3.46%
Max	1518	2.50%	4927	8.80%
Min	0	0.00%	121	0.18%
Stdev	374	0.63%	1105	1.92%

Abbreviations: KCN, keratoconus; Max, maximum; Min, minimum; Stdev, standard deviation.

patients, and with previous reports.[2] Of the 94 eyes included in the study, 47 were oculus sinister and 47 were oculus dexter. Mean postoperative time since CXL operation was 17.65 ± 20.83 months, with a range of 1 to 72 months.

Most patients enrolled in the group had bilateral CXL operation, and thus both eyes were included in the study, while in some patients only one eye was included in the study. For some patients, images from more than one visit were included in the study (separated by at least 3 months).

Materials

The OptoVue RTVue (OptoVue Inc, Fremont, CA, USA) AS-OCT system was employed in the study. Using the L-Cam lens, a 6 mm long Hi-Res Cross Line Scan, centered at the pupil center along the vertical meridian, was recorded. The meridional cross-sectional images were processed with the RTVue software (version 5.1.0, processing algorithm A5, 1, 0, 90). The software averages up to 32 successive acquisitions. In our study, we included images consisting of at least five averages.

Our novel investigation technique

All images from both groups were investigated for possible quantitative evidence of changes induced by CXL. Evidence of such was considered as the existence of the intrastromal hyper-reflective demarcation line. To search for such a line, images were loaded into commercially available software, Adobe Photoshop CS5 Version 12.04 (Adobe Systems Inc, San Jose, CA, USA).

For every meridional cross-sectional image, the pixels associated with the stromal cross-section were selected with the marquee tool. The area separated by 10 pixels from the anterior and the exterior corneal surfaces were deselected, as they are typically of higher luminosity (Figure 1). The extent (pixel count) of the selected stromal image area was determined with the histogram tool report. The dialog box for this tool also provides the mean ± standard deviation of the luminosity for the selected area.

The hyper-reflective demarcation area was quantitatively defined in this study as the population of pixels (pixel count) having luminosity greater than the value defines as luminosity mean +2 × standard deviations, as obtained in the previous step.

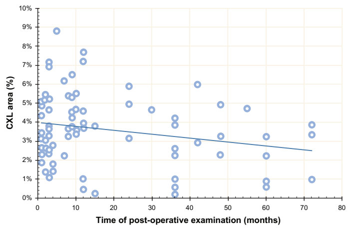

Figure 2 Demarcation line area as a function of time elapsed since the CXL operation.
Note: The trend line shows that over time, this area diminishes.
Abbreviation: CXL, cross-linking.

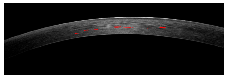

Figure 4 Example of epithelium-on CXL cornea with minimal appearance of the demarcation line.
Note: Of the 61,770 pixels (cornea cross-section), only 443 correspond to a hyper-reflective area.
Abbreviation: CXL, cross-linking.

width extent of the corneal cross-section. As shown in Table 2, on average the extent of the hyper-reflective area (CXL width) was 483.35 ± 200.82 pixels (range, 853–38), corresponding to an average of 56.20% of the cross-section width, ranging from 99.19% to 4.42%. Of the subgroup of 78 corneas with more than a 2.50% hyper-reflective area, the minimum was 12.45%.

Axial extent (depth) of demarcation

The axial extent of demarcation corresponds to what we describe as the depth of the CXL effect. The quantitative assessment is subject to the corneal thickness, which varies significantly among images. In each image studied, the corneal thickness was measured in pixels (vertical line total in Table 2), and was found to correspond to an average of 61.93 ± 8.18 pixels (max to min, 80–38). Considering that 6 mm across the image corresponded to 860 pixels, the 61.93 pixels corneal thickness translates to 432 μm of thickness.

Having measured the corneal thickness of each individual section, the distance in pixels (vertical line CXL) from the anterior corneal surface was measured. On average, it was found to be 43.81 ± 6.96 pixels (range, 65–30), corresponding to 305.6 μm or 70.98% of the total corneal thickness. The over time (postoperative) development of the depth of the area of demarcation, that is CXL area over time, is presented in Figure 3.

