Clinical Ophthalmology

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CASE REPORT

The management of cornea blindness from severe corneal scarring, with the Athens Protocol (transepithelial topography-guided PRK therapeutic remodeling, combined with same-day, collagen cross-linking)

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Purpose: To evaluate the safety and efficacy of combined transepithelial topography-guided photorefractive keratectomy (PRK) therapeutic remodeling, combined with same-day, collagen cross-linking (CXL). This protocol was used for the management of cornea blindness due to severe corneal scarring.

Methods: A 57-year-old man had severe corneal blindness in both eyes. Both corneas had significant central scars attributed to a firework explosion 45 years ago, when the patient was 12 years old. Corrected distance visual acuity (CDVA) was 20/100 both eyes (OU) with refraction: +4.00, −4.50 at 135° in the right eye and +3.50, −1.00 at 55° in the left. Respective keratometries were: 42.3, 60.4 at 17° and 35.8, 39.1 at 151.3°. Cornea transplantation was the recommendation by multiple cornea specialists as the treatment of choice. We decided prior to considering a transplant to employ the Athens Protocol (combined topography-guided partial PRK and CXL) in the right eye in February 2010 and in the left eye in September 2010. The treatment plan for both eyes was designed on the topography-guided wavelight excimer laser platform.

Results: Fifteen months after the right eye treatment, the right cornea had improved translucency and was topographically stable with uncorrected distance visual acuity (UDVA) 20/50 and CDVA 20/40 with refraction +0.50, −2.00 at 5°. We noted a similar outcome after similar treatment applied in the left eye with UDVA 20/50 and CDVA 20/40 with −0.50, −2.00 at 170° at the 8-month follow-up.

Conclusion: In this case, the introduction of successful management of severe cornea abnormalities and scarring with the Athens Protocol may provide an effective alternative to other existing surgical or medical options.

Keywords: Athens Protocol, collagen cross-linking, cornea blindness, cornea scarring, photorefractive keratectomy, vision

Video abstract

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Case report

A 57-year-old man had severe corneal blindness from cornea scarring attributed to a firework explosion accident that occurred 45 years ago, when the patient was 12 years old. When we first evaluated the patient in 2009, the uncorrected distance visual acuity (UDVA) was 20/400 in both eyes, with pinhole improvement to 20/100 in the right eye and 20/70 in the left eye. There was no improvement to his visual function with

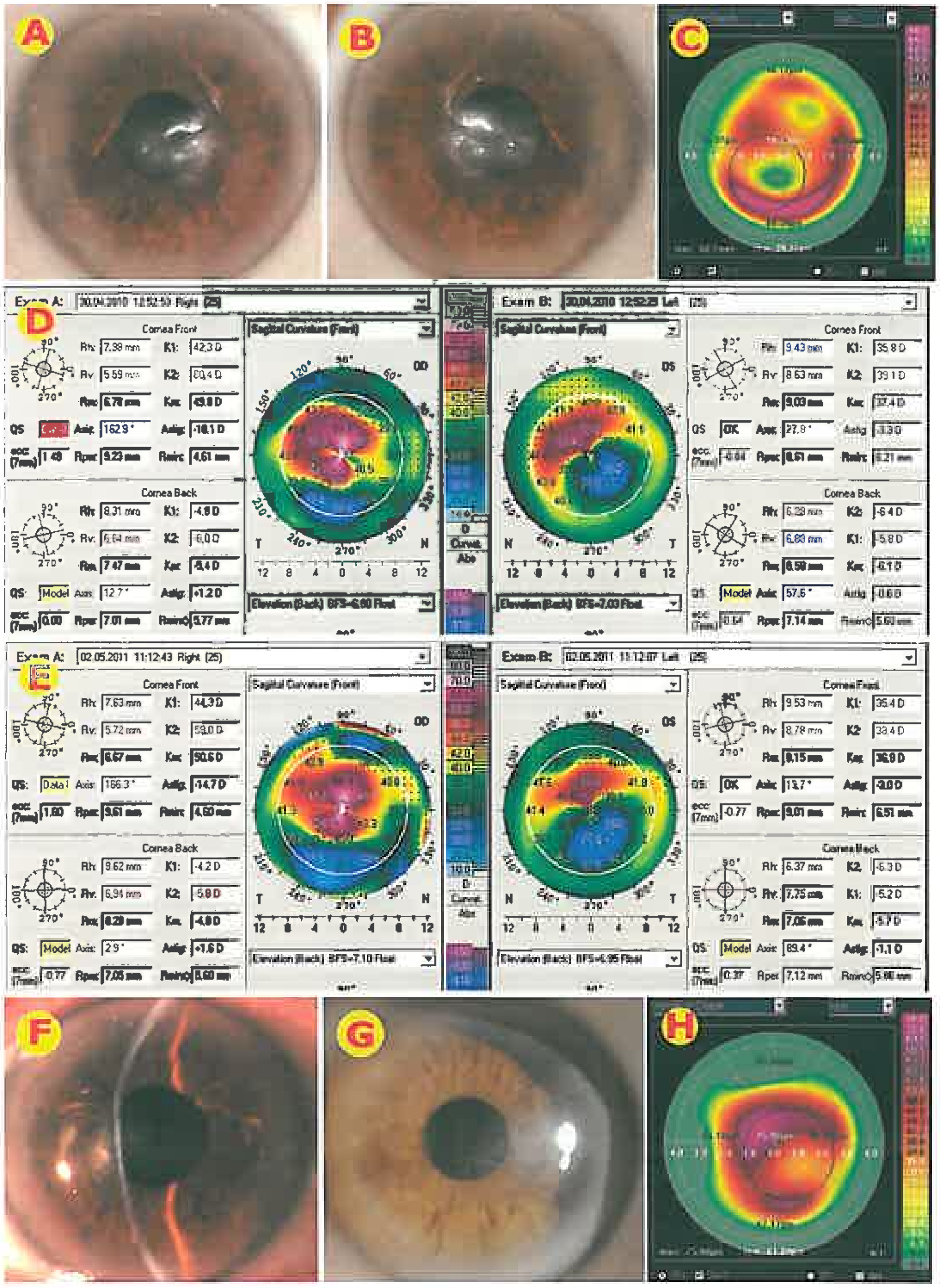

Figure 1 **(A)** Slit-lamp image of the OD at presentation, showing a significant horizontal cornea scar. **(B)** Slit-lamp picture of the OS; there was central corneal scarring similar to the OD. **(C)** The treatment plan on the wavelight excimer platform for topography-guided partial PRK employed for the OD treatment. The treatment plan, pivotal to the application of the Athens Protocol, combines a myopic ablation over the elevated cornea and a partial hyperopic application peripheral to the flattened (by scarring) inferior cornea. This combination treatment enhances the normalization of the severe irregularity with small ablation (35 µm) over the thinnest cornea. **(D)** Tomography maps (Oculyzer, Wavelight, Erlangen, Germany) of the OD and OS preoperative to the Athens Protocol. **(E)** Tomography maps of the OD and OS postoperative to the Athens Protocol, 15 months following the OD and 8 months following the OS. **(F)** Slit-lamp picture of the OD, 15 months following treatment; cornea regularity and improvement in translucency is evident (when compared to **A**). **(G)** Slit-lamp picture of the OS, 8 months following treatment; cornea regularity and improvement in translucency is evident (when compared to **B**). **(H)** The treatment plan on the wavelight excimer platform employed for topography-guided partial PRK of the OS.

Abbreviations: OD, right eye; OS, left eye; PRK, photorefractive keratectomy.

Figure 2 Preoperative cornea OCT showing the dense, deep stromal scarring (hyper-reflective spots) along with the very irregular stromal surface, partly masked by epithelium thinning over the peaks and thickening over the deep valleys.
Abbreviation: OCT, optical coherence tomography.

spectacle refraction or soft contact lenses, and there was intolerance to gas-permeable contact lenses in both eyes.

Due to the dense scarring in the right eye, an endothelial cell count (ECC) was not possible. The ECC was 2000 cells/mm^2 in the left eye. Slit lamp biomicroscopy revealed severe horizontal central corneal scars in both eyes (see Figure 1A is the right eye and B the left eye). Dilated fundus examination revealed no cataracts, normal disks, macula, and retina vessels.

CDVA was 20/100 both eyes (OU) with refraction: +4.00, −4.50 at 135 in the right eye (OD), +3.50, −1.00 at 55 in the

Figure 3 Picture showing the same portion of cornea as in Figure 2, in a cornea OCT 12 months following the treatment. The scar has been significantly reduced, the stromal surface smoothed, the epithelium has become more uniform in thickness, and the overall cornea thickness has been reduced.
Abbreviation: OCT, optical coherence tomography.

left eye (OS). Respective keratometries were: 42.3, 60.4 at 17 and 35.8, 39.1 at 151.3.

Tomographic evaluation (Oculyzer II, Wavelight, Erlangen, Germany) of both eyes is noted in Figure 1D and shows the thinnest pachymetry of 467 μm in the right eye and 448 μm in the left eye, respectively. Considering the options of lamellar and penetrating keratoplasty, we discussed with the patient the possibility of normalizing the cornea surface, removing some of the scar and additionally utilizing collagen cross-linking (CXL) to biomechanically reinforce the thinned corneas and potentially reduce scarring by suppressing stromal keratocytes.

Potential complications were extensively discussed. The patient decided to proceed with our recommendation and we employed the Athens Protocol (combined topography-guided partial photorefractive keratectomy [PRK] and CXL) in the right eye in February 2010 and in the left eye 7 months later, in September 2010. We have previously reported on this technique[1–5] for the management of cornea ectasia. The excimer laser treatment plan for both eyes was designed on the wavelight excimer laser platform and is demonstrated in Figure 1C and H. The treatment plan, pivotal to the application of the Athens Protocol, combines a myopic ablation over the elevated cornea and a partial hyperopic application peripheral to the flattened (by scarring), inferior cornea. This combination treatment enhances the normalization of the severe irregularity with small ablation (35 μm) over the thinnest cornea. Fifteen months after the treatment of the right eye, the cornea had cleared and was topographically stable with UDVA at 20/50 and corrected distance visual acuity (CDVA) of 20/40 with refraction +0.50, –2.00 at 5°. We noted a similar outcome for the left eye 8 months after the treatment with UDVA of 20/50 and CDVA of 20/40 with –0.50, –2.00 at 170°.

The postoperative slit-lamp photos of the anterior segment are seen in Figure 1 (right eye: F and left eye: G). His tomographic keratometry in the right eye has improved to 44.3, 59.0 at 13.7°and in the left eye to 35.4, 38.4 at 166.3°(Figure 1E shows the right eye on the left and the left eye on the right). Endothelial cell counts (ECC) were possible postoperatively in the right eye, most likely due to improved cornea clarity, and were 1600 cells/mm^2. The postoperative ECC in the left eye was measured at 2010 cells/mm^2.

The preoperative cornea optical coherence tomography (OCT) is shown in Figure 2 and the postoperative in Figure 3. Due to improved visual rehabilitation, the patient has recently obtained a driver's license and has assumed a more independent lifestyle.

In this particular patient, the therapeutic aim of the topography-guided PRK was to attempt to normalize the highly irregular corneal surface, and the employment of the CXL had a two-fold objective: to reduce corneal scarring by eliminating keratocytes, and to stabilize the thinner cornea produced by the removal of corneal tissue with the therapeutic topography-guided ablation.

We feel that in this case the introduction of successful management of severe cornea abnormalities and scarring with the Athens Protocol may provide an effective alternative to other surgical options such as lamellar or penetrating keratoplasty. Further studies in a large cohort of patients with a longer follow-up are needed to further establish the effectiveness and safety of this technique.

Disclosure

The author reports no conflicts of interest in this work.

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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 visual performance, 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/cm^2) 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/cm^2 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, Erlagen, 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 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

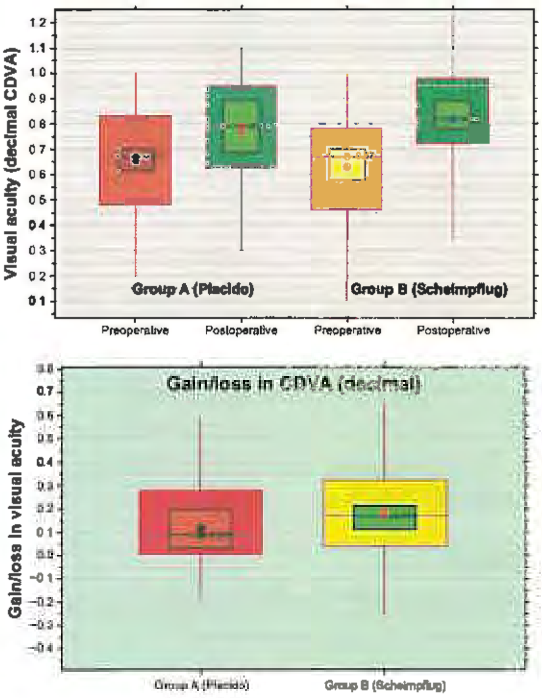

Figure 1 Box plots of corrected distance visual acuity, expressed as decimals. Top, preoperative and postoperative values for both groups. Bottom, gain/loss expressed as difference between postoperative minus preoperative corrected distance visual acuity.

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 seven anterior surface indices are reported for the two groups in Table 3.

Anterior surface keratometry showed the following mean 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 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 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 trend towards 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,

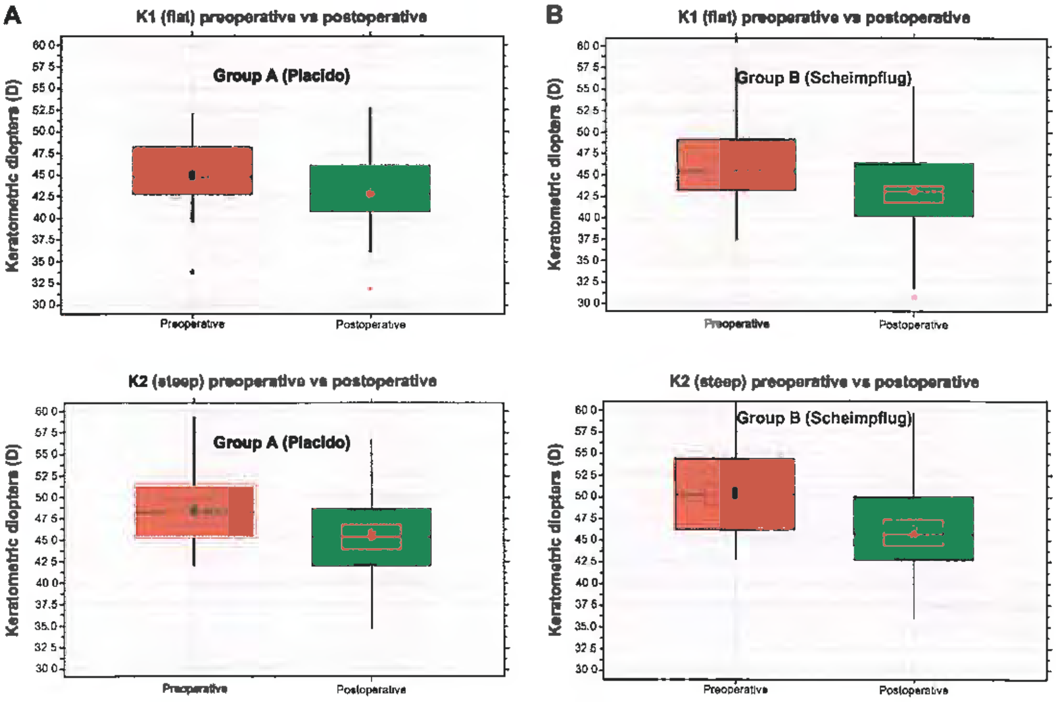

Figure 2 (**A**) Box plot describing induced changes (preoperative versus postoperative values) for anterior flat (top) and steep (bottom) keratometry (in diopters, D) for group A (Placido). (**B**) Box plot describing induced changes (preoperative versus postoperative values) for anterior flat (top) 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.

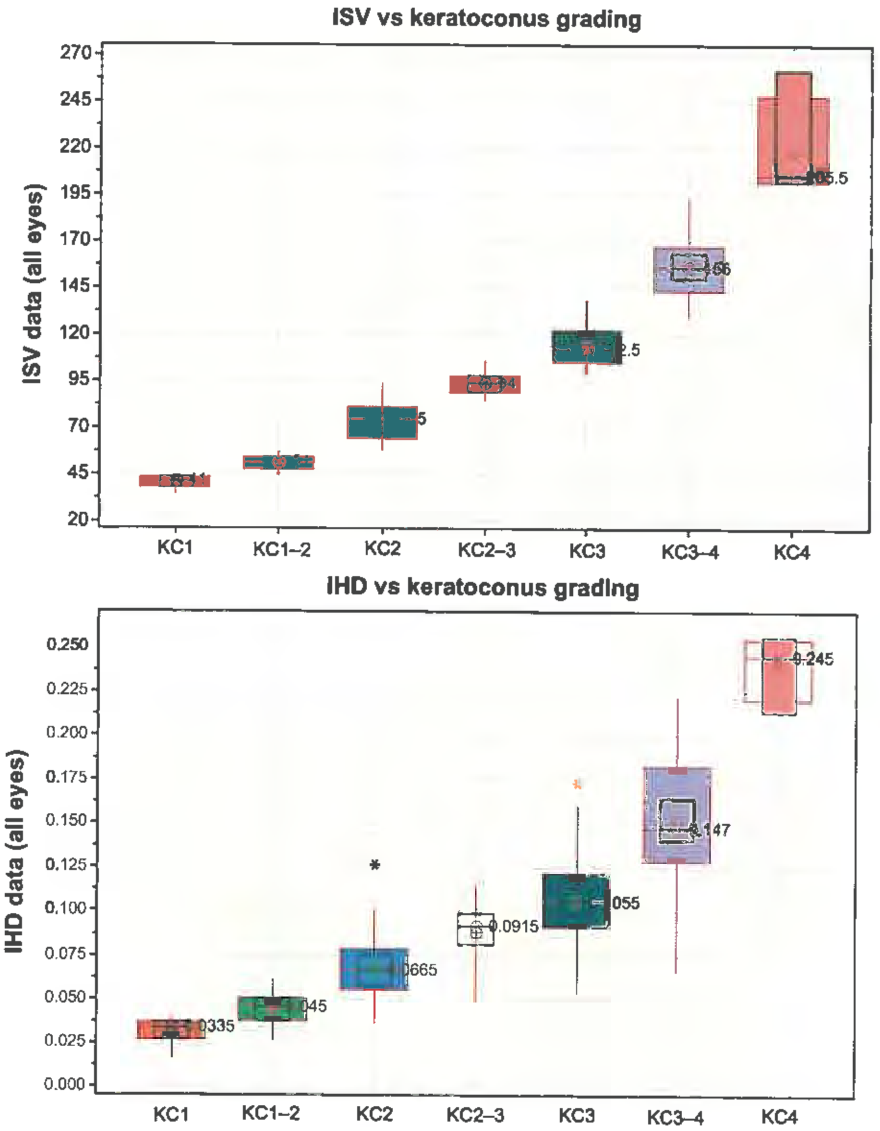

Figure 3 Top, box plot of preoperative ISV, and bottom, preoperative IHD versus keratoconus grading, as produced by the Oculyzer software.
Notes: Median level is indicated by ⊗, average by ⊕, the 95% median confidence range box by the back borderline, and the interquartile intervals range box by the 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

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

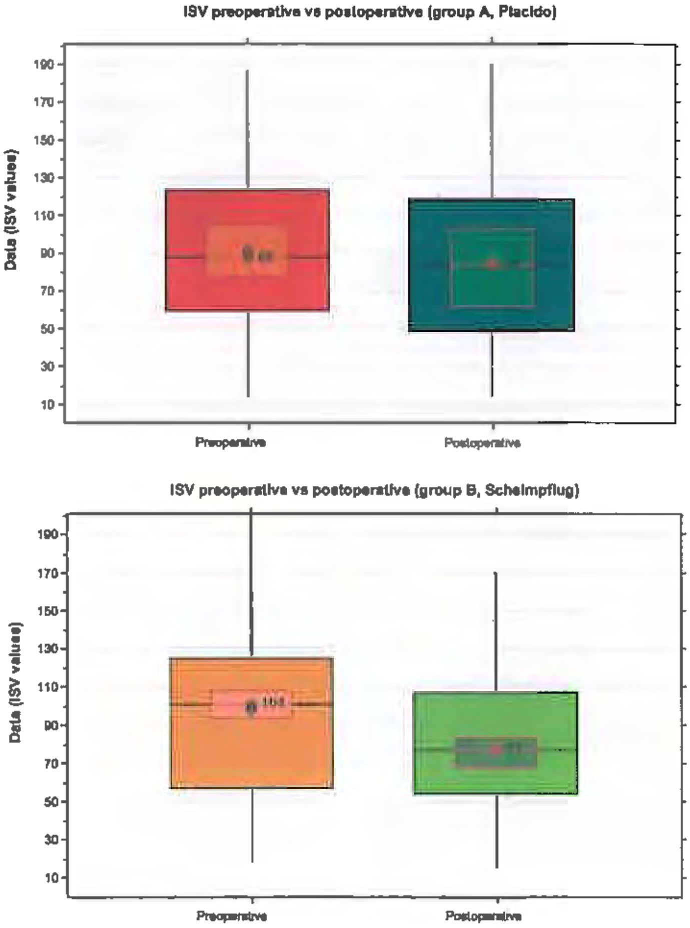

Figure 4 Box plot describing changes (preoperative versus postoperative values) induced for ISV in the two groups: top, group A, Placido; bottom, group B, Scheimpflug.
Notes: ⊗, median level; ⊕, average; red borderline, 95% median confidence range box; black borderline, interquartile intervals range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

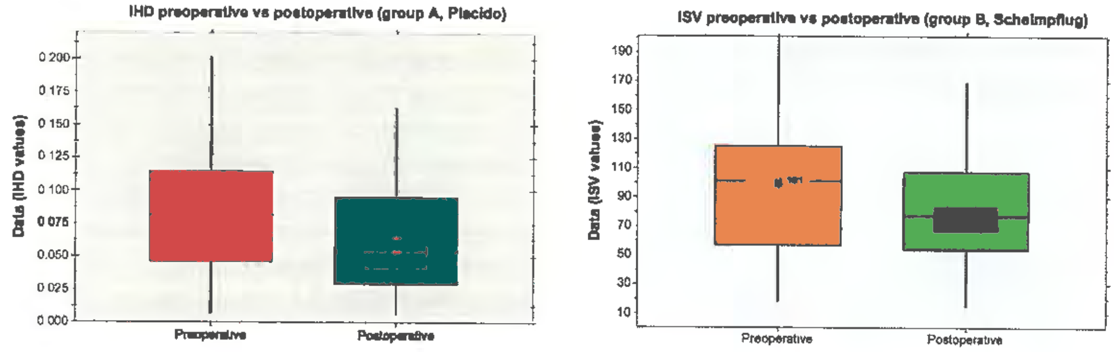

Figure 5 Box plot describing changes (preoperative versus postoperative values) induced for IHD for the two groups: top, group A, Placido; bottom, group B, Scheimpflug.

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

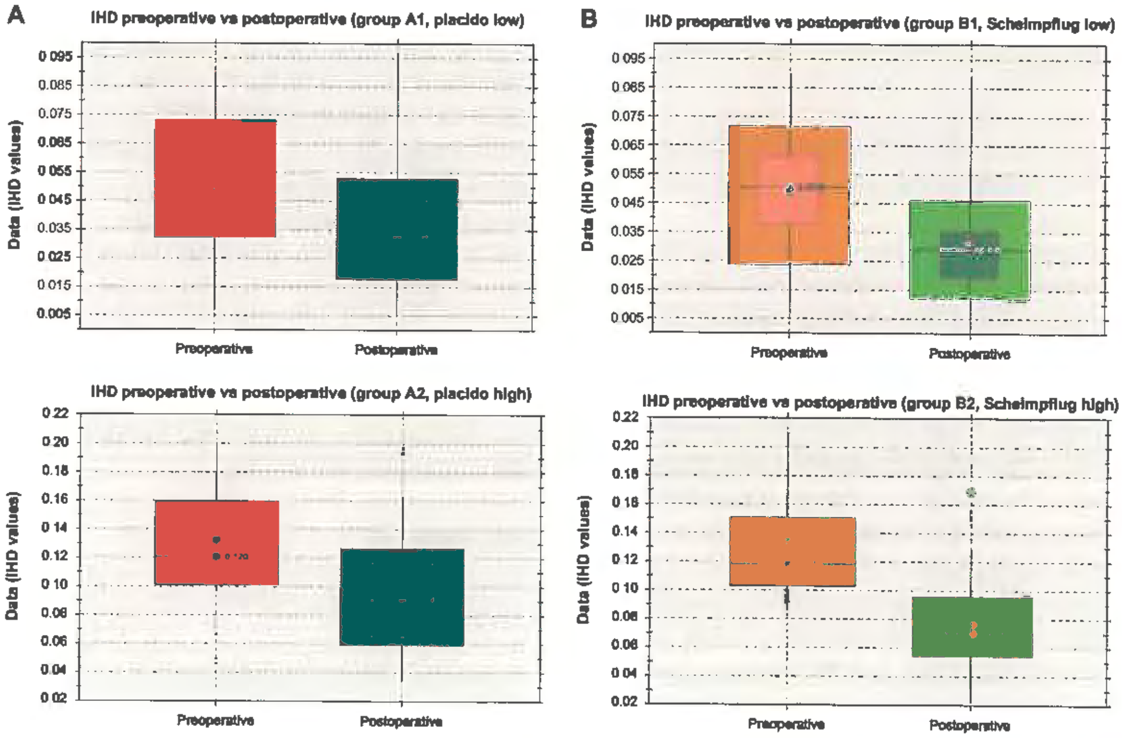

Figure 6 (**A**) Box plot describing preoperative versus postoperative changes in IHD induced for the subgroups. Top, group A1 (Placido low) indicating less affected keratoconic eyes; bottom, group A2 (Placido high) indicating more affected keratoconic eyes. (**B**) Box plot describing preoperative versus 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.

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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Keratoconus Management: Long-Term Stability of Topography-Guided Normalization Combined With High-Fluence CXL Stabilization (The Athens Protocol)

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ABSTRACT

PURPOSE: To investigate refractive, topometric, pachymetric, and visual rehabilitation changes induced by anterior surface normalization for keratoconus by partial topography-guided excimer laser ablation in conjunction with accelerated, high-fluence cross-linking.

METHODS: Two hundred thirty-one keratoconic cases subjected to the Athens Protocol procedure were studied for visual acuity, keratometry, pachymetry, and anterior surface irregularity indices up to 3 years postoperatively by Scheimpflug imaging (Oculus Optikgeräte GmbH, Wetzlar, Germany).

RESULTS: Mean visual acuity changes at 3 years postoperatively were +0.38 ± 0.31 (range: -0.34 to +1.10) for uncorrected distance visual acuity and +0.20 ± 0.21 (range: -0.32 to +0.90) for corrected distance visual acuity. Mean K1 (flat meridian) keratometric values were 46.56 ± 3.83 diopters (D) (range: 39.75 to 58.30 D) preoperatively, 44.44 ± 3.97 D (range: 36.10 to 55.50 D) 1 month postoperatively, and 43.22 ± 3.80 D (range: 36.00 to 53.70 D) up to 3 years postoperatively. The average Index of Surface Variance was 98.48 ± 43.47 (range: 17 to 208) preoperatively and 76.80 ± 38.41 (range: 7 to 190) up to 3 years postoperatively. The average Index of Height Decentration was 0.091 ± 0.053 μm (range: 0.006 to 0.275 μm) preoperatively and 0.057 ± 0.040 μm (range: 0.001 to 0.208 μm) up to 3 years postoperatively. Mean thinnest corneal thickness was 451.91 ± 40.02 μm (range: 297 to 547 μm) preoperatively, 353.95 ± 53.90 μm (range: 196 to 480 μm) 1 month postoperatively, and 370.52 ± 58.21 μm (range: 218 to 500 μm) up to 3 years postoperatively.

CONCLUSIONS: The Athens Protocol to arrest keratectasia progression and improve corneal regularity demonstrates safe and effective results as a keratoconus management option. Progressive potential for long-term flattening validates using caution in the surface normalization to avoid overcorrection.

[*J Refract Surg*. 2014;30(2):88-92.]

Keratoconus is a degenerative bilateral, noninflammatory disorder characterized by ectasia, thinning, and irregular corneal topography.[1] The disorder usually has onset at puberty and often progresses until the third decade of life, may manifest asymmetrically in the two eyes of the same patient, and can present with unpredictable visual acuity, particularly in relation to corneal irregularities.[2] One of the acceptable options[3] for progressive keratoconus management is corneal collagen cross-linking (CXL) with riboflavin and ultraviolet-A.[4]

To further improve the topographic and refractive outcomes, CXL can be combined with customized anterior surface normalization.[5-7] Our team has developed a procedure[8,9] we have termed the Athens Protocol,[10] involving sequentially excimer laser epithelial debridement (50 μm), partial topography-guided excimer laser stromal ablation, and high-fluence ultraviolet-A irradiation (10 mW/cm^2), accelerated (10', or minutes) CXL. Early results[11] and anterior segment optical coherence tomography quantitative findings[12] are indicative of the long-term stability of the procedure.

Detailed studies on postoperative visual rehabilitation and anterior surface topographic changes by such combined CXL procedures are rare,[13-16] particularly those reporting results longer than 1 year. This study aims to investigate safety and efficacy of the Athens Protocol procedure by analysis of long-term (3-year) refractive, topographic, pachymetric, and visual rehabilitation changes on clinical keratoconus management with the Athens Protocol in a large number of cases.

PATIENTS AND METHODS

This clinical study received approval by the Ethics Committee of our Institution and adhered to the tenets of the Declaration

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TABLE 1

Visual Acuity Data (N = 231 Eyes)[a]

		Postoperative					
Value	Preop	1 Month	3 Months	6 Months	12 Months	24 Months	36 Months
UDVA							
Average	0.18	0.42	0.49	0.55	0.57	0.59	0.59
SD (±)	±0.20	±0.27	±0.29	±0.29	±0.28	±0.28	±0.28
Gain/loss	n/a	+0.23	+0.30	+0.36	+0.36	+0.39	+0.38
CDVA							
Average	0.62	0.69	0.76	0.80	0.81	0.82	0.82
SD (±)	±0.23	±0.22	±0.20	±0.20	±0.19	±0.19	±0.19
Gain/loss	n/a	+0.07	+0.14	+0.18	+0.18	+0.19	+0.20

preop = preoperative; UDVA = uncorrected distance visual acuity; SD = standard deviation; n/a = not applicable; CDVA = corrected distance visual acuity

[a]Expressed as the difference of postoperative minus preoperative values (gain/loss). Units are decimal.

of Helsinki. Written informed consent was obtained from each participant at the time of the intervention or the first clinical visit.

PATIENT INCLUSION CRITERIA

Two hundred thirty-one consecutive keratoconic cases subjected to the Athens Protocol procedure between 2008 and 2010 were investigated. All procedures were performed by the same surgeon (AJK) using the Alcon/WaveLight 400 Hz Eye-Q[17] or the EX500 excimer lasers.[18] Inclusion criteria were clinical diagnosis of progressive keratoconus, minimum age of 17 years, and corneal thickness of at least 300 µm. All participants completed an uneventful Athens Protocol procedure and all 231 eyes were observed for up to 3 years. Exclusion criteria were systemic disease, previous eye surgery, chemical injury or delayed epithelial healing, and pregnancy or lactation (female patients).

MEASUREMENTS AND ANALYSIS

Postoperative evaluation included uncorrected distance visual acuity (UDVA), manifest refraction, corrected distance visual acuity (CDVA) with this refraction, and slit-lamp biomicroscopy for clinical signs of CXL.[12] For the quantitative assessment of the induced corneal changes, postoperative evaluation was performed by a Pentacam Scheimpflug imaging device (Oculyzer II, WavLight AG, Erlangen, Germany)[19] and processed via Examination Software (Version 1.17r47). Specific anterior surface irregularity indices provided by the Scheimpflug imaging analysis were evaluated in addition to keratometric and pachymetric values. These indices are employed in grading and classification based on the Amsler and Krumeich criteria.[20,21] These are the Index of Surface Variance, an expression of anterior surface curvature irregularity, and the Index of Height Decentration, calculated with Fourier analysis of corneal height (expressed in microns) to quantify the degree of cone decentration.[22] Index of Surface Variance and Index of Height Decentration were computed for the 8-mm diameter zone.

Descriptive and comparative statistics, analysis of variance, and linear regression were performed by Minitab version 16.2.3 (MiniTab Ltd., Coventry, UK) and Origin Lab version 9 (OriginLab Corp., Northampton, MA). Paired analysis *P* values less than .05 were considered statistically significant. Visual acuity is reported decimally and keratometry in diopters (D). Results are reported as mean ± standard deviation and range as minimum to maximum.

RESULTS

The 231 eyes enrolled belonged to 84 female and 147 male participants. Mean participant age at the time of the operation was 30.1 ± 7.5 years (range: 17 to 57 years). All eyes were followed up to the 3-year follow-up.

VISUAL ACUITY CHANGES

Table 1 presents preoperative and postoperative UDVA and CDVA. UDVA increased by +0.38 ± 0.31 (range: -0.34 to +1.10) and CDVA by +0.20 ± 0.21 (range: -0.32 to +0.90). **Figure 1** illustrates, in the form of box plots, visual acuity gained or lost 3 years postoperatively. These graphs (the 95% median confidence range box) indicate that 95% of the cases had at least +0.1 increase in UDVA and 95% had positive change in CDVA.

KERATOMETRIC AND ANTERIOR SURFACE INDICES PROGRESSION

Anterior keratometry continued to flatten over the 3-year follow-up (**Figure 2**). Descriptive statistics for anterior keratometry, preoperatively and postoperatively, are presented in Table A (available in the online version of this article).

The values for the Index of Surface Variance and the Index of Height Decentration continued to

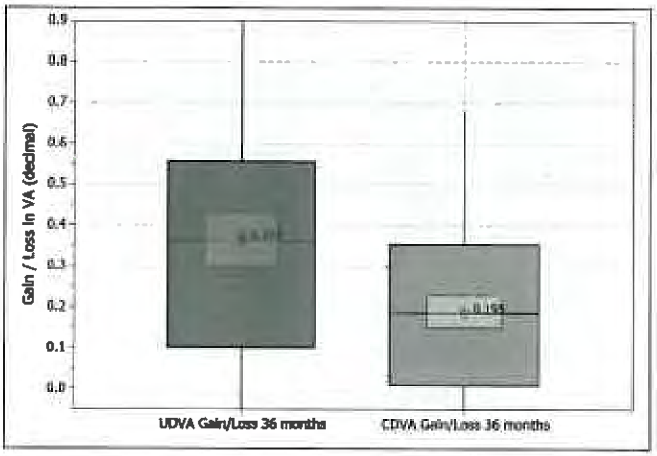

Figure 1. Change (gain/loss) in visual acuity, expressed as the difference of postoperative minus preoperative values (expressed decimally), showing median level (indicated by (+), average symbol (x), 95% median confidence range box (red borderline boxes), and interquartile intervals range box (black borderline boxes).

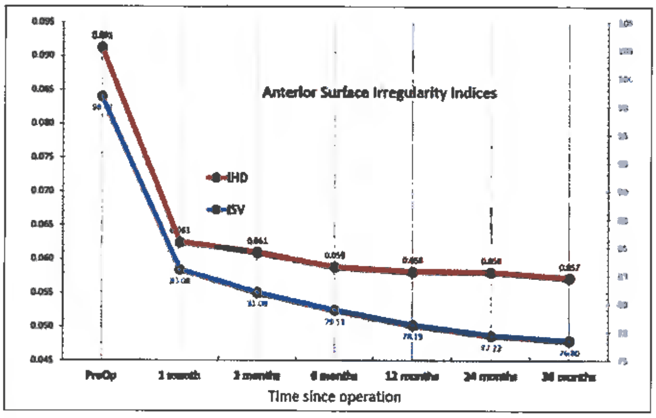

Figure 3. Anterior surface topometric indices Index of Surface Variance (no units) and Index of Height Decentration (units μm) as measured by the Scheimpflug imaging device (Oculyzer II, WavLight AG, Erlangen, Germany) preoperatively, 1 month postoperatively, and up to 36 months postoperatively.

decrease over time (Figure 3, Table B, available in the online version of this article).

PACHYMETRIC PROGRESSION

The thinnest corneal decreased as a result of excimer laser ablation but then stabilized over time without additional thinning (Table 2).