Discussion

By examining high-resolution corneal OCT images, we encountered statistically different findings between the treated group (KCN; group B) and the control group (A).

It appears that there is a statistically significant difference between the control group and the KCN group regarding the presence of a demarcation line, as quantitatively measured by the extent of the area of the hyper-reflective demarcation line, indicating a localized change in stromal (treated) density over the underlying (untreated) stroma.

In 72 of 94 cases, the demarcation line area corresponded to more than 2.50% of the total corneal cross-sectional area, with a mean ± standard deviation of 3.46% ± 1.92%. In the entire control group A, by applying the same luminosity criteria, the similar area had a mean of 0.74% ± 0.63%. We believe that these pixel counts represent merely signal noise rather than reflect actual changes in stromal density. Thus, we can ascertain that the demarcation line viewed by OCT can be a good indication of the extent of collagen density changes induced by CXL.

Over time, these density changes become less apparent. The trend line shown in Figure 2 has a negative slope (reduced

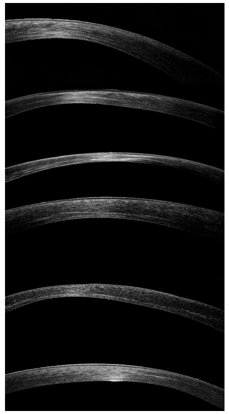

Figure 5 Example of corneal cross-sectional images examined in the study showing various degrees of demarcation line extent.

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ORIGINAL RESEARCH

Long-term safety and efficacy follow-up of prophylactic higher fluence collagen cross-linking in high myopic laser-assisted in situ keratomileusis

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Background: The purpose of this study was to evaluate the safety and efficacy of ultraviolet A irradiation cross-linking on completion for cases of high myopic laser-assisted in situ keratomileusis (LASIK).

Methods: Forty-three consecutive LASIK cases treated with femtosecond laser flap and the WaveLight excimer platform were evaluated perioperatively for uncorrected visual acuity, best corrected spectacle visual acuity, refraction, keratometry, topography, total and flap pachymetry, corneal optical coherence tomography, and endothelial cell count. All eyes at the completion of LASIK had cross-linking through the repositioned flap, with higher fluence (10 mW/cm^2) ultraviolet light of an average 370 μm wavelength and 10 mW/cm^2 fluence applied for 3 minutes following an earlier single instillation of 0.1% riboflavin within the flap interface. Mean follow-up duration was 3.5 (range 1.0–4.5) years.

Results: Mean uncorrected visual acuity changed from 0.2 to 1.2, best corrected spectacle visual acuity from 1.1 to 1.2, spherical equivalent from −7.5 diopters (D) to −0.2 D, keratometry from 44.5 D to 38 D, flap pachymetry from 105 μm to, total pachymetry from 525 to 405, and endothelial cell count from 2750 to 2800. None of the cases developed signs of ectasia or significant regression during follow-up.

Conclusion: Prophylactic collagen cross-linking for high-risk LASIK cases appears to be a safe and effective adjunctive treatment for refractive regression and potential ectasia. This application may be viewed as prophylactic customization of the biomechanical behavior of corneal collagen.

Keywords: prophylactic collagen cross-linking, laser-assisted in situ keratomileusis, high-risk, post-LASIK ectasia

Video abstract

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Introduction

Ectasia is a well recognized and serious complication following laser-assisted in situ keratomileusis (LASIK).[1,2] Several risk factors and preventive measures for ectasia have been identified and investigated.[3–8] A number of treatment modalities have been historically described, and include contact lenses,[9] intracorneal ring segments,[10] conductive keratoplasty,[11] and, more recently, collagen cross-linking.[12–14]

We have introduced the concept of collagen cross-linking in post-LASIK ectasia,[12,13] and have had long experience in utilizing novel cross-linking techniques following progressive keratoconus and ectasia. We have also pioneered the concept of prophylactic cross-linking after LASIK and photorefractive keratectomy, largely as a result of practicing in a patient population that appears to have a high rate of keratoconus. We have discovered that several patients whom

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Corneal collagen cross-linking (CXL) with riboflavin and ultraviolet-A irradiation is a common technique for tissue stabilization.[5,6] Several studies have shown that CXL is an effective intervention to halt the progression of keratoconus and corneal ectasia.[7]

Anterior-segment optical coherence tomography (AS-OCT) is a promising imaging mode providing high-resolution cross-sectional images across a meridian of choices that can be employed in KCN diagnosis.[8,9] The most advanced AS-OCT systems invariably employ Fourier spectral-domain signal processing. As of today, there are a number of different spectral domain OCT systems commercially available.[10,11]

The ability to provide real-time cross sectional mapping, in conjunction with the very principle of operation, namely photon back scattering, provides the understudied application of quantitative assessment of the extent of stromal changes due to CXL.

OCT and CXL demarcation line observations

To date, the efficacy of CXL treatment can be monitored only indirectly by postoperative follow-up observations, such as with a Scheimpflug camera,[12] or with corneal confocal microscopy.[13]

In addition, a corneal stromal demarcation line indicating the transition zone between cross-linked anterior corneal stroma and untreated posterior corneal stroma can be detected in slit-lamp examination as early as 2 weeks after treatment.[14] In our clinical assessment, the presence of this finding over the anterior two-thirds of the stroma confirms that sufficient CXL treatment has occurred.

Following our presentation and the introduction in the peer-reviewed literature of the use of OCT imaging in order to evaluate the CXL-induced demarcation line, OCT has seen some recent interest as a tool for investigating CXL effects, such as corneal thickness before and after CXL for KCN, and demarcation line depth following CXL.[15–22]

The principle lies in the fact that although these lines do not appear to affect vision, as they correspond to changes in stromal density, they appear as brighter (hyper-reflective) areas on cross-sectional corneal OCT scans. However, the depth and extent of stromal changes induced by CXL has been difficult to evaluate quantitatively in the clinic.

The motivation for our study was to advance this aforementioned theory by examining not only the demarcation line depth between the suspected CXL and the deeper cornea with corneal OCT, but also to attempt to quantitatively assess the extent of this area on a large number of patients over a large postoperation interval. Our novel technique is based on digital signal processing on cross-sectional OCT images of corneas, and evaluates quantitatively and, in our opinion, free of examiner bias, the extent of CXL changes in the corneal stroma.

Methods

This prospective interventional case series study received approval by the Ethics Committee of our Institution and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject at the time of the CXL intervention or at the first clinical visit. The study was conducted in our clinical practice on patients during their regular clinical visits (control group) and scheduled postoperative procedure visits (KCN group).

Patient inclusion criteria

The control group (50 patients, 100 eyes) consisted of patients with eyes with unoperated corneas (ie, normal eyes with no ocular pathology other than refractive error). Mean patient age was 35.2 ± 9.1 years (range 19–48), equally divided between males and females. Before OCT corneal mapping, a complete ocular examination and tomographic topography was performed to screen for corneal abnormalities.

The second group (47 patients, 94 eyes) consisted of KCN patients previously operated with CXL by employing the Athens Protocol, which combined same-day phototherapeutic keratectomy epithelial removal and partial topographically-guided photorefractive keratectomy normalization of the cornea ectasia, followed by high-fluence, short-duration riboflavin induced CXL.[21]

The mean patient age in this group was 28.1 ± 7.1 years (range 16–45 years). There is a bias towards males in this group (33 males, 14 females), which is consistent with our clinical experience of the male–female incidence of keratoconic

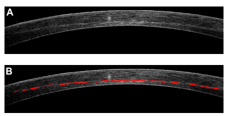

Figure 1 (**A**) Typical cornea cross-sectional meridian image of a patient with KCN. (**B**) The selected hyper-reflective intrastromal area is indicated in red.