DISCUSSION

Many reports describe the effects of CXL with or without same-session excimer laser ablation corneal normalization.[3] There is general consensus that the intervention strengthens the cornea, helps arrest the ectasia progression, and improves corneal keratometric values, refraction, and visual acuity.

The key question is the long-term stability of these induced changes. For example, is the cornea 'inactive' after the intervention and, if not, is there steepening or flattening and/or thickening or thinning? These issues are even more applicable in the case of the Athens Protocol, due to the partial corneal surface ablation. Ablating a thin, ectatic cornea may sound unorthodox. However, the goal of the topography-guided ablation is to normalize the anterior cornea and thus help improve visual rehabilitation to a step beyond that a simple CXL would provide.

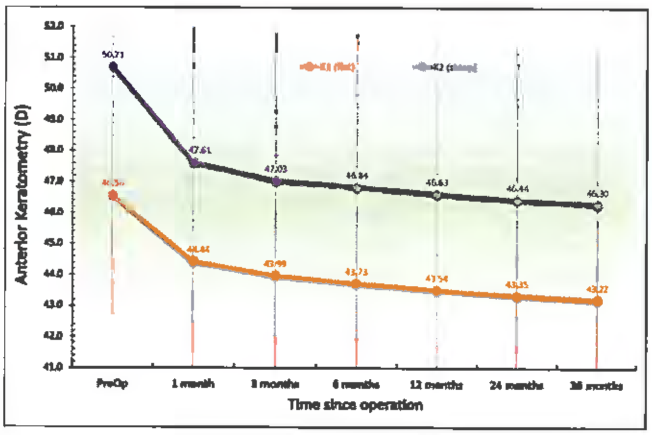

Figure 2. Anterior keratometry (K1 flat and K2 steep) as measured by the Scheimpflug device (Oculyzer II, WavLight AG, Erlangen, Germany) preoperatively up to 3 years postoperatively. All units in keratometric diopters (D).

This study aims to address some of the above issues. The large sample and follow-up time permit sensitive analysis with confident conclusion of postoperative efficacy. We monitored visual acuity changes and for the quantitative assessment we chose to standardize on one Scheimpflug screening device and to focus on key parameters of visual acuity, keratometry, pachymetry, and anterior surface indices.[23] All of these parameters reflect changes induced by the procedure and describe postoperative progression. However, variations in the two anterior surface indices (Index of Surface Variance and Index of Height Decentration) may provide a more valid analysis than keratometry and visual function.[24] Our results indicate that the apparent disadvantage of thinning the cornea is balanced by a documented long-term rehabilitating improvement and synergy from the CXL component.

VISUAL ACUITY CHANGES

Based on our results, the Athens Protocol appears to result in postoperative improvement in both UDVA and CDVA. Average gain/loss in visual acuity was consistently positive, starting from the first postoperative month, with gradual and continuous improvement toward the 3-year visit. These visual rehabilitation improvements appear to be superior to those reported in cases of simple CXL treatment.[25]

However, it is noted that the visual acuity presented with large variations. The standard deviation of UDVA

TABLE 2

Thinnest Corneal Thickness Measured by the Scheimpflug Device (N = 231 Eyes) (μm)

Value	Preoperative	Postoperative 1 Month	3 Months	6 Months	12 Months	24 Months	36 Months
Average	451.91	353.95	356.67	364.92	367.15	370.52	370.52
SD	±40.02	±53.90	±56.41	±53.64	±55.70	±57.84	±58.21
Maximum	547	480	501	501	490	500	500
Minimum	297	196	179	220	216	218	218

SD = standard deviation

was ±0.20 preoperatively and ±0.28 postoperatively. Likewise, the standard deviation of CDVA was ±0.23 preoperatively and ±0.20 postoperatively.

We theorize that the reason for visual acuity in keratoconic cases having such large fluctuations (and often being unexpectedly good) can be attributed to a 'multifocal' and 'soft' (ie, adaptable) cornea, in addition to advanced neural processing in the individual visual system. However, these 'advantages' are essentially negated with CXL treatment, which stiffens the cornea. Over time, possibly due to further topography improvement and adaptation to the partially normalized cornea, a noteworthy improvement in visual acuity is observed.

KERATOMETRIC AND ANTERIOR SURFACE INDICES PROGRESSION

After the 1-month visit, keratometric values are reduced. This progressive potential for long-term flattening has been clinically observed in many cases over at least 10 years. Peer-reviewed reports on this matter have been rare and only recent.[26,27]

The two anterior surface indices, Index of Surface Variance and Index of Height Decentration, also demonstrated postoperative improvement. A smaller value is indication of corneal normalization (lower Index of Surface Variance, less irregular surface, lower Index of Height Decentration, cone less steep and more central). These changes are therefore suggestive of corneal topography improvement, in agreement with other smaller sample studies.[13] Such changes in Index of Surface Variance and Index of Height Decentration have been reported only recently.[28]

The initial more 'drastic' change of the Index of Height Decentration can be justified by the chief objective of surface normalization, cone centering,[6] which is noted even by the first month. The subsequent surface normalization, as also indicated by keratometric flattening, suggests further anterior surface improvement.

PACHYMETRIC PROGRESSION

As expected by the fact that Athens Protocol includes a partial stromal excimer ablation, there is reduction of postoperative corneal thickness, manifested by the thinnest corneal thickness. What seemed to be a 'surprising' result is that the cornea appears to rebound, by gradually thickening, up to 3 years postoperatively. Postoperative corneal thickening after the 1-month 'lowest thickness baseline' has also been discussed recently.[29,30] In another report,[31] the lowest thinnest corneal thickness was noted at the 3-month interval. In that study of 82 eyes treated only with CXL, the average cornea thickened by +24 μm after 1 year compared to the 3-month baseline. In our study of 212 eyes treated with the Athens Protocol procedure, the cornea thickening rate after the baseline first postoperative month was approximately half (+12 μm over the first year), in agreement with a recent publication.[29]

Therefore, it is possible that stromal changes initiated by the CXL procedure are not just effective in halting ectasia, but are prompting corneal surface flattening and thickening, which appears to be longer lasting than anticipated.

We note, however, that CXL alone results not just in corneal reshaping, but also in stromal density and refractive index, both possibly influencing the reported thickness by the Scheimpflug device. Therefore, true corneal thickness differences may not be accurately explored by Scheimpflug imaging due to the principle of operation (densitometry), which has been our clinical experience with abnormal density corneas (ie, corneal scars or arcus senilis corneas). Further studies of corneal thickness chances by modalities, such as anterior segment optical coherence tomography, which currently also measure epithelial thickness,[32] may be warranted. In addition, corneal biomechanical analysis and corneal volume studies may be necessary to further validate such findings.

Our study indicates a significant improvement in all parameters studied. The changes induced by the procedure indicate a consistent trend toward improved visual rehabilitation, corneal flattening (validating ectasia arrest), and anterior surface improvement. The Athens Protocol procedure demonstrates impressive refractive, keratometric, and topometric results. Progressive potential for long-term flattening documented in this study suggests employment of caution in the surface normalization process to avoid overcorrection.

AUTHOR CONTRIBUTIONS

Study concept and design (AJK, GA); data collection (AJK, GA); analysis and interpretation of data (AJK, GA); drafting of the manuscript (GA); critical revision of the manuscript (AJK, GA); statistical expertise (GA); administrative, technical, or material support (AJK); supervision (AJK)

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TABLE A

Anterior Keratometry (K) Measured by the Scheimpflug Device (N = 231 Eyes)[a]

Value	Preop	Postoperative					
		1 Month	3 Months	6 Months	12 Months	24 Months	36 Months
K1 (flat)							
Average	46.56	44.44	43.99	43.73	43.54	43.35	43.22
SD	±3.83	±3.97	±3.86	±3.76	±3.73	±3.74	±3.80
Maximum	58.30	55.50	53.75	53.70	53.70	53.70	53.70
Minimum	39.75	36.10	36.10	36.10	36.10	36.10	36.00
K2 (steep)							
Average	50.71	47.61	47.03	46.84	46.63	46.44	46.30
SD	±5.14	±5.15	±4.99	±4.92	±4.91	±4.88	±4.91
Maximum	66.62	62.75	61.25	60.25	60.00	60.00	60.00
Minimum	42.60	38.00	37.90	37.90	37.90	37.90	37.20

preop = preoperative; SD = standard deviation

[a] *All units in keratometric diopters (D).*

TABLE B

Anterior Surface Topometric Indices and Postoperative Progression (N = 231 Eyes)

Value	Preoperative	Postoperative					
		1 Month	3 Months	6 Months	12 Months	24 Months	36 Months
Index of Surface Variance							
Average	98.48	83.08	81.08	79.51	78.19	77.22	76.80
SD	±43.47	±38.73	±38.13	±37.79	±38.04	±38.28	±38.41
Maximum	208	190	190	190	190	190	190
Minimum	17	18	17	16	15	14	7
Index of Height Decentration (μm)							
Average	0.091	0.063	0.061	0.059	0.058	0.058	0.057
SD	±0.053	±0.041	±0.040	±0.040	±0.040	±0.040	±0.040
Maximum	0.275	0.208	0.208	0.208	0.208	0.208	0.208
Minimum	0.006	0.001	0.001	0.001	0.001	0.001	0.001

SD = standard deviation

Anterior-Segment Optical Coherence Tomography Investigation of Corneal Deturgescence and Epithelial Remodeling After DSAEK

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Purpose: The aim of this study was to evaluate via Fourier-domain anterior-segment optical coherence tomography 3-dimensional corneal, epithelial, and graft thickness changes after Descemet stripping automated endothelial keratoplasty (DSAEK).

Methods: Sixteen eyes were investigated preoperatively and up to 6 months postoperatively for preoperative and postoperative central corneal thickness (CCT), minimum corneal thickness, central graft thickness (CGT), and for epithelial topographic thickness variability. An age-matched and gender-matched control group of 32 healthy eyes was used for comparison.

Results: In the DSAEK group, the preoperative CCT was 582.32 ± 45.24 (550–615) μm. One-month postoperatively, the CCT was 736.26 ± 34.52 (713–771) μm, and the CGT was 210.42 ± 34.52 (145–243) μm. Three months postoperatively, the CCT was 641.39 ± 38.75 (569–684) μm, and the CGT was 171.23 ± 27.54 (119–185) μm. The preoperative center epithelial thickness was 55.74 ± 9.29 (45–74) μm, the minimum was 32.53 ± 14.30 (13–53) μm, the maximum was 76.00 ± 11.32 (64–105) μm, and the topographic thickness variability was 10.84 ± 4.09 (5.90–18.80) μm. Three months postoperatively, the center epithelial thickness was 47.21 ± 5.45 (43–56) μm, the minimum was 35.11 ± 4.70 (30–41) μm, the maximum was 58.11 ± 6.51 (49–65) μm, and the topographic variability was 4.77 ± 1.48 (2.90–6.50) μm. The average differences were −8.53, +4.53, and −17.89 μm for the center, minimum, and maximum ($P < 0.001$, <0.001, and <0.001). Similar results were obtained 3 and 6 months postoperatively.

Conclusions: We present a near-term postoperative investigation of the corneal and epithelial thickness changes after DSAEK for bullous keratopathy, by in vivo, clinical anterior-segment optical coherence tomography. Epithelial thickness recovery and normalization and corneal deturgescence were noted as early as in the first postoperative month.

Key Words: anterior-segment optical coherence tomography, epithelium imaging, epithelial thickness distribution, epithelial layer topography, bullous keratopathy, Descemet stripping automated endothelial keratoplasty, DSAEK, OCT

(*Cornea* 2014;33:340–348)

Since its introduction in 2002,[1] Descemet stripping automated endothelial keratoplasty (DSAEK) is considered the treatment of choice[2] for endothelial dysfunction.[3,4] In penetrating (full thickness) keratoplasty, all corneal layers are replaced; however, in endothelial disorders, such as bullous keratopathy (BK),[5] the compromised clarity of the edematous cornea can be restored[6] by replacing only the endothelium and Descemet membrane with a healthy donor endothelium attached to the graft Descemet membrane and a thin layer of posterior stroma.[7,8] Because DSAEK thus involves the posterior cornea in a closed-chamber procedure, it is considered safer, provides faster visual recovery,[9] it usually requires few sutures and causes less astigmatic change,[10] overcoming some of the limitations of penetrating keratoplasty, such as prolonged visual rehabilitation, unpredictable cylindrical refractive changes (high postoperative astigmatism), susceptibility to ocular surface complications (wound dehiscence), and vulnerability to traumatic wound rupture.[11,12]

BK,[13] a pathological condition often derived from stage-2 Fuchs endothelial dysfunction, in which epithelial microcysts (vesicles) coalesce and form bullae,[14,15] represents one of the most frequent indications for DSAEK, in addition to endothelial trauma during a previous intraocular surgery.[16] In BK, the epithelium is highly irregular, as the bullae rupture (risking infectious keratitis), whereas areas of intense epithelial edema are also present.

Since the first report of corneal optical coherence tomography (OCT) imaging in 1994,[17] continuous improvements have led to the increased applicability of anterior-segment OCT (AS-OCT) in corneal evaluation,[18] including cases with Fuchs dystrophy.[19] OCT systems using Fourier-domain OCT[20,21] offering a higher speed and increased resolution have recently enabled in vivo epithelial layer 3-dimensional thickness mapping.[22–24] Complementing epithelial layer thickness measurement, corneal thickness pachymetry is also considered a very important clinical investigative tool for corneal edema[25] in cases

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Design and conduct of the study (A.J.K.); collection (A.J.K.), management (A.J.K.), analysis (A.J.K., G.A.), interpretation of the data (A.J.K., G.A.); manuscript preparation (A.J.K., G.A.), manuscript review (A.J.K., G.A.), and manuscript approval (A.J.K.).

Consultant/advisory positions: A.J. Kanellopoulos: Alcon/WaveLight, Avedro, i-Optics, Oculus.

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such as BK.[26–31] To the best of our knowledge, there is no peer-reviewed published study that evaluates the combination of corneal and epithelial layer thickness changes after DSAEK.

This study aims to investigate longitudinal postoperative corneal deturgescence, epithelial changes, and graft thickness evolution in cases of DSAEK implemented for BK treatment. This study evaluates longitudinally quantitative and qualitative changes up to 6 months postoperatively in such cases, using a clinical spectral-domain AS-OCT system.

MATERIALS AND METHODS

This prospective, consecutive, longitudinal case series study received approval from the Ethics Committee of our Institution, adherent to the tenets of the Declaration of Helsinki. Informed written consent was obtained from each subject at the time of the first clinical visit or before the operation.

Inclusion–Exclusion Criteria

The study group A (n = 16 eyes) consisted of patients diagnosed with BK, confirmed by a complete ophthalmologic evaluation. In all these cases, DSAEK surgery was performed by the same surgeon (A.J.K.), over the preceding 2 years in our institution. The control group B consisted of 32 eyes of a healthy, age- and gender-matched population, otherwise selected randomly from the pool of patients presented in our Institution for routine screening.

DSAEK Surgery

All the procedures were performed under monitored anesthesia with a peribulbar block.[32] Grafts were prepared with a Moria artificial chamber (Moria Surgical, Antony, France), the Moria LSK turbine-driven microkeratome with a 350-μm head and a disposable single-use Moria blade. A 4-mm clear-cornea incision was used to enter the recipient anterior chamber, which was supported by an anterior chamber maintainer to prevent collapse during surgery. The Descemet membrane was stripped from the central 8-mm area. The peripheral edge of the rolled endothelial graft was grasped from a Busin inserter (Moria) in the corneal tunnel and pulled into the anterior chamber with a coaxial microforceps. When the donor tissue entered the host anterior chamber, it was properly unrolled with the initiation of BSS infusion from the anterior chamber maintainer. A small air bubble was injected to lift the donor tissue anteriorly and attach it to the posterior host stromal surface. After centering the graft, the anterior chamber was completely filled with air. After approximately 10 minutes, the air bubble was reduced to about 80% of the size of the endothelial graft.

Imaging Instrumentation

The Fourier-domain AS-OCT system RTVue-100 (Optovue Inc, Fremont, CA), running on analysis and report software version A6 (9,0,27) was used in the study. Data output included total corneal and epithelial thickness maps corresponding to a 6-mm diameter area. In all cases, to avoid potential artifacts (eg, caused by possible drop instillation), OCT imaging preceded the ocular clinical examination during each visit. All OCT imaging was conducted by the same trained investigator. The settings were L-Cam lens, 8 meridional B-scans per acquisition, consisting of 1024 A-scans each with a 5-μm axial resolution, acquired in <0.5 seconds. The 8 radial meridional scans were used by the system software to produce, by interpolation, the 3-dimensional thickness maps. Images with quality as determined by the signal strength index parameter, a measure of the average signal strength across the scan, of >30 have been considered for the study.