Table 2 Horizontal and axial extent of hyper-reflective area in group B (KCN)

	CXL width (pixels)	Horizontal extent	V line total	Axial extent	% V
		Overall width		V line CXL	
Mean	483.35	56.20%	61.93	43.81	70.98%
Max	853	99.19%	80	65	86.67%
Min	38	4.42%	38	30	40.00%
Stdev	200.82	23.35%	8.18	6.96	7.85%

Abbreviations: KCN, keratoconus; CXL, cross-linking; V, vertical; Max, maximum; Min, minimum; Stdev, standard deviation.

Subsequently, after using the histogram tool report again, the extent (pixel count) of the hyper-reflective intrastromal area was recorded, as well as its horizontal extent (pixels across the y axis), and this was compared to the horizontal extent of the captured image, which was set to a standard of 860 pixels across the y-axis.

Similarly, the axial extent (depth of demarcation line) was assessed and compared to the depth of the corneal section (vertical line in the image; that is, pixels in the x-axis) to which it corresponded.

Descriptive statistics (average, minimum, maximum, standard deviation, bias, and range), comparative statistics, and linear regression were performed in Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, USA) and OriginLab version 8 (OriginLab Corp, Northampton, MA, USA). Analysis of variance between groups was performed using the OriginLab statistics tool.

Results

Areal extent (depth and diameter) of demarcation

Cross-sectional meridian area measurements had an average of 59,183 pixels (±5778), ranging from 80,729 to 39,951 (maximum to minimum). This corresponds to an area of 2.88 mm^2. Mean luminosity values were, on a grayscale of 0 to 255, 63 ± 13, ranging from 89 to 25 (maximum to minimum).

As shown in Table 1, the intrastromal hyper-reflective area found with this technique for group A (control) had a mean area of 427.25 ± 373.81 pixels (range, maximum to minimum, 1518-0), corresponding to a mean of 0.74% ± 0.63% (range, 2.50%–0.00%), corresponding to 0.02 mm^2. This contrasts with group B (KCN), in which the mean hyper-reflective area had a mean of 2018.21 ± 1104.70 (range, 4927–121), corresponding to a mean of 3.46% ± 1.92% (range, 8.80%–0.18%), or 0.098 mm^2 of the corneal cross-sectional area. Of the 94 cases examined, 72 had more than 2.50% hyper-reflective areas, whereas six were close to and 16 were below this mark. The two groups were found to be statistically different (comparison of hyper-reflective area pixel count; $P < 0.02$). The over time development of the extent of the area of demarcation; that is, the CXL area over post-operative time, is plotted in Figure 2.

Horizontal extent of demarcation

The horizontal extent of demarcation was assessed for the KCN group and was compared to the standard 860 pixel

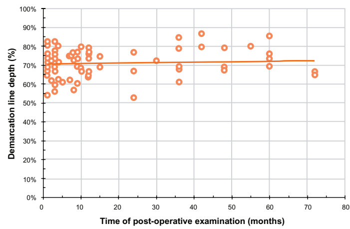

Figure 3 Demarcation line depth as a function of time elapsed since the CXL operation.
Note: The trend line shows that over time this depth remains constant to about two-thirds of the corneal depth.
Abbreviation: CXL, cross-linking.

by 0.02% per month), indicating that the demarcation line area fades away by postoperative month 12, in agreement with our clinical findings.[15]

The depth of the demarcation line, found to be on average of 305 μm, is consistent with the accepted notion that in order to avoid ultraviolet-A irradiation damage to the corneal endothelium,[23] the CXL parameters are set in a way that effective treatment occurs only in the first 300 μm of the corneal stroma.[12]

The depth of the demarcation line appears, on the other hand, to be stable over time, even after 3 years following operation, at approximately 70% of the corneal depth. However, a deeper demarcation line depth (relative to the corneal depth) is associated with thinner corneal thickness, as measured postoperatively. In the selected 12 thinner corneas, the depth of the demarcation line was found to be 83% of the total corneal thickness.

One clinical example of ineffective CXL action is demonstrated in Figure 4, in which a case of a cornea treated in another institution with epithelium-on CXL technique demonstrated minimal signs of hyper-reflective areas.[24] This case, which was not part of the case study, was presented to our practice with progressive ectasia following the CXL operation in another practice. Examples of corneal cross-sectional images examined in the study showing various degrees of demarcation line extent are presented in Figure 5.

Conclusion

AS-OCT appears to demonstrate reproducible early (1 month) and long-term (up to 3 years) CXL cornea findings. The hyper-reflective lines may represent induced cornea density changes or subtle intrastromal cornea scarring. This novel quantitative and qualitative technique may constitute a possible benchmark for a noninvasive measurement to evaluate and titrate the amount, extent, and depth of intrastromal effects of the CXL treatment in KCN and possibly ectasia eyes.

Disclosure

The authors report no conflicts of interest in this work.

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we have treated in the past with LASIK had siblings or close relatives with topographically or tomographically diagnosed keratoconus that we did not know of at the time of the original LASIK procedure. We have also reported on performing in situ intrastromal higher fluence cross-linking in progressive keratoconus and corneal edema facilitated by a femtosecond laser-created intrastromal pocket.[15,16] We used CXL in a prophylactic fashion in this consecutive case series.

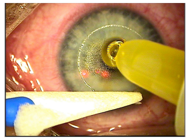

Figure 1 Riboflavin solution applied over the bare stroma without contact with the LASIK flap for 60 seconds.
Abbreviation: LASIK, laser-assisted in situ keratomileusis.

Materials and methods

All patients provided their written informed consent prior to treatment, in agreement with the tenets of the Declaration of Helsinki. These were 23 consecutive LASIK patients with high myopia and/or myopic astigmatism, defined as myopia > −6 diopters (D) of spherical equivalent. All cases had a 110 µm LASIK flap created with the IntraLase FS60 femtosecond laser (Abbott Medical Optics, Irvine, CA) and LASIK ablation using the WaveLight 400 Hz IQ excimer laser (WaveLight, Erlagen, Germany). Perioperatively, we evaluated uncorrected distance visual acuity, corrected distance visual acuity, subjective refraction, keratometry, Placido disc-generated corneal topography (Topolyzer, WaveLight), Scheimpflug-generated corneal topometry (Oculyzer, WaveLight) intraoperative subtraction flap ultrasound pachymetry (Sonogage, Cleveland, OH), corneal optical coherence tomography (Optovue, W Fremont, CA), and preoperative and postoperative endothelial cell counts.

Surgical technique

On completion of the LASIK excimer ablation procedure, a drop of customized 0.1% riboflavin sodium phosphate solution (Leiter's Pharmcy, San Jose, CA) was placed on the bare stromal bed, and left to soak in for 60 seconds. Special care was taken not to allow the riboflavin solution to come into contact with the already folded LASIK flap (Figure 1). After the 60-second riboflavin soak, the LASIK flap was reflected into place, copiously irrigated, and ironed with a Johnston applanator (Rhein Medical, St Petersburg, FL). Figure 2 shows the LASIK flap repositioned and the riboflavin yellow tinge visualized within the corneal stroma.

Following flap repositioning, the surface was kept moist with a drop of ofloxacin solution (Ocuflox®, Allergan, Dublin, Ireland) and irradiated with 10 mW/cm^2 ultraviolet light (Priavision, Menlo Park, CA) of average wavelength 370 nm, for a total of three minutes. No further drops of riboflavin were administered. During the ultraviolet irradiation phase, the corneal surface was kept moist with a few drops of ofloxacin solution.

A bandage contact lens was then placed on the ocular surface and the patient was treated with ofloxacin and 0.1% dexamethasone solution four times a day for a week. Patients were followed up on the first day following contact lens removal. Further follow-up examinations were performed at the end of week 1, months 1, 3, and 6, and annually thereafter.

Results

The mean age of the patients was 26 ± 7 years, with 14 being female and nine being male. Mean uncorrected distance visual acuity showed an improvement from 0.2 ± 0.2 to 1.2 ± 0.07 logMAR. Best spectacle-corrected visual acuity to corrected distance visual acuity improved from 1.1 ± 0.8 to 1.2 ± 0.9. Spherical equivalent improved from an average of −7.5 ± 2.5 D to −0.2 ± 0.5 D.