Data Collection and Analysis

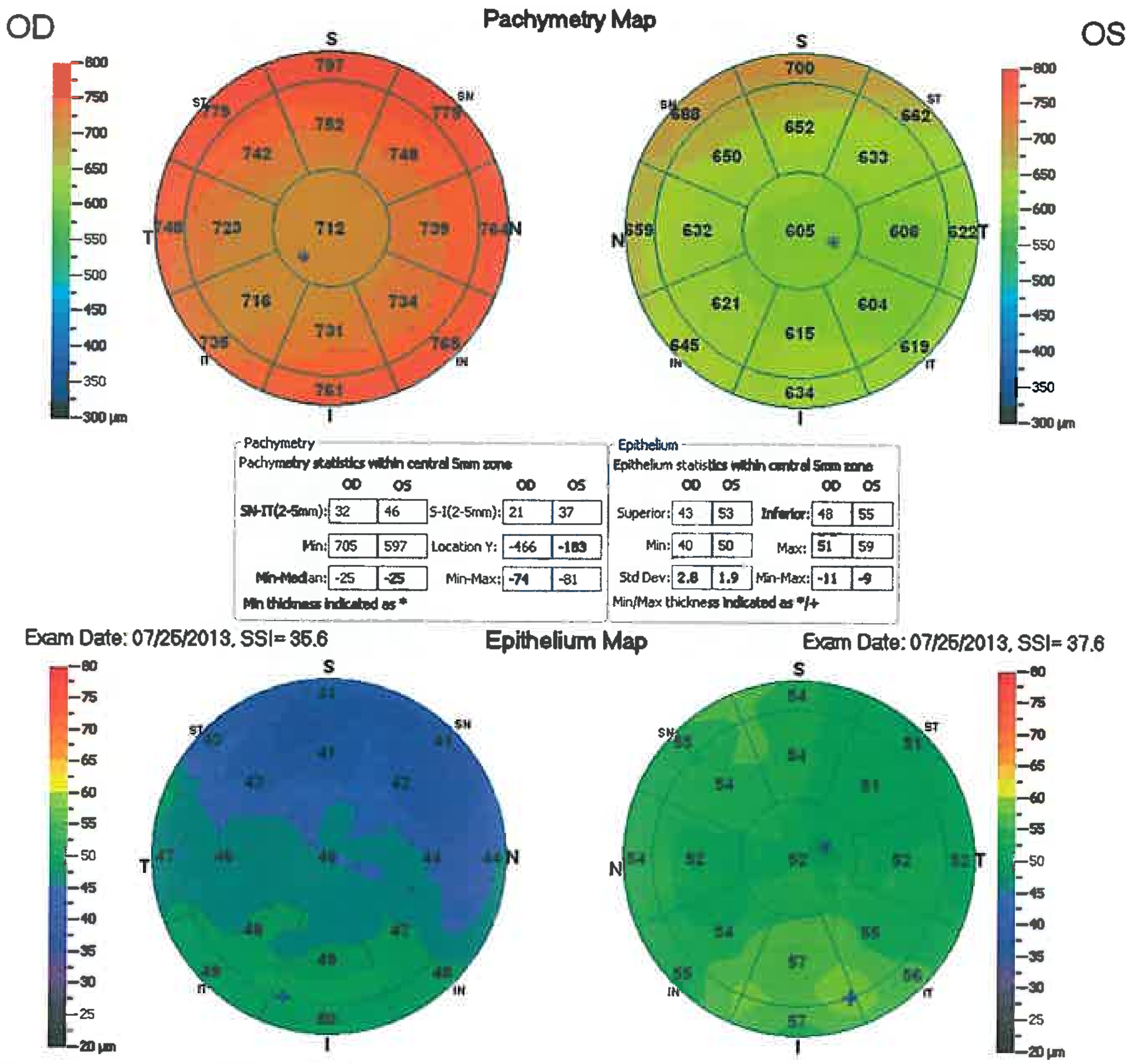
The preoperative imaging was performed the day preceding the operation, and the postoperative measurements were conducted on the first day after the operation, the first week and the first, third, and sixth months. Two consecutive individual acquisitions were obtained at each visit to ensure data validity.

The main analysis report produced by the AS-OCT system displayed total corneal (reported as pachymetry) and epithelial 3-dimensional thickness maps covering the 6-mm central diameter area. As shown in the series of images presented in Figure 1, each pachymetry map is divided into 17 sectors. Specifically, these are a 2-mm-diameter pupil center disk of a 12.56-mm^2 area, 8 octants within the annulus between the 2- and 5-mm zones, each of an area of 8.24 mm^2, and 8 octants within the annulus of 5- to 6-mm zones, each of a 4.32-mm^2 area. For each one of these sectors, the average thickness is displayed numerically in integer form with a minimum difference of 1 μm, over the corresponding area.

In this study, the reported central corneal thickness (CCT) was provided by the integer indication over the center disk, and minimum corneal thickness (MinCT) was provided by the data output in tabular form. Donor lenticule central graft thickness (CGT), defined in this study as axial length from the host–graft interface to posterior endothelium, was investigated in high-resolution meridional scans (Fig. 2) using the built-in caliper tool.

The "epithelium center" thickness was provided by the integer indication over the center disk. The mean epithelial thickness was calculated by the average of all segments, and peripheral epithelial thickness was computed by the average of the epithelial thickness corresponding to 18 equispaced points along the 5-mm radius (data harvested by mouse-over indication over the epithelial thickness map). The epithelial topographic thickness variability was calculated from the SD over the entire imaged area of all local epithelial thickness points.

Descriptive statistics, linear regression analysis to seek possible correlations, paired analysis t tests, and analysis of variance were performed by Minitab version 16.2.3 (MiniTab Ltd, Coventry, United Kingdom) and Origin Lab version 9 (OriginLab Corp, Northampton, MA). Paired t test analysis P values <0.05 were considered an indication of statistically significant results.



Pachymetry
Pachymetry statistics within central 5mm zone

	OD	OS		OD	OS
SN-IT(2-5mm):	32	46	S-I(2-5mm):	21	37
Min:	705	597	Location Y:	-466	-183
Min-Median:	-25	-25	Min-Max:	-74	-81

Min thickness indicated as *

Epithelium
Epithelium statistics within central 5mm zone

	OD	OS		OD	OS
Superior:	43	53	Inferior:	48	55
Min:	40	50	Max:	51	59
Std Dev:	2.8	1.9	Min-Max:	-11	-9

Min/Max thickness indicated as */+

FIGURE 1. Total corneal (top) and epithelial thickness (bottom) 3-dimensional pachymetry maps. Depicted are the oculus dexter eye (left in the image), 3 months after the DSAEK for BK, and the fellow oculus sinister eye (right in the image) of the same patient. The symbol * indicates the thickness minimum (in both corneal and epithelial maps) and the symbol + maximum (epithelial map only).

RESULTS

The average ± SD subject age in study group A (5 men and 11 women) at the time of the operation was 49.9 ± 15.3 (38–75) years of age. Of the 16 different eyes, 5 were right, and 11 were left. The preoperative best-spectacle distance corrected visual acuity (CDVA) for all cases enrolled in group A was 0.36 ± 0.25 (decimal), ranging from 0.01 to 0.8. The 1-month postoperative average CDVA was 0.66 ± 0.33 (0.1–0.8), 3-month CDVA was 0.71 ± 0.28 (0.15–0.85) and 6-month CDVA was 0.72 ± 0.25 (0.2–0.85).

Corneal Thickness Changes

Regarding study group A, preoperatively, the average ± SD CCT for all the eyes was 582.32 ± 45.24 (550–615) µm. One day postoperatively, the CCT was 785.81 ± 80.75 (688–943) µm; the statistically significant ($P < 0.001$) thickness difference of +205.42 ± 57.77 (+114 to +348) µm was in correlation with the respective lenticule CGT, as measured on the same day of 258.10 ± 68.78 (165–330) µm ($P = 0.181$).

One week postoperatively, the CCT was 736.26 ± 34.25 (713–771) µm; the average difference between the

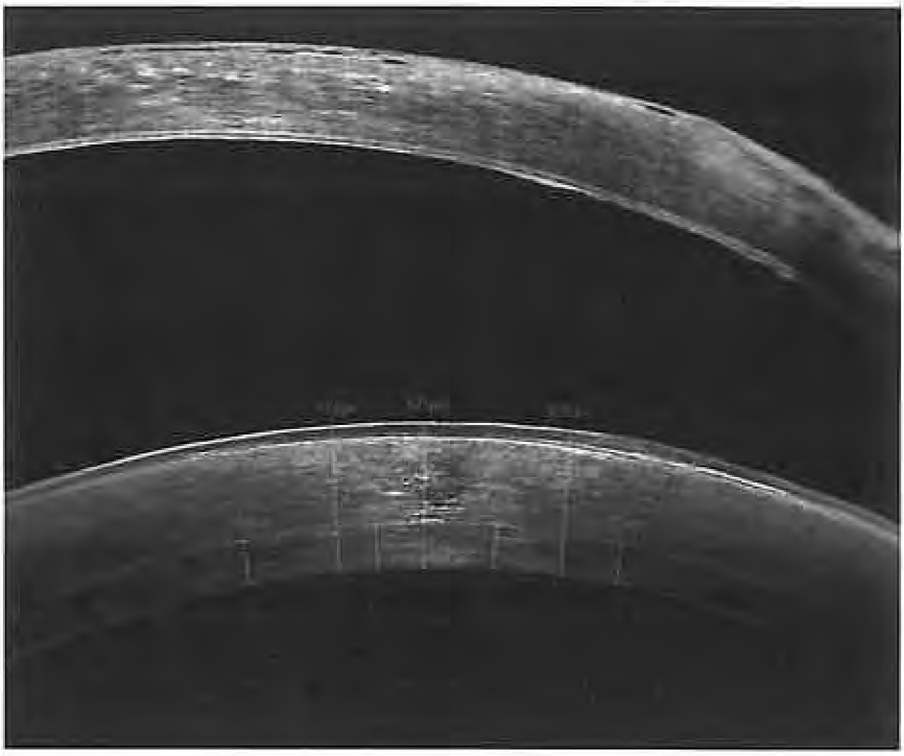


FIGURE 2. High-resolution meridional scans. Top, preoperative, showing signs of BK with areas of epithelial detachment shown as dark "islands" in the base of the epithelial layer; bottom, 1 week postoperatively of the same meridian. The interface is clearly seen. The epithelial layer in this sections appears more homogenous in thickness as also seen in the topographic epithelial thickness maps postoperatively.

1-week postoperative minus the respective preoperative CCT, on a one-per-one basis of +153.95 ± 37.78 (+127 to +185) μm was statistically significant ($P < 0.001$); the CGT was 210.42 ± 34.52 (145–243) μm ($P = 0.173$). Four weeks (1 month) postoperatively, the CCT was 643.53 ± 33.83 (567–691) μm; the average difference between the 4-week postoperative minus the respective preoperative CCT on a one-per-one basis of +61.21 ± 42.77 (−73 to +135) μm was statistically significant ($P = 0.032$);

TABLE 1. Descriptive Statistics for Preoperative, 1-Day, 1-Week, 4-Week, and 12-Week Postoperative Donor Lenticule CGT and Corneal (Central, CCT, and Minimum, MinCT) and for all the Cases in Study Group A

	CGT	CCT	MinCT		Change in CCT	Change in MinCT
Preop		582.33	555.53	Average		
		±45.24	±33.75	Stdev		
		615	589	Max		
		550	534	Min		
Postop	258.09	785.81	724.16	Average	205.42	168.63
1 d	±68.78	±80.75	±84.20	Stdev	±57.77	±69.81
	330	943	880	Max	348	297
	165	688	599	Min	114	62
Postop	210.42	736.26	701.58	Average	153.95	146.05
1 wk	±34.52	±34.25	±45.87	Stdev	±37.78	±35.38
	243	771	723	Max	185	177
	145	713	663	Min	127	114
Postop	175.84	643.53	596.63	Average	61.21	41.11
4 wks	±31.27	±33.83	±47.81	Stdev	±42.77	±49.61
	218	691	664	Max	135	121
	120	567	523	Min	−73	−25
Postop	171.23	641.39	596.06	Average	59.07	40.53
12 wks	±27.54	±38.75	±44.85	Stdev	±45.95	±43.28
	185	684	662	Max	128	118
	119	569	525	Min	−54	−29

The values noted are thickness reduction values in relation to the pre-DSAEK(preoperative) corneal measurements taken with the AS-OCT. All units are in micrometers.

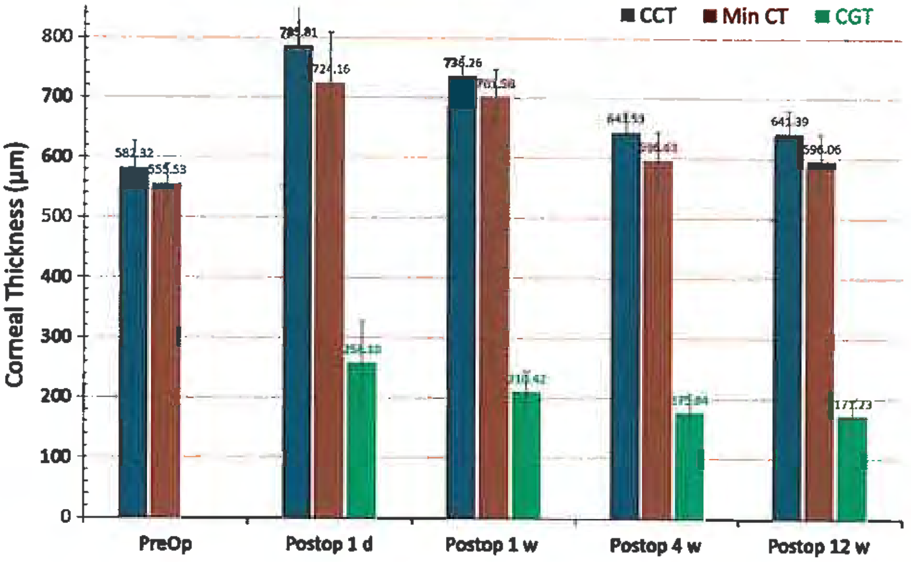


FIGURE 3. Average CCT (blue columns) and MinCT (red): preoperatively (Preop), at 1 day (Postop 1 day), 1 week (Postop 1 week), 4 weeks (Postop 4 weeks), and 3 months (Postop 12 weeks) postoperatively. The green columns indicate the CGT at the respective postoperative intervals. Error bars indicate the SD. All units are in micrometers.

the CGT was 175.84 ± 31.27 (120–218) μm ($P = 0.073$). Twelve weeks (3 months) postoperatively, the CCT was 641.39 ± 38.75 (569–684) μm; the average difference with the preoperative CCT was +59.07 ± 45.95 (−54 to +128) μm; the CGT was 171.23 ± 27.54 (119–185) μm ($P = 0.056$). Results similar to those of the 3-month visit were recorded at the 6-month visit on all the parameters measured, namely, CCT, MinCT, and CGT.

A similar trend was observed for the MinCT. Descriptive statistics for CCT, MinCT, and CGT for the study group A are given in Table 1 and illustrated in Figure 3. Regarding reference group B, CCT and MinCT results are given in Table 2.

Epithelial Thickness Results

Preoperative and postoperative descriptive statistics for epithelial layer thickness center, minimum, maximum, topographic variability, and mean and peripheral epithelial thickness are presented for group A in Table 3. Postoperative minus preoperative epithelial thickness differences for the center, mean, minimum, and maximum are illustrated in Figure 4. Regarding the control group B, descriptive statistics for center, minimum, maximum, topographic thickness variability, mean and midperipheral epithelium thickness results are given in Table 4.

TABLE 2. Descriptive Statistics for Corneal Thickness (Central, CCT and Minimum, MinCT) for all the Cases in Control Group B

		CCT	MinCT
Group B	Average	537.58	525.42
(n = 32)	Stdev	±33.53	±35.45
	Max	624	611
	Min	489	487

All units are in micrometers.

For group A, preoperatively, the center epithelial thickness was on average 55.74 ± 9.29 (45–74) μm, minimum epithelial thickness was 32.53 ± 14.30 (13–53) μm, maximum epithelial thickness was 76.00 ± 11.32 (64–105) μm, and topographic thickness variability was 10.84 ± 4.09 (5.90–18.80) μm.

One day postoperatively, the center epithelial thickness was on average 58.58 ± 3.37 (51–60) μm, minimum epithelial thickness was 38.37 ± 6.98 (23–44) μm, maximum epithelial thickness was 76.10 ± 10.93 (55–84) μm, and topographic thickness variability was 10.65 ± 3.93 (2.70–14.70) μm. The average difference in the epithelial thickness, computed on a one-to-one basis as the 1-day postoperative minus the respective preoperative of +2.84, +5.89, and +0.10 μm for center, minimum, and maximum, respectively, were all statistically significant (paired analysis $P = 0.032$, <0.001, and 0.045, respectively).

One week postoperatively, the center epithelial thickness was 55.37 ± 4.98 (49–60) μm, the minimum was 42.79 ± 3.69 (41–45) μm, the maximum was 77.11 ± 13.16 (55–90) μm, and the topographic thickness variability was 9.02 ± 3.22 (2.60–11.50) μm. The average difference in the epithelial thickness of −0.37, +12.21, and +1.11 μm for center, minimum, and maximum, respectively, had P values 0.075, <0.001, and 0.054, respectively.

Four weeks after the operation, the center epithelial thickness was 47.21 ± 5.45 (43–56) μm, the minimum was 35.11 ± 4.70 (30–41) μm, the maximum was 58.11 ± 6.51 (49–65) μm, and the topographic thickness variability was 4.77 ± 1.48 (2.90–6.50) μm. The average difference in the epithelial thickness, in comparison with the preoperative value, was −8.53, +4.53, and −17.89 μm for center, minimum, and maximum, respectively. These differences were statistically significant (paired analysis $P < 0.001$, <0.001, and <0.001, respectively).

Three months after the operation, the center epithelial thickness was 46.72 ± 5.23 (43–55) μm, the minimum was 35.48 ± 4.63 (31–42) μm, the maximum was 50.87 ± 5.86

TABLE 3. Descriptive Statistics for Preoperative and Postoperative Epithelial Thicknesses and Corresponding Changes for Study Group A, Computed on a 1-to-1 Basis, in Comparison With Preoperative values, on 1 Day, 1 Week, 1 Month, and 3 Months Postoperatively

	Center	Epi min	Epi max	Epi Stdev	Mean	Midperipheral	
Preop	55.74	32.53	76.00	10.84	53.84	53.46	Mean
	±9.29	±14.30	±11.32	±4.09	±6.87	±6.47	Stdev
	74	53	105	18.80	69.50	68.60	Max
	45	13	63	5.90	43.92	43.50	Min
Postop 1 d	58.58	38.37	76.10	10.65	59.71	59.93	Mean
	±3.37	±6.98	±10.93	±3.93	±4.50	±4.76	Stdev
	60	44	84	14.70	62.50	63.00	Max
	51	23	55	2.70	50.08	49.90	Min
Postop 1 wk	55.37	42.79	77.11	9.02	57.97	58.49	Mean
	±4.98	±3.69	±13.16	±3.22	±5.28	±5.40	Stdev
	60	45	90	11.50	62.50	63.00	Max
	49	41	55	2.60	50.08	49.90	Min
Postop 4 wks	47.21	35.11	58.11	4.77	45.21	44.82	Mean
	±5.45	±4.70	±6.51	±1.48	±2.21	±2.45	Stdev
	56	41	65	6.50	48.50	47.00	Max
	43	30	49	2.90	42.92	42.90	Min
Postop 12 wks	46.72	35.48	50.87	3.77	44.14	43.51	Mean
	±5.23	±4.63	±5.86	±1.46	±3.21	±3.89	Stdev
	55	42	63	5.47	49.32	47.43	Max
	43	31	49	2.75	43.04	43.10	Min

	Change in: Center	Change in: Epi min	Change in: Epi max	Change in: Epi Stdev	Change in: Mean6	Change in: Midperipheral
Preop						
Postop 1 d	2.84	5.89	0.10	−0.19	5.86	6.47
	±11.60	±13.91	±13.81	±3.63	±9.44	±9.04
	15	28	21	5.10	17.17	17.80
	−17	−26	−21	−7.80	−10.83	−9.60
Postop 1 wk	−0.37	3.58	6.16	−1.82	4.13	5.03
	±11.12	±9.41	±9.95	±4.36	±9.10	±8.74
	15	18	23	5.60	16.75	17.50
	−17	−11	−14	−7.30	−10.83	−9.60
Postop 4 wks	−8.53	2.58	−17.89	−6.06	−8.63	−8.65
	±11.97	±16.59	±13.40	±3.49	±7.94	±7.20
	10	28	−1	−0.80	4.58	3.50
	−29	−14	−48	−14.20	−24.33	−23.40
Postop 12 wks	−9.02	2.95	−25.13	−7.07	−9.70	−9.95
	±10.74	±11.05	±10.64	±2.75	±6.45	±7.26
	9	24	−3	−1.20	4.21	2.31
	−29	−12	−49	−14.75	−25.75	−24.76

All units are in micrometers.