Figure 3 demonstrates postoperative uncorrected distance visual acuity and corrected distance visual acuity

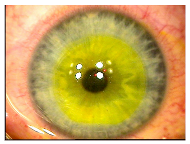

Figure 2 Flap is repositioned, and the riboflavin-yellow tinge is visualized in the corneal stroma prior to application of higher fluence ultraviolet light.

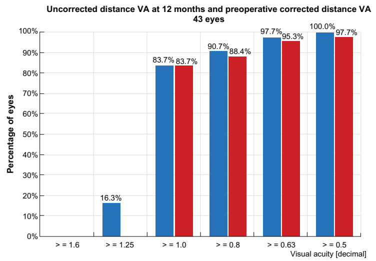

Figure 3 Postoperative uncorrected and corrected distance visual acuity at 12 months.

at 12 months. Cornea keratometry was 44.5 ± 2.4 D on average preoperatively and reduced to 38 ± 2.1 D postoperatively. Figure 4 shows the keratometric stability of the group during the first 24 months postoperatively. Figure 5 shows the safety data for the group at the 12-month postoperative follow-up. Figure 6 shows the group efficacy data at 12 months.

Mean flap thickness was measured intraoperatively to be 105 ± 7 µm. Mean minimal cornea thickness evaluated by Scheimpflug tomography was 525 µm preoperatively and 455 µm measured at 12 months after surgery. Mean endothelial cell counts were 2750 ± 250 preoperatively and 2800 ± 220 postoperatively, with the change possibly attributable to discontinuation of contact lens use after surgery.

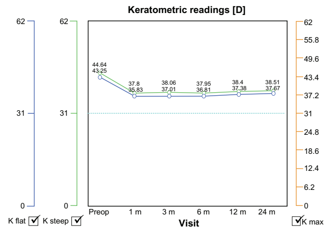

Figure 4 Image showing keratometric stability over the first 24 months for the group measured by Scheimpflug-based tomography.

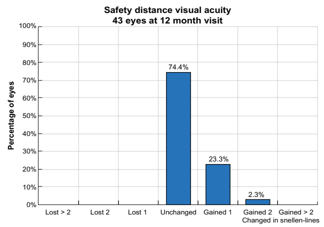

Figure 5 Safety data for the group at 12 months.

None of the patients had developed signs of ectasia at a mean 3.5 ± 1.6 years of follow-up. Cornea optical coherence tomography showed signs of hyper-reflectivity surrounding the flap interface in the majority of cases, as seen in Figure 7.

Discussion

For over 10 years now, we have treated patients relatively successfully combining cross-linking with laser refractive normalization of the ocular surface, a technique known locally as the Athens protocol.[17–23] As noted earlier, it is well known that LASIK reduces the biomechanical stability of the cornea by intersecting with structural lamellae in the anterior cornea and, of course, by removing some of the structural lamellae in lieu of ablation.

Although post-LASIK ectasia continues to be an extremely rare occurrence, we have long advocated the potential benefit of cross-linking at the completion of LASIK to

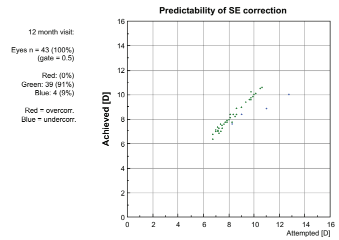

Figure 6 Spherical equivalent correction predictability for the group at 12 months.

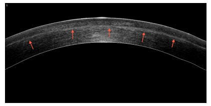

Figure 7 Anterior segment OCT image of a treated cornea.
Note: There is hyper-reflectivity evident over and under the LASIK flap (red arrows).
Abbreviations: OCT, optical coherence tomography; LASIK, laser-assisted in situ keratomileusis.

prevent this complication. We introduced this concept mainly as a result of practicing in a population with a particularly high rate of keratoconus[24] and after discovering that several patients whom we have treated in the past with LASIK have siblings or close relatives with clinical keratoconus that we did not know of at the time of the original LASIK procedure. The rationale of treatment using a LASIK flap (as opposed to irradiating the riboflavin-soaked stroma) is to reduce stromal exposure time and the risk of flap dehydration.