(49–63) μm, and topographic thickness variability was 3.77 ± 1.46 (2.75–5.47) μm. The average difference in the epithelial thickness, in comparison with the preoperative value was −9.02, +2.95, and 25.13 μm for center, mean and periphery, respectively. These differences were all statistically significant (paired analysis $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively).

DISCUSSION

To evaluate the efficacy of the DSAEK in reducing stromal edema and epithelial layer irregularity, we examined near-term longitudinal development of corneal thickness, in the form of CCT and MinCT. The CCT is typically used in corneal edema and endothelial function monitoring,[33] ocular hypertension management,[34] and planning of refractive and cataract surgery.[35]

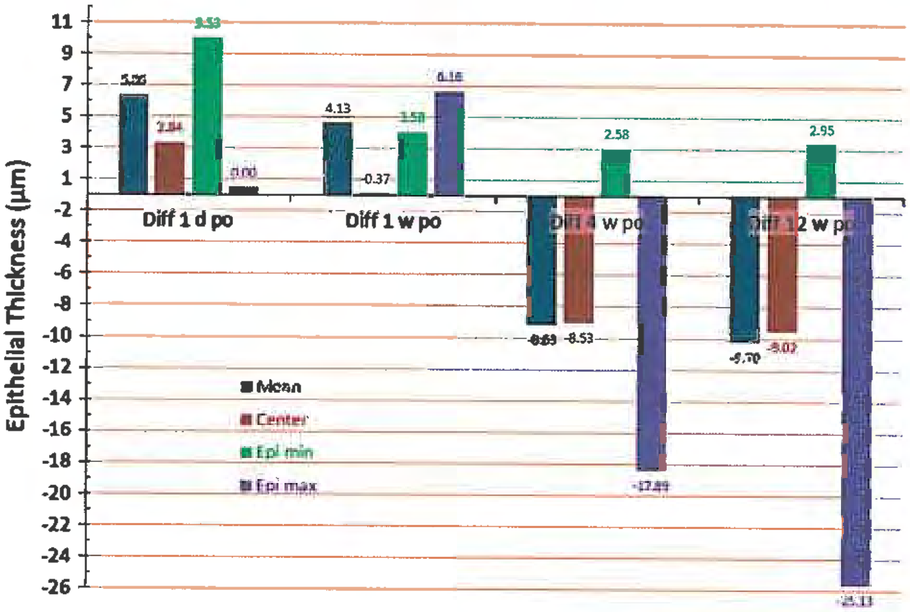


FIGURE 4. The average postoperative difference in the epithelial thickness: mean epithelial thickness (mean, blue columns), at the pupil center (center, red), minimum (Epi min, green), and maximum (Epi max, purple): shown on 1 day (Diff 1 day Po), 1 week (Diff 1 week Po), 4 weeks (Diff 4 weeks Po), and 3 months postoperatively (Diff 12 weeks Po). All units are in micrometers.

Near-term stromal deturgescence and epithelial layer remodeling and recovery of homogenous thickness and stromal attachment after DSAEK is related to the postoperative rehabilitation of the affected eye, particularly in BK cases. In addition, the epithelial thickness, which can be an indicator of the healing process and restoration of adequate endothelial function, has been monitored up to 6 months postoperatively. In this work, we monitored mean, minimum and maximum epithelial thickness and, in addition, the topographic epithelial thickness variability.

We have recently reported AS-OCT epithelial thickness quantitative and qualitative evaluation in the normal eye,[22] keratoconic eye,[36] and in the dry eye population.[37] In addition, our team has investigated near-term epithelial layer thickness postoperative evolution after myopic laser in situ keratomileusis[38] and cataract surgery.[39] In our practice, we routinely screen all presurgery patients for corneal structure and thickness,[35] and, additionally, for epithelial layer thickness. These examinations are also included in our postoperative evaluation protocols.

Our study indicated that both CCT and MinCT, and the epithelial layer thickness (central, mean, maximum, and minimum) were presented with a statistically significant increase the day after the DSAEK intervention, maintaining these levels at the 1-week postoperative visit. The corneal increase was consistent with the extra thickness because of the graft insertion; the difference in the CCT increase was correlated to the measured CGT.

At the 1- and 3-month postoperative visits, however, the reduced CCT and MinCT (−142.28 and −127.53 μm at the 1 month and −144.42 and −128.10 μm at the 3 months, respectively) indicated corneal deturgescence, particularly if we consider that the lenticule CGT was practically consistent (210.42 ± 34.52 μm at the first week, 175.84 ± 31.27 μm at 1 month, and 171.23 ± 27.54 μm at the 3 months).

The recovery of the epithelial layer thickness was even more impressive, if we consider the drastic reduction of the topographic thickness variability (Stdev), which was 10.84 ± 4.09 μm preoperatively: 1 month postoperatively StDev was 4.77 ± 1.48 μm and 3 months postoperatively, it was 3.77 ± 1.46 μm (Table 3). These levels compare with the reference group B variability of 1.95 ± 1.25 μm (Table 4). Also, the large range of maximum and minimum epithelial thicknesses has been dramatically improved: preoperatively maximum and minimum epithelial thicknesses were 76.00 ± 11.32 μm and 32.53 ± 14.30 μm; 1 month the respective values were 58.11 ± 6.51 μm and 35.11 ± 4.70 μm, and 3 month postoperatively, the values were 50.87 ± 5.86 μm and 35.48 ± 4.63 μm, respectively.

In this study, we investigated corneal and epithelial layer thickness longitudinal changes in 16 consecutive eyes

TABLE 4. Descriptive Statistics for the Epithelial Thickness for the Control Group B (n = 32 Eyes)

	Center	Minimum	Maximum	Topographic Variability	Mean	Midperipheral
Average	52.35	46.43	54.95	1.95	51.27	51.14
Stdev	±3.17	±3.39	±3.91	±1.25	±3.23	±3.53
Max	58	56	65	5.6	57.27	56.64
Min	46	30	47	0.7	42.25	45.32

All units are in micrometers.

operated with DSAEK for BK with a clinically available AS-OCT system, using raw data obtained from the system report and analysis software, and as such, it presents a novel longitudinal benchmark study. This information can be helpful to readers and investigators interested in studies pertaining to corneal and epithelial layer thickness after DSAEK and other keratoplasty interventions.

The potential applications of this technology may offer multiple benefits in post-DSAEK corneal imaging. Specifically, the changes in overall host and donor corneal thickness alert the clinician for possible rejection episodes and/or graft failure. This technology can monitor the donor (graft) lenticule thickness changes currently, manually, via an on-screen caliper tool, but potentially in the future automated, DSAEK graft 3-dimensional imaging, serving a similar crucial assessment, may be developed. Lastly, 3-dimensional epithelial imaging seems to follow a standard pattern in the postoperative period. If further studies establish this finding, the epithelial pattern in DSAEK-operated eyes can become another clinical marker of graft survival and efficacy. Very early 3-dimensional assessment by the AS-OCT of the graft–host interface may provide adjunct data to slit-lamp biomicroscopy on graft adherence and efficacy.

Further and longer-term studies, particularly pertaining to the >6-month changes in the corneal and epithelium thickness profile after DSAEK, larger imaging zone extending beyond the 6-mm diameter area imaged in this study, may further validate the findings and establish the long-term patterns of corneal and epithelial reshaping after DSAEK surgery.

CONCLUSIONS

Early postoperative investigation of the corneal and epithelial thickness longitudinal changes after DSAEK for BK, by in vivo, clinically applicable Fourier-domain AS-OCT producing 3-dimensional thickness maps. A standard pattern of epithelial thickness recovery and normalization, and corneal deturgescence mainly by the first month postoperatively, has been observed. The clinical relevance of these data is that this noninvasive corneal diagnostic device can aid the clinician to confirm early DSAEK graft adherence to the host cornea and successful reversal of host and graft stromal swelling, as well as host epithelial remodeling toward normality.

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ORIGINAL ARTICLE

Corneal Refractive Power and Symmetry Changes Following Normalization of Ectasias Treated With Partial Topography-Guided PTK Combined With Higher-Fluence CXL (The Athens Protocol)

Anastasios John Kanellopoulos, MD; George Asimellis, PhD

ABSTRACT

PURPOSE: To investigate preoperative and postoperative anterior and posterior keratometry and simulated corneal astigmatism in keratoconic eyes treated with collagen cross-linking combined with anterior surface normalization by partial topography-guided excimer ablation (the Athens Protocol).

METHODS: Anterior and posterior corneal keratometry were measured by Scheimpflug imaging for 267 untreated keratoconic eyes. Following treatment, they were assessed 1 year postoperatively.

RESULTS: Before treatment, average anterior keratometric value was 47.06 ± 6.02 diopters (D) for flat and 51.24 ± 6.75 D for steep. The posterior keratometric values were -6.70 ± 0.99 D (flat) and -7.67 ± 1.15 D (steep). Anterior astigmatism was on average with-the-rule (-1.97 ± 6.21 D), whereas posterior astigmatism was against-the-rule (+0.53 ± 1.02 D). The posterior and anterior astigmatism were highly correlated (r^2 = 0.839). After treatment, anterior keratometric values were 43.97 ± 5.81 D (flat) and 46.55 ± 6.82 D (steep). Posterior keratometric values were -6.58 ± 1.05 D (flat) and -7.69 ± 1.22 D (steep). Anterior astigmatism was on average with-the-rule (-1.56 ± 3.80 D), whereas posterior astigmatism was against-the-rule (+0.45 ± 1.29 D). The statistically significant ($P < .05$) keratometric changes indicated anterior surface flattening -3.09 ± 2.67 D (flat) and -4.19 ± 2.96 D (steep). The posterior keratometric changes were not statistically significant ($P > .05$).

CONCLUSIONS: Before treatment, there was a strong correlation between posterior and anterior corneal astigmatism. After treatment, statistically significant anterior keratometric values flattened. The posterior surface keratometric values did not demonstrate statistically significant postoperative change: there was minimal posterior change, despite the significant anterior surface normalization.

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Keratoconus assessment employs indicators such as keratometric values, inferior-superior index, skew percentage, astigmatism, and the KISA% index.[1] Acceptable quantitative keratometric criteria include central corneal refractive power larger than 47.2 diopters (D), inferior-superior dioptric asymmetry larger than 1.2 D, and simulated astigmatism, expressed as the difference between steep and flat keratometric values greater than 1.5 D.[2] The steep and flat meridian keratometric values correspond to the smaller and larger anterior corneal curvature radius, respectively.

Corneal cross-linking (CXL) is an in vivo intrastromal photo-oxidative technique with riboflavin and ultraviolet-A light aiming to address the advancing corneal ectasia and, consequently, the keratoconus progression. With CXL, additional covalent bonding between stromal collagen can be achieved, which stabilizes the collagen framework structure.[3] The remodeling effects of CXL on the cornea can be described by the reduction of mean anterior surface keratometric values.[4] Few studies have been published on the quantitative link between anterior and posterior keratometric values in keratoconic eyes or particularly on the postoperative effects of CXL on either corneal surface.

This study aims to investigate the distribution of and relationship between anterior and posterior corneal keratometric values and simulated anterior and posterior astigmatism on a large group of clinically diagnosed, untreated keratoconic eyes, and the 1-year postoperative effects on both anterior and posterior keratometric values and astigmatism induced by a combined procedure known as the Athens Protocol,[5,6] which intends to arrest the keratoconus progression and normalize the anterior corneal surface.

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PATIENTS AND METHODS

This study was performed in patients visiting our clinical practice and which received approval by the ethics committee of our institution and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all patients at the time of the first clinical visit.

INCLUSION CRITERIA AND SURGICAL TECHNIQUE

The study group consisted of 267 eyes. Patients' ages at the time of the screening ranged from 19 to 57 years. Each patient received a complete ocular examination, including subjective refraction, visual acuity, and slit-lamp biomicroscopy for clinical signs of keratoconus. Inclusion criteria included definite findings consistent with keratoconus, described by the Collaborative Longitudinal Evaluation of Keratoconus group.[7] Exclusion criteria included systemic disease, previous corneal surgery, history of chemical injury or delayed epithelial healing, and pregnancy or lactation (female patients) during the study.

The same cases received treatment with the Athens Protocol,[8] which involved excimer laser epithelial debridement (50 µm), partial (maximum ablation 80 µm) topography-guided excimer laser stromal ablation, and high-fluence ultraviolet-A irradiation (10 mW/cm^2), accelerated (10') CXL performed with the Avedro KXL System (Avedro, Inc., Waltham, MA). The Athens Protocol treatments employed the Oculyzer II (WaveLight AG, Erlagen, Germany)[9,10] for corneal topography imaging. The Oculyzer II is a high-resolution Pentacam Scheimpflug imaging rotating camera (Oculus Optikgeräte GmbH, Wetzlar, Germany) incorporated by a proprietary network in the WaveLight Refractive Suite (WaveLight AG)[11] to provide corneal elevation data to the excimer laser, namely the EX500 (Alcon Laboratories, Fort Worth, TX).

For a patient to be considered for the Athens Protocol procedure, the criteria included clinical diagnosis of progressive keratoconus, minimum age of 18 years, and 300-µm minimum corneal thickness. Further details of the Athens Protocol procedure have been published.[12,13] All patients were observed at 1 week and 1, 3, 6, and 12 months postoperatively, and on an annual basis thereafter. The corneal data reported in this study after treatment comprised measurements obtained at the 12-month postoperative visit.

IMAGING, MEASUREMENT, AND ANALYSIS

The Scheimpflug camera (Oculyzer II) was regularly calibrated according to manufacturer recommendations. The measurements were obtained and processed via the Examination Software (Version 1.17r47; WaveLight AG). The default settings and 25 images per single acquisition were implemented. Keratometric and simulated astigmatism data were obtained with the best fit toric ellipsoid reference surface.

Linear regression analysis was performed to seek possible correlations. Descriptive and comparative statistics and analysis of variance were performed with statistics tools provided by Minitab version 16.2.3. (MiniTab Ltd., Coventry, UK) and Origin Lab version 9 (OriginLab Corp, Northampton, MA). A P value less than .05 was considered statistically significant.

RESULTS

The sample consisted of 267 eyes (82 female and 185 male). There was preponderance toward male gender, consistent with our clinical experience in male-to-female incidence in keratoconic patients[14] and keratoconus incidence studies.[15] Of the 267 eyes, 140 were right eyes and 127 were left eyes. The average age for all patients at the time of the procedure was 30.80 ± 7.25 years (range: 19 to 57 years). The average preoperative corrected distance visual acuity was 20/32, ranging from 20/200 to 20/20 (0.628 ± 0.241). One year postoperatively, average corrected distance visual acuity was 20/25, ranging from 20/100 to 20/16 (0.762 ± 0.225).

ANTERIOR AND POSTERIOR KERATOMETRY AND CORNEAL ASTIGMATISM BEFORE TREATMENT

Average, standard deviation, and maximum and minimum anterior and posterior central corneal surface keratometric values before and after treatment with the Athens Protocol are reported in **Table 1**.

The astigmatism sign is dependent on the flat meridian horizontal or vertical orientation: the sign is considered positive if the flat meridian orientation is between +45° and +135°, which is called "against-the-rule," whereas it is considered negative if between -45° and +45°, which is called "with-the-rule."

After treatment, the resulting anterior astigmatism was on average with-the-rule, whereas the posterior astigmatism was against-the-rule (**Figure 1**). Paired analysis of the differences regarding astigmatism change indicated a P value of .067 for the anterior surface and .358 for the posterior surface.

KERATOMETRIC CHANGES AND ANALYSIS

Figure 1 illustrates the correlation between posterior versus anterior astigmatism in the form of scatter and fitted line plots with 95% confidence intervals and 95% prediction intervals before and after treatment. Before treatment, the coefficient of determination (r^2) was 0.839 with a P value less than .001. After

TABLE 1

Anterior and Posterior Corneal Surface Keratometry and Astigmatism as Measured in the 8-mm Diameter Zone Before and After Treatment

Parameter	Before Treatment				After Treatment			
	Average (D)	SD (D)	Max (D)	Min (D)	Average (D)	SD (D)	Max (D)	Min (D)
Anterior cornea								
Flat	47.06	±6.02	78.50	33.70	43.97	±5.81	73.2	30.1
Steep	51.24	±6.75	80.70	39.50	47.04	±6.86	81.3	33.9
Mean	49.03	±6.21	78.80	38.80	46.37	±6.73	80.9	31.9
Astigmatism	-1.97	±6.21	11.30	-12.40	-1.56	±3.80	12.4	-11.5
Posterior cornea								
Flat	-6.70	±0.99	-4.60	-9.90	-6.58	±1.05	-3.3	-10.4
Steep	-7.67	±1.15	-5.60	-11.00	-7.69	±1.22	-5.2	-13.2
Mean	-7.08	±1.40	8.50	-10.20	-7.08	±1.06	-4.2	-11.5
Astigmatism	+0.53	±1.02	+4.00	-2.60	+0.45	±1.29	+4.3	-5.3

SD = standard deviation; D = diopters; Max = maximum; Min = minimum

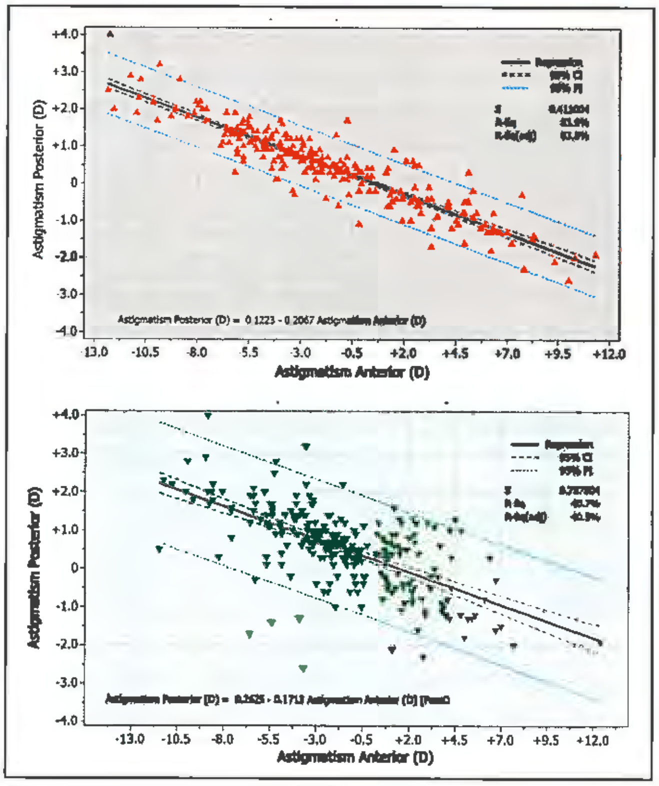

Figure 1. Scatter and fitted line plots of posterior astigmatism expressed in diopters (D) versus anterior astigmatism (also expressed in D) with 95% confidence intervals (CI) and 95% prediction intervals (PI). (Top) Before and (bottom) after treatment.

treatment, r^2 was 0.407 and *P* value less than .001 (**Table 2**).

Data analysis indicates that the mean of the paired differences regarding the flat anterior keratometric values was reduced (flattened) postoperatively by -3.09 ± 2.69 D, or -6.56%, and was statistically significant ($P < .05$) (**Table 2**). The uncertainty associated with estimating the difference from sample data indicated, with a 95% confidence interval, that the true difference was between -2.76 and -3.41 D. The steep anterior keratometric values showed a postoperative flattening by -4.19 ± 2.96 D, or -8.19%, again statistically significant ($P < .05$). The true 95% difference was between -3.84 and -4.55 D.

The mean of the paired differences regarding the flat posterior keratometric values showed an increase of +0.12 ± 0.61 D, or -1.76% (considering the negative sign of the posterior keratometric values). The 95% true difference was between -0.191 and -0.0449 D. The analysis for the steep posterior keratometric values showed a postoperative change of -0.02 ± 0.55 D or +0.04% (95% true difference between -0.0485 and +0.0829 D). These differences were not statistically significant (flat $P = .135$, steep $P = .606$).

DISCUSSION

In this study, a rotating Scheimpflug camera was employed to measure both the anterior and posterior corneal curvature in a large number (267) of keratoconic cases, before and after (1 year postoperatively) a combined CXL and anterior surface excimer laser normalization. In the case of keratoconus, highly irregular keratometric values were present. For example, the simultaneous investigation of anterior and posterior corneal keratometric values has indicated statistically significant differences between normal and keratoconus-suspect eyes.[16] In a study evaluating keratometric values in keratoconic compared to normal eyes, the

TABLE 2

Anterior and Posterior Corneal Surface Keratometry Changes Before and After Treatment[a]

Parameter	K1 Anterior (D)	K2 Anterior (D)	K1 Posterior (D)	K2 Posterior (D)
Relative change (%)	-6.56	-8.19	-1.76	-0.04
Average change	-3.09	-4.19	0.12	-0.02
SD	2.67	2.96	0.61	0.55
Max	4.95	1.70	3.60	2.00
Min	-17.30	-17.30	-1.50	-2.90
P^b	< .01	< .01	.135	.606

K = keratometry; K1 = flat; K2 = steep; D = diopters; SD = standard deviation; Max = maximum; Min = minimum

[a] Average change is defined as the postoperative (after treatment) minus the preoperative value (before treatment), computed on each individual. Relative change is defined as the percent of the average change of the parameter with regard to the respective preoperative value.

[b] Two sample t test.

mean value was 43.28 ± 1.17 D (range: 41.53 to 45.40 D) for normal eyes and 49.29 ± 4.37 D (range: 42.97 to 60.33 D) for keratoconic eyes.[17]

In our study, the average keratometric values before treatment were 47.06 ± 6.02 D (range: 33.7 to 78.5 D) for flat and 51.24 ± 6.75 D (range: 39.5 to 80.7 D) for steep. As shown in the corresponding box plots in **Figures A-C** (available in the online version of this article), 95% of the sample population had a steep keratometric value greater than 46.025 D, consistent with the Collaborative Longitudinal Evaluation of Keratoconus group standards.[7]

In the current study, before treatment the results were characterized by a pattern of linear correlation between anterior and posterior astigmatism, as shown in the fitted line plot of **Figure 1**. The anterior astigmatism before treatment is generally with-the-rule and the posterior astigmatism is against-the-rule, with a linear fit coefficient ratio of -0.2067 and a robust coefficient of determination (r^2) of 0.839. Thus, posterior corneal keratometric values appeared in this large keratoconic population to be associated with the anterior keratometric values.

However, this pattern does not seem to be consistent after treatment (**Figure 1**). Although the ratio was similar (-0.26), the coefficient of determination was considered poor ($r^2 = 0.405$). Our results indicate that this was due to the induced changes in the anterior surface. Specifically, there was a statistically significant reduction in the anterior keratometric values after the Athens Protocol procedure demonstrated by a flattening of -3.09 D for the flat and -4.19 D for the steep meridians, in agreement with other studies of keratoconic cases receiving CXL treatment.[18] The observed changes in the posterior keratometric values were not statistically significant, and thus no measurable change in the posterior corneal surface could be established in our study.

The issue of posterior surface change following CXL,[19] surface ablation,[20] or a combination of both procedures has to be viewed with skepticism. We present these data with the reservation that measurements of the posterior surface might be influenced by the algorithm involving corneal thickness measurements, which, in the case of the densitometry principle-based imaging, might be influenced in the CXL-treated corneas.[21,22] Scheimpflug imaging in its current form can only provide data for the posterior surface on clear, normal corneas. Any significant cornea irregularity or light conduction interference may bias the findings. Also possible is that the denser CXL effect observed with application of the Athens Protocol may mask posterior surface changes. Therefore, although we observed some posterior surface changes, as expected, due to the dramatic alteration of the anterior surface and cornea stromal changes, these appear to be non-significant in comparison to the anterior surface changes.

There is an obvious clinical dilemma in deciding to ablate thin corneas with ectasia. Traditional clinical experience in the pro-CXL era may consider this dangerous for the ectasia progression. We investigated the principle of posterior curvature stability in these eyes because of a critical factor of establishing the safety of ablating these corneas. As expected, the posterior surface keratometric values did not show statistically significant postoperative change. Various data suggest that there is minimal change in the biomechanical behavior of the ectatic cornea after the Athens Protocol, despite the dramatic change in the anterior surface cone.

Before treatment the elevated anterior and posterior keratometric values were highly correlated. After treatment showed statistically significant anterior surface flattening, consistent with our previous studies. The posterior surface did not show a statistically significant change, validating the accomplished cornea stability despite the interventional thinning.

AUTHOR CONTRIBUTIONS

Conception and design (AJK); data collection (AJK); analysis and interpretation of data (AJK, GA); writing the manuscript (GA); critical revision of the manuscript (AJK, GA)

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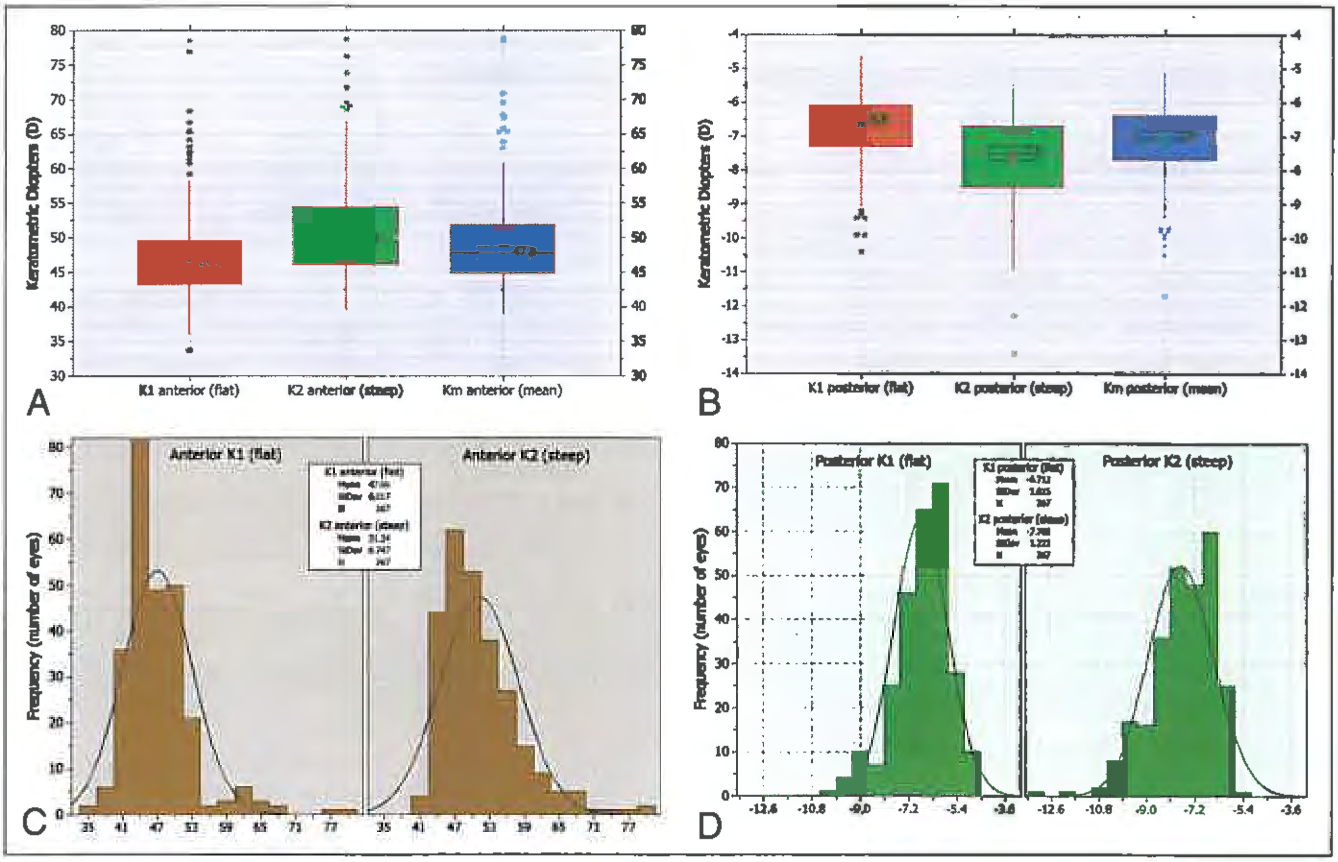

Figure A. Anterior and posterior surface keratometric values (K1 [flat], K2 [steep], and Km [mean]) before treatment. (A, B) Box plots showing median level (indicated by ⊗, average symbol ⊕), 95% median confidence range box (black line boxes), and interquartile intervals range box (red line boxes). (C, D) The corresponding histogram plots)for K1 and K2. All units in keratometric diopters (D).

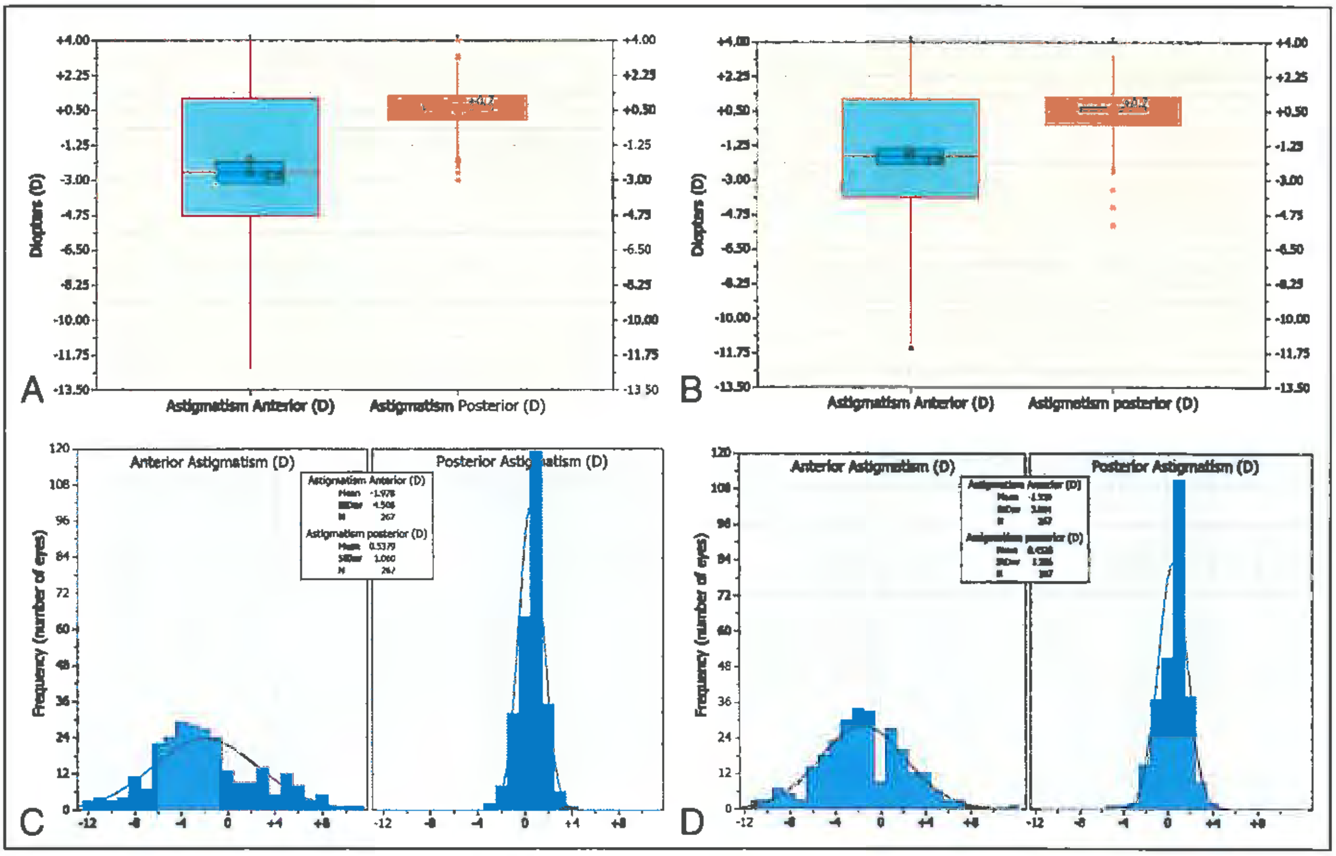

Figure B. Corneal astigmatism for the (left) before and (right) after treatment. (A, B) Box plots showing anterior and posterior astigmatism median level (indicated by ⊗, average symbol ⊕), 95% median confidence range box (black line boxes), and interquartile intervals range box (red line boxes). (C, D) The corresponding histogram plots for anterior and posterior astigmatism. All units in diopters (D).

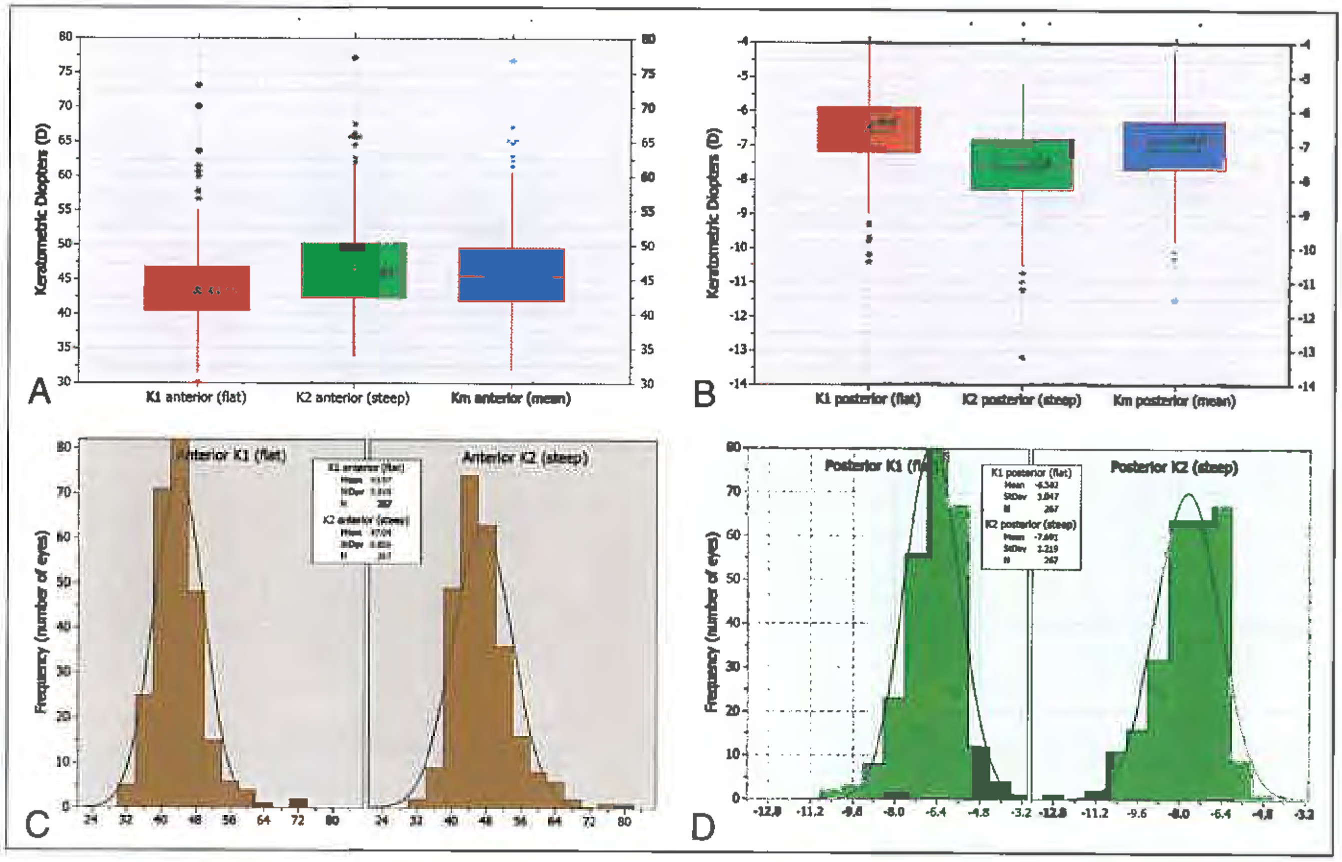

Figure C. Anterior and posterior surface keratometric values (K1 [flat], K2 [steep], and Km [mean]) after treatment. (A, B) Box plots showing median level (indicated by ⊗, average symbol ⊕), 95% median confidence range box (black line boxes), and interquartile intervals range box (red line boxes). (C, D) The corresponding histogram plots for K1 and K2. All units in keratometric diopters (D).