In the Southern Mediterranean region, specifically in our clinical setting in Athens, it would probably be justified to take measures to prevent corneal ectasia, in addition to screening for irregular topography and topometry and ensuring an adequate residual stromal bed (we use 320 µm as the minimum planned residual stroma bed after LASIK) in patients who are undergoing LASIK for high myopia, are of young age, and/or have a corneal thickness that would prompt us to do so (original corneal thickness less than 530 µm).

There is no published literature to date evaluating the effect of prophylactic collagen cross-linking in routine LASIK cases. As noted previously, prophylactic cross-linking may offer a significant benefit, especially in younger patients with unknown family member corneal status,especially in younger patients in countries with high incidence of keratoconus. The risk of a family member or sibling having irregular topograohically corneas may be higher and thus an increased risk for post-LASIK ectasia may exist, even when all parameters evaluated in the specific patient apopear normal. We generally employ prophylactic CXL routinely in LASIK cases with one or more of the below: a-over 6 diopters of myopia, b-cases with over 1 diopter of astigmatism, c-patients under 30 years old and last d-when co=minimal cornea pachymetry is under 520 µm. It is our understanding that some of the so-called LASIK "regressions" may actually be biomechanical responses to thinning of the cornea and interruption of the collagen lamellae in the surface of the corneal stroma. These changes may create a "controlled" rather than ectasia-like change of the cornea, making it steeper with time. This phenomenon may be a mechanical effect on the cornea from one or a combination of several mechanisms, ie, blinking, eye rubbing, intraocular pressure pushing from in towards out, continuous pulsating mechanical change onto the cornea induced by the heartbeat pulse pressure wave in the body, and eye collagen content in the years following the procedure.

In this small study, we established that prophylactic collagen cross-linking is safe in routine LASIK cases. We had seen no adverse effects or overcorrection in any of our patients, nor any significant unpredicted refractive result. It would be interesting to use one eye as a control in a prospective study in regard to prophylactic cross-linking, but this unfortunately was not done in the present study. Technology such as the Corvis® ST (Oculus, Germany) or the ORA could be used in controlled one-eye studies, to document the efficacy of cross-linking. We have recently switched to using the KXL (Avedro, Waltham, MA) and applying 30 mW/cm^2 for just one minute, given that this device delivers the same total fluence of ultraviolet light to the corneal stroma and reduces treatment time, and reduces treatment time. We have since emloyed yet higher fluence of UV light for this purpose. We currently utililize the KXL device (Avedro, Waltham, MA) with settings of 30 mW/cm^2 for 90 seconds instead of the 10 mW/cm^2 for 5 minutes described herein.

Of course, one would wonder why there is a need for prophylactic collagen cross-linking when corneal ectasia is an extremely rare occurrence. Nonetheless, this concept should be evaluated in larger studies to establish the possibility that this intervention may offer greater stability of the LASIK effect, which has shown surprising changes in a large proportion of patients in several long-term studies. Almost 10% of patients who have had high myopia corrected show changes over a period of 10 years.[25,26] Prophylactic cross-linking may reduce the possibility of such changes.

In general, it could be said that one of the major disadvantages of LASIK compared with photorefractive keratectomy is the reductions of the biomechanical stability of the cornea. If one could then establish that biomechanical stability has recurred after use of collagen cross-linking in routine LASIK cases, then that would further enforce LASIK as the primary refractive procedure because it has a favorable safety record, is tolerated by patients very well, and enables a rapid return into daily activities. Although not tested in this small group, it would be interesting to study the potential difficulty of retreatment in patients who have undergone

LASIK with prophylactic cross-linking. Larger studies and better follow-up would establish the efficacy and safety of this proposed novel intervention.

Disclosure

Part of this work was presented as a paper at the American Academy of Ophthalmology annual meeting in San Francisco, CA, October 24–27, 2009, and as a poster at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, May 3–7, 2009. Otherwise, the author reports no conflict of interest in this work.

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