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ORIGINAL ARTICLE

Evaluation of Visual Acuity, Pachymetry and Anterior-Surface Irregularity in Keratoconus and Crosslinking Intervention Follow-up in 737 Cases

Anastasios John Kanellopoulos, Vasiliki Moustou, George Asimellis

ABSTRACT

Purpose: To investigate visual acuity, corneal pachymetry, and anterior-surface irregularity indices correlation with keratoconus severity in a very large pool of clinically-diagnosed untreated keratoconic eyes, and in keratoconic eyes subjected to cross-linking intervention.

Materials and methods: Total of 737 keratoconic (KCN) cases were evaluated. Group A was formed from 362 untreated keratoconic eyes, and group B from 375 keratoconic eyes subjected to partial normalization via topography-guided excimer laser ablation and high-fluence collagen crosslinking. A control group C of 145 healthy eyes was employed for comparison. We investigated distance visual acuity, uncorrected (UDVA), best-spectacle corrected (CDVA), and Scheimpflug-derived keratometry, pachymetry (central corneal thickness, CCT and thinnest, TCT), and two anterior-surface irregularity indices, the index of surface variance (ISV) and the index of height decentration (IHD). The correlations between these parameters *vs* topographic keratoconus classification (TKC) were investigated.

Results: Keratometry for group A was K1 (flat) 46.67 ± 3.80 D and K2 (steep) 50.76 ± 5.02 D; for group B K1 44.03 ± 3.64 D and K2 46.87 ± 4.61 D; for group C, K1 42.89 ± 1.45 D and K2 44.18 ± 1.88 D. Visual acuity for group A was UDVA 0.12 ± 0.18 and CDVA 0.59 ± 0.25 (decimal), for group B, 0.51 ± 0.28 and 0.77 ± 0.22, and for group C, 0.81 ± 0.31 and 0.87 ± 0.12.

Correlation between ISV and TKC (r^2) was for group A 0.853, and for group-B 0.886. Correlation between IHD and TKC was for group A $r^2 = 0.731$, and for group B 0.701. The ROC analysis 'area under the curve' was for CDVA 0.550, TCT 0.596, ISV 0.876 and IHD 0.887.

Conclusion: Our study indicates that the traditionally employed metrics of visual acuity and corneal thickness may not be robust indicators nor provide accurate assessment on either keratoconus severity or postoperative evaluation. Two anterior surface irregularity indices, derived by Scheimpflug-imaging, ISV and IHD, may be more sensitive and specific tools.

Précis: Visual acuity, Scheimpflug-derived pachymetry and anterior-surface irregularity correlation to keratoconus severity in untreated cases (A), treated with crosslinking (B), and in a control group (C) reveals that visual acuity and pachymetry do not correlate well with keratoconus severity.

Keywords: Athens Protocol, Combined topography guided PRK and higher fluence CXL, Visual rehabilitation in keratoconus, Severity criteria, Keratoconus progression, Keratoconus classification, Pentacam, Keratoconic Scheimpflug topometric indices, Visual acuity, Keratoconus, Grading anterior surface Pentacam Indices, Keratoconus Amsler and Krumeich grading, Corneal pachymetry, Receiver operating characteristic ROC analysis.

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INTRODUCTION

Keratoconus (KCN), derived from the Greek words κερατοειδής: cornea; κώνος: cone, meaning cone-shaped protrusion, is a corneal disorder, defined as a noninflammatory degenerative axial thinning of an ectatic cornea.[1] Vision is affected by increased myopia due to the cone protrusion, and irregular astigmatism due to substantial corneal asymmetry.[2-4]

Our long clinical experience with keratoconic screening and rehabilitation[5-7] indicates that neither corneal pachymetry nor visual acuity (uncorrected distance visual acuity, UDVA, and best-spectacle corrected distance visual acuity, CDVA) can be reliable indicators of ectasia and/or keratoconus progression assessment.[8] One may expect that the presence of large amounts of corneal irregularities might hamper sufficient spectacle-correction of visual acuity. However, at least in our experience, often enough keratoconic patients present with surprisingly high CDVA, even near 20/20, despite severe topographic irregularity and/or pachymetric thinning present. This makes keratoconus diagnosis a difficult and potentially dangerous process, as most early, many advanced and even some severe cases can be missed with traditional screening methods. We have also encountered cases with progressive keratoconus with no clinically significant reduction in visual acuity.

To the best of our knowledge, the subject of quantitative correlation of visual acuity with keratoconus grading[9-11] has been reported only in very few peer-review publications.

This study aims to investigate the possible correlations of visual acuity (UDVA and CDVA), corneal pachymetry, and specific Scheimpflug-imaging derived anterior-surface topographic irregularity indices with keratoconus severity, in a large pool of clinically-diagnosed keratoconic eyes, and in a group of keratoconic eyes subjected to cross-linking and anterior-surface normalization intervention, and examine the applicability of these indicators in keratoconus screening, ectasia severity classification, and clinical keratoconus management follow-up.

MATERIALS AND METHODS

This study received approval by the Ethics Committee of our Institution, adherent to the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject at the time of the first clinical visit.

Patient Inclusion Criteria

A total of seven hundred thirty seven (737) keratoconic eyes were evaluated, enrolled in the study over the course of the past 7 years. Each patient enrolled in the study was subjected to a complete ocular examination, including slit-lamp biomicroscopy for clinical signs of keratoconus.

Group A consisted of unoperated eyes clinically diagnosed with keratoconus. Mean age or patients in this group at the time of the examination was 30.3 ± 6.9 (19 to 55) years of age. In this 'unoperated KCN' group A, 362 different eyes were enrolled, of which 196 were right (OD) and 166 left (OS). Gender specifics were 124 eyes belonging to female patients, and 238 to male patients.

Inclusion criteria were a minimum age of 18 years and clinical diagnosis of keratoconus. Exclusion criteria were systemic disease, any previous corneal surgery, history of chemical injury or delayed epithelial healing, and pregnancy or lactation during the study (for the female patients).

Group B (AP-treated) was formed from keratoconic patients whose eyes received anterior surface normalization by partial topography-guided excimer ablation combined with higher fluence CXL, a procedure we introduced and reported as the Athens Protocol.[12,13] The same surgeon (AJK) performed the operations. Mean age or patients in this group, at the 6 months postoperative examination, was 31.2 ± 7.3 (20 to 57) years. In this 'AP-treated KCN' group, 375 different eyes were enrolled, of which 199 were right (OD) and 176 left (OS). 142 eyes belonged to female patients and 233 to male patients. The noted preponderance in both groups toward male population is consistent with our clinical experience in male-female incidence in keratoconic patients,[8] and keratoconus incidence large studies.[14] Inclusion criteria for group B were uneventful Athens-protocol rehabilitation, and no other ocular complications.

The control group C (n = 145 different eyes, 75 right and 70 left, 83 belonging to male and 62 to female patients) consisted of unoperated, normal eyes with no current or past ocular pathology other than refractive error, no previous surgery and no present irritation or dry eye disorder, all confirmed by a complete ophthalmologic evaluation. Contact lens wearers were excluded from this group C.

Imaging, Measurement and Analysis

In each case, clinical examination included monocular UDVA and subjective refraction and CDVA with the best spectacle refraction. Both UDVA and CDVA were measured in mesopic conditions.

Scheimpflug imaging was performed with the WaveLight Oculyzer (WaveLight, Erlangen, Germany), a Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) Scheimpflug rotating camera.[15,16] The device was calibrated according to manufacturer recommendations prior to undertaking the measurements. The measurements were obtained and processed via the Examination Software (Version 1.17r47). The default settings of twenty-five images per single acquisition was used. Scheimpflug imaging was conducted in order to provide anterior surface keratometry (K1 flat and K2 steep meridian, reported in keratometric diopters (D)), corneal pachymetry, (TCT, thinnest corneal thickness, measured in μm), and keratoconus Amsler & Krumeich classification. The topographic keratoconus classification (TKC) scale with increasing severity, was: (–), KC1, KC1-2, KC2, KC2-3, KC3, KC3-4, and KC4. Corneal surface irregularity was evaluated by two anterior-surface topometric indices, measured in the central 8 mm corneal zone. These indices were: the (unitless) index of surface variance (ISV), an expression of corneal surface curvature irregularity, expressing the standard deviation of the sagittal radius values from the mean; and the index of height decentration (IHD), calculated with Fourier analysis of corneal height data to quantify the degree of vertical cone decentration.[8] The decentration is calculated on a ring of 3 mm radius.

For groups A and C, measurements from the most recent clinical visit has been included in the study. For group B, measurements from the closest to the one-year postoperative visit was considered.

Linear regression analysis was performed to seek possible correlations. Descriptive and comparative statistics, analysis of variance between keratoconus TKC severity and regression analysis, and receiver operating characteristics (ROC) curve analysis were performed with statistics tools provided by Minitab version 16.2.3 (MiniTab Ltd, Coventry, UK) and IBM SPSS Statistics version 21.0 (IBM Corporation, New York, NY).

RESULTS

Keratometric, Topometric, Pachymetric and Visual Acuity Results

As shown in Table 1, average keratometry for group A (unoperated KCN), K1 (flat) was 46.67 ± 3.80 D, and K2 (steep) 50.76 ± 5.02 D. For group B (AP treated) K1 was

Table 1: Average, standard deviation (St Dev), maximum (Max) and minimum (Min) anterior corneal surface keratometry, topometry, pachymetry, and visual acuity, for two groups in the study

	Keratometry		*Topometry*		*Pachymetry*	*Visual acuity*	
	K1 (flat)	*K2 (steep)*	*ISV*	*IHD*	*TCT*	*UDVA*	*CDVA*
Units	*D*	*D*	-	-	*µm*	*Decimal*	*Decimal*
Group A (unoperated KCN eyes)							
Average	46.67	50.76	99.6	0.093	444.64	0.12	0.59
St Dev	±3.80	±5.02	±43.28	±0.052	±37.14	±0.18	±0.25
Max	58.3	65.65	218	0.275	528	0.94	1.22
Min	39.5	42.17	17	0.006	297	0	0.07
Group B (AP-treated KCN eyes)							
Average	44.03	46.87	79.21	0.059	364.91	0.51	0.77
St Dev	±3.64	±4.61	±36.58	±0.037	±61.51	±0.28	±0.22
Max	55.5	62.75	190	0.208	501	1.25	1.25
Min	36.2	39.9	11	0.001	179	0.01	0.1
Group C (control)							
Average	42.89	44.18	31.83	0.023	525.15	0.81	0.87
St Dev	±1.45	±1.88	±23.43	±0.016	±27.93	±0.31	±0.12
Max	48.7	47.2	37	0.037	575	1.35	1.35
Min	40.3	39.1	14	0.001	449	0.1	0.74

D: diopters; ISV: index of surface variance; IHD: index of height decentration; TCT: thinnest corneal thickness; UDVA: uncorrected distance visual acuity; CDVA: best-spectacle corrected distance visual acuity

44.03 ± 3.64 D and K2 46.87 ± 4.61 D, and for group C K1 was 42.89 ± 1.45 D and K2 was 44.18 ± 1.88 D.

Our analysis indicated that more than 95% of the sample population in group A (unoperated KCN eyes) had a steep meridian keratometry >46.025 D, consistent with the CLEK group standards.[1]

Corneal surface irregularity, as expressed by the indices ISV and IHD, was: for group A ISV 99.60 ± 43.28 and IHD 0.093 ± 0.052, for group B ISV 79.21 ± 36.58, and IHD 0.059 ± 0.037, and for group C ISV 31.83 ± 23.81 and IHD 0.031 ± 0.19.

Average thinnest corneal pachymetry for group A was 444.64 ± 37.14 µm, for group B 364.91 ± 61.51 µm, and for group C 525.15 ± 27.93 µm.

Visual acuity, as reported by the decimal expressions of UDVA and CDVA was, for group A, 0.12 ± 0.18 and 0.59 ± 0.25, for group B 0.51 ± 0.28 and 0.77 ± 0.22 and for group C 0.81 ± 0.31 and 0.87 ± 0.12.

Keratoconus Severity Grading

The histograms based on the Scheimpflug severity grading of each eye in seven alphanumeric TKC grades for groups A and B are presented in Figure 1. To facilitate statistical analysis we introduced a numeric conversion, that is grade (–) was set to 0, KC1 to 1, KC1-2, to 2, KC2 to 3, KC2-3 to 4, KC3 to 5, KC3-4 to 6 and KC4 to 7. Based on this conversion, for group A average TKC grade was 3.81 ± 1.95 (the average was between KC2 and KC2-3, closer to the KC2-3 grade), and for group B, average TKC grade was 3.39 ± 1.89, closer to the KC2 grade. Group C, comprised of healthy, nonkeratoconic eyes, had average TKC (–).

Linear fit between Visual Acuity, Thinnest Pachymetry, Topometric Indices and TKC Grading

The linear fit between the various parameters studied (UDVA, CDVA, TCT, ISV and IHD) and the Scheimpflug-derived TKC classification is presented in the form of marginal plots (Figs 2 to 6) and the coefficients of determination (r^2) are reported in Table 2.

Figure 2 illustrates UDVA *vs* TKC grading for both groups, and Figure 3, CDVA *vs* TKC grading for both groups. Based on these graphs, and as reported in Table 2, the coefficient of determination (r^2) was, for the group A, between UDVA and TKC, 0.071 and between CDVA and TKC, 0.292. Likewise, for the group B, between UDVA and TKC r^2 was 0.292 and between CDVA and TKC, 0.175.

The linear fit between thinnest cornea (TCT) and TKC grading is presented in Figure 4 for both groups. Based on these graphs, the coefficient of determination (r^2) between TCT and TKC, was, for group A, 0.236 and for group B, 0.180.

The linear fit between the anterior-surface indices ISV and IHD and TKC grading is presented in Figures 5 and 6. Based on these graphs, the coefficient of determination (r^2) between ISV and TKC was for group A, 0.853, and for group B, 0.886. Likewise, the coefficient of determination (r^2) between IHD and TKC was for group A, 0.731 and for group B, 0.701 respectively.

Receiver Operating Characteristic Curve Analysis

Receiver operating characteristics (ROC) curve analysis, area under curve (area), standard error (Std. error),

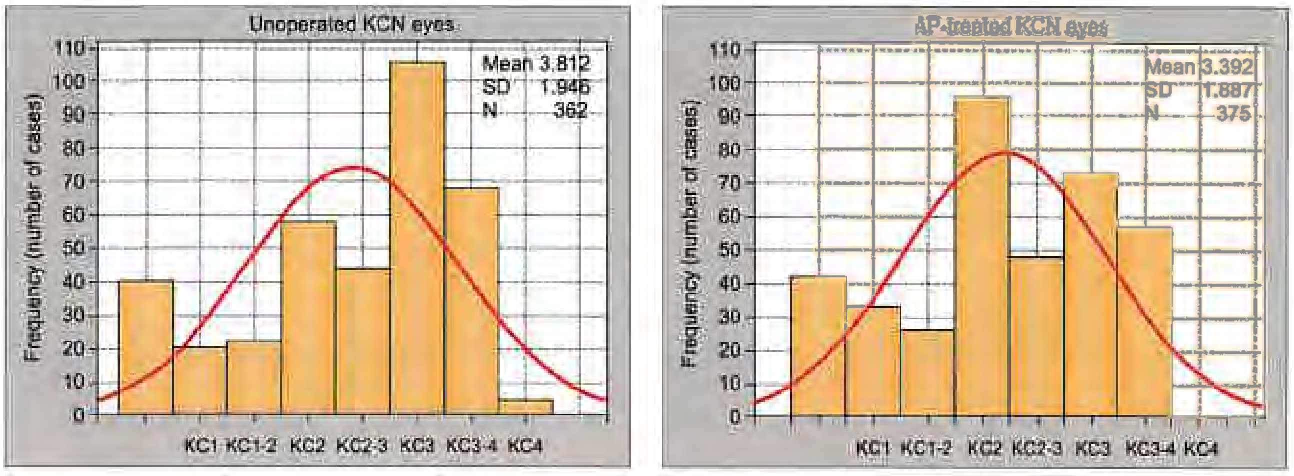

Fig. 1: Histograms of keratoconus classification for the two groups under study. Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes

Table 2: Coefficient of determination (r^2) and pearson correlation coefficient for the two groups in the study between UDVA and TKC, CDVA and TKC, TCT and TKC, ISV TKC, IHD and TKC

	Coefficient of determination (r^2)	*Pearson correlation coefficient*
UDVA vs TKC		
Group A, unoperated KCN eyes	0.071	−2.931
Group B, AP-treated KCN eyes	0.263	−3.367
CDVA vs TKC		
Group A, unoperated KCN eyes	0.292	−4.285
Group B, AP-treated KCN eyes	0.175	−3.549
TCT vs TKC		
Group A, unoperated KCN eyes	0.236	−0.0245
Group B, AP-treated KCN eyes	0.176	−0.0131
ISV vs TKC		
Group A, unoperated KCN eyes	0.853	0.0415
Group B, AP-treated KCN eyes	0.886	0.0485
IHD vs TKC		
Group A, unoperated KCN eyes	0.731	31.9
Group B, AP-treated KCN eyes	0.701	43.1

KCN: keratoconus; UDVA: uncorrected distance visual acuity (decimal); TKC: topographic keratoconus classification; CDVA: best-spectacle corrected distance visual acuity (units, decimal); TCT: thinnest corneal thickness (units, µm); ISV: index of surface variance; IHD: index of height decentration; AP: Athens-protocol

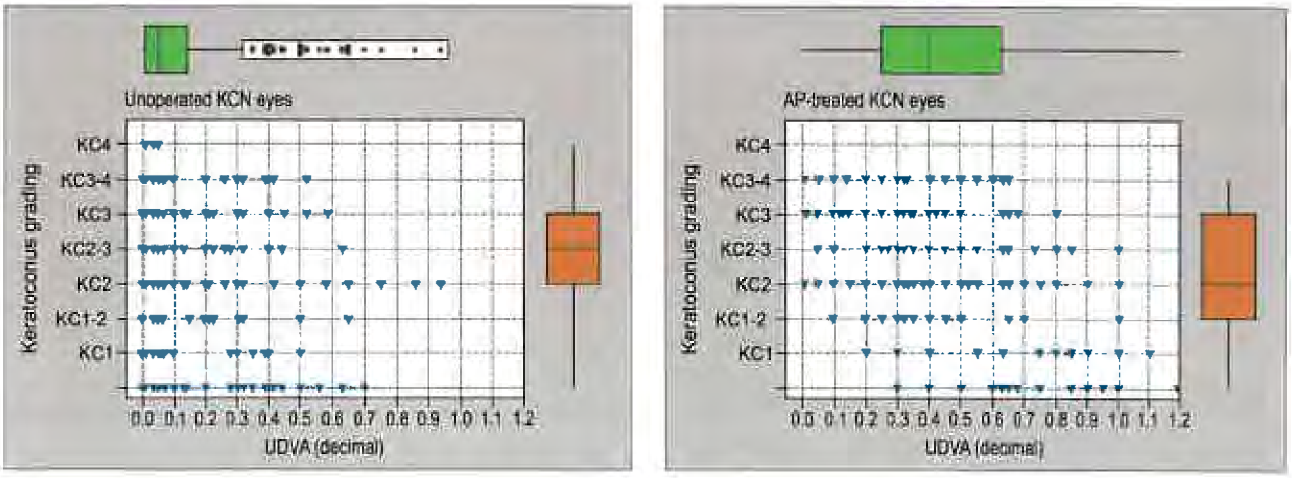

Fig. 2: Marginal plot of UDVA (expressed decimally) and TKC grading with overlying box plots showing mean levels and outliers. Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes

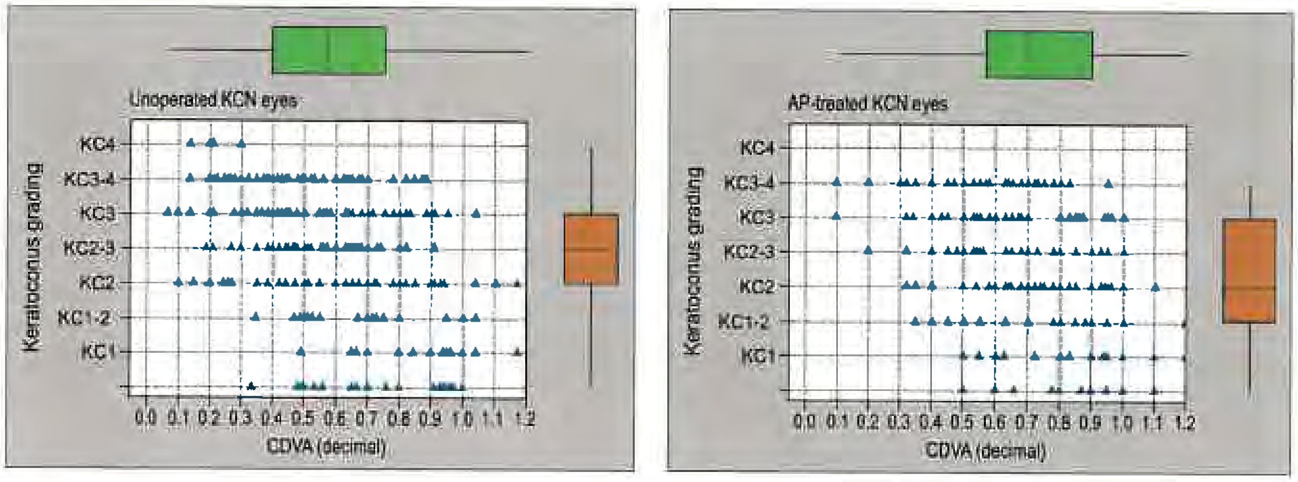

Fig. 3: Marginal plot of CDVA (expressed decimally) and TKC grading with overlying box plots showing mean levels and outliers. Left — group A, unoperated KCN eyes and, right — group B Athens-protocol (AP) treated KCN eyes

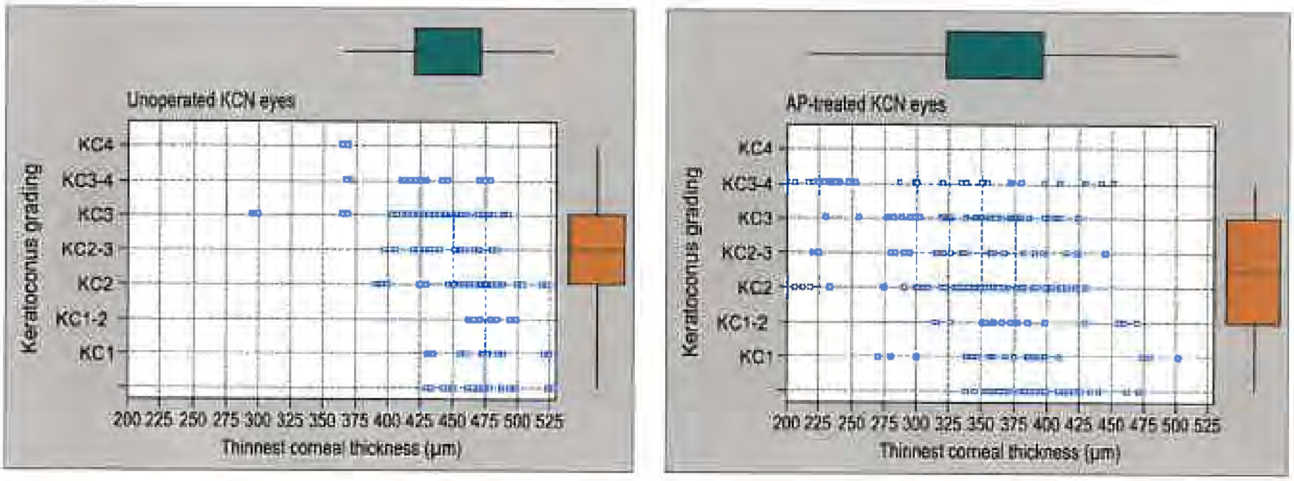

Fig. 4: Marginal plot of TCT, thinnest corneal thickness (expressed in μm), and TKC grading with overlying box plots showing mean levels and outliers. Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes

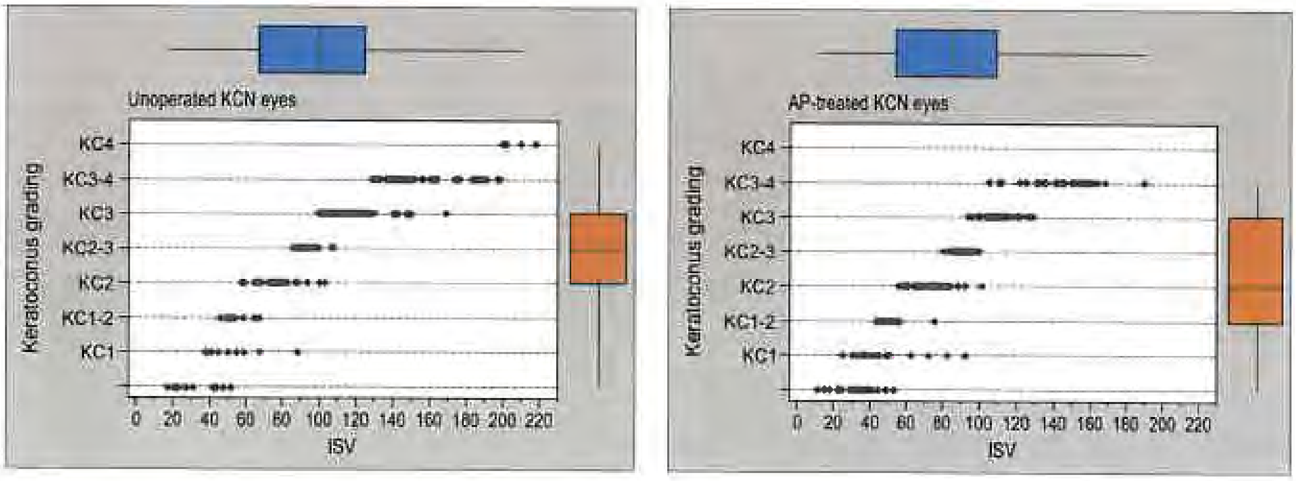

Fig. 5: Marginal plot of ISV, index of surface variance, and TKC grading with overlying box plots showing mean levels and outliers Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes

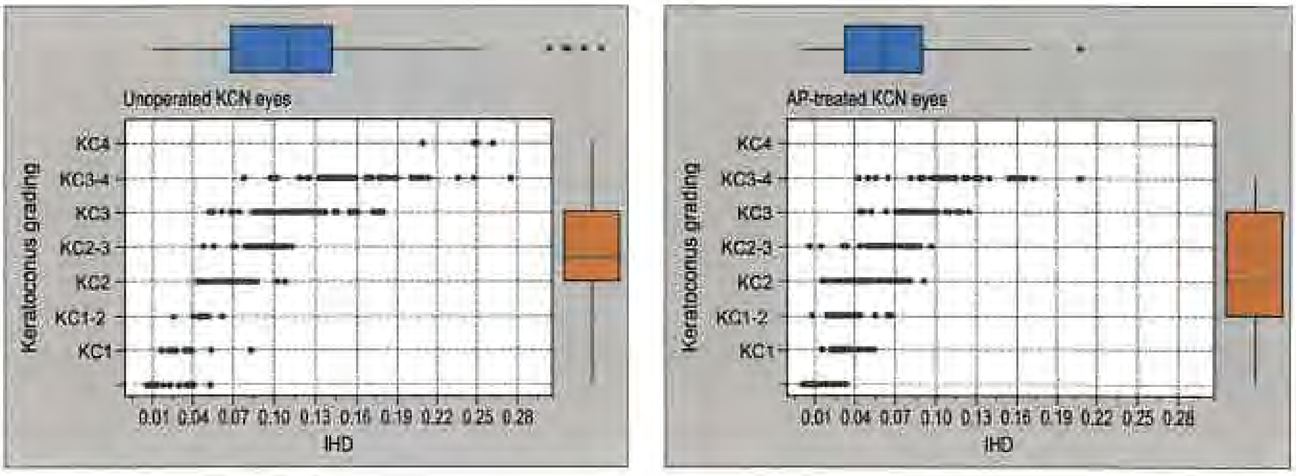

Fig. 6: Marginal plot of IHD, index of height decentration, and TKC grading with overlying box plots showing mean levels and outliers. Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes

Table 3: Receiver operating characteristics (ROC) curve analysis, area under curve, standard error, asymptotic signature and 95% confidence interval results

Test result variable(s)	*Area under curve*	*Std. error* [a]	*Asymptotic signature* [b]	*Asymptotic 95% confidence interval*	
				Lower bound	*Upper bound*
CDVA	0.550	0.039	0.000	0.524	0.677
TCT	0.596	0.070	0.009	0.535	0.621
ISV	0.876	0.035	0.000	0.808	0.944
IHD	0.887	0.036	0.000	0.817	0.957

CDVA: best-spectacle corrected distance visual acuity; TCT: thinnest corneal thickness; ISV: index of surface variance; IHD: index of height decentration; *Notes*: (a) Under the nonparametric assumption (b) Null hypothesis: true area = 0.5

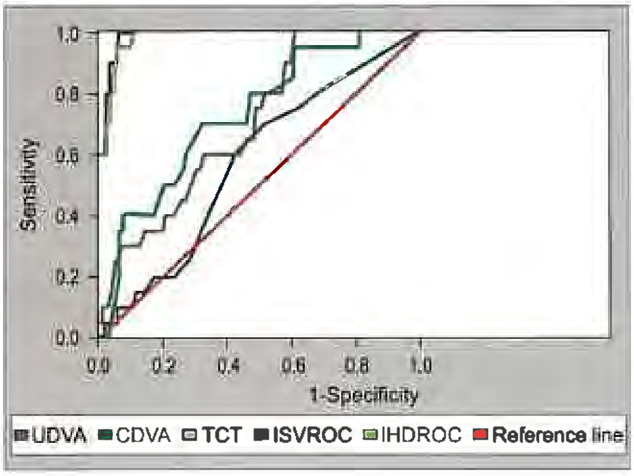

Fig. 7: Receiver operating characteristics plot for the four variables, CDVA, TCT, ISV and IHD. (CDVA: best-spectacle corrected distance visual acuity; TCT: thinnest corneal thickness; ISV: index of surface variance; IHD: index of height decentration)

asymptotic signature and 95% confidence interval results are reported in Table 3 (also plotted in Figure 7), for the following parameters: CDVA, TKC, ISV and IHD. Based on this analysis, the 'area under the sensitivity *vs* specificity curve' was for CDVA 0.550 for TCT 0.596 for ISV, 0.876 and for IHD 0.887.

DISCUSSION

There have been several reports in the peer-review literature lately, regarding the keratectasia and keratoconus assessment[17] and progression monitoring,[18,19] as well as postoperative follow-up due to various CXL interventions.[20] The current options of the clinical investigator include quantitative evaluation of corneal morphologic parameters[21] derived from topography[22,23] or Scheimpflug topometry.[24,25] The latter modality provides specific anterior-surface corneal irregularity indices developed for the grading and classification of keratoconus stages.[26-28]

The association of visual performance from optical quality metrics has been investigated in length for normal eyes and in highly aberrated eyes with keratoconus.[29,30] Visual acuity, which is commonly measured in mesopic conditions, provides a high-contrast forced choice test for establishing threshold values of visual performance, and it is highly sensitive to disturbances in the visual pathway, presenting challenges in the quantification.

To the best of our knowledge, we identified only two reports in this matter of correlation of the above Scheimpflug-derived indices with either best spectacle corrected distance visual acuity (CDVA)[9] or with the severity of keratoconus classification.[31]

The assessment of keratoconus severity with visual function has yielded poor results in a number of front surface-derived parameters in keratoconic eyes. As indicated in results presented in,[9] for example, the average correlation coefficients (r) among CDVA and keratometric and anterior surface irregularity parameters were between 0.421 and 0.643, which, in turn, translate to coefficients of determination (r^2) 0.177 and 0.413. As noted in our results, the spread of CDVA measurements within the same 'severity stage', e.g. KC3, KC3-4 was found to be too large. The lower tier, as well as the upper end of either UDVA or CDVA values were fluctuating in several stages of TKC, from moderate (e.g. KC1 or lower) to severe (e.g. KC3 or higher), therefore lacking the continuum of measurements needed to provide a smooth gradation of the condition from low to severe stage. The correlation between CDVA and TKC (Table 2), had coefficients of determination 0.292 for the unoperated KCN eyes and 0.175 for the AP-treated KCN eyes. The correlation between TCT and TKC was also poor ($r^2 = 0.236$ for the untreated KCN group A and 0.176 for the AP-treated KCN group B). These low coefficient of determination values indicate that visual acuity and/or corneal pachymetry may not be a dependable indicator of keratoconus severity and/or progression.

There are many possible reasons that may explain why visual performance is not well correlated to keratoconus. The large noted fluctuation of visual performance is partly determined by factors unrelated to corneal shape, such as tear film breakup, lenticular shape and opacities, and neurological factors (possible advanced neural processing development in the individual). The effects of optical aberrations on image formation are also very complex. A soft, keratoconic cornea may display 'multifocality', i.e. the cornea may be adaptable, which may further add variability in the measured visual acuity. Additionally, simple clinical reasons may exist as well, such as the fact that in clinical evaluation we refract these young patients monocularly and thus allow them to tilt their head in many directions in order to benefit from the cornea multifocality, use significant accommodation and pinholing and well as squinting.

Likewise, corneal thickness has been suggested in our work as a poor indicator of keratoconus severity. Although it is true that keratoconus is a thinning disease, any individual thickness has large variance and poor sensitivity to distinguish keratoconus from normal corneas.

The data provided herein suggest that clinical assessment of keratoconus severity and/or progression based on visual acuity and/or thinnest pachymetry alone may be misleading. Moreover, the poor correlation found in the AP-treated group B indicates that visual acuity and corneal thickness also cannot be employed as specific disease staging markers in the postoperative assessment of interventions aiming to arrest the keratoconus progression such as cross-linking with riboflavin (CXL).[32] The possible advantages of a cornea 'multifocality' and 'adaptation' in an untreated keratoconic eye, are to a large degree compromised with a CXL procedure, since the cornea becomes stiffer.

In this extremely large sample of patients evaluated, the compelling disease staging markers appear to be the two anterior surface irregularity indices, namely the ISV and the IHD. This work establishes that a better approach may be the examination of quantitative indicators that reflect the anterior-surface variance across the cornea. These anterior shape-based indices provide positive results, and provide a quantitative tool for keratoconus classification and progression assessment. Specifically, the average coefficient of determination (r^2), as reported in Table 2, between ISV and the determined TKC keratoconus severity grade had an average of 0.793 for both keratoconic groups, and between IHD and TKC, 0.716, respectively. In other words, our study indicates that there is a significant correlation (Table 2, Figs 5 and 6) between the two anterior-surface irregularity indices and keratoconus classification, which is within the same margins either the untreated keratoconic group A and the AP-treated group B.

These findings are also quantitatively supported by the receiver operating characteristics (ROC) analysis. Specifically, the area under the curve, indicative of the sensitivity of the index under study, as reported in Table 3, was found to be 0.55 for the CDVA, 0.596 for the TCT, and substantially larger for the ISV and IHD indices, whose respective values were 0.876 and 0.887, indicating that ISV and IHD are more sensitive indicators for keratoconus severity classification. In countries were keratoconus appears to be rampant -we estimate that 1 in every 50 young adults has topographic signs of the disease- topography screening may be the most important public health diagnostic medical tool. With the time-proven disease course alteration by CXL and other technique introduced since, like the Athens Protocol, screening teenagers for KCN may prove a life changing medical assessment in regard to their visual function and adult life work and habitual opportunities.

CONCLUSION

Our study indicates that visual acuity and corneal thickness may be poor indicators for keratoconus severity grading and accurate assessment of postoperative assessment. The compelling disease staging markers appear to be two anterior-surface irregularity indices derived by Scheimpflug imaging, namely the index of surface variance and the index of height decentration, which appear to be more sensitive and specific tools than visual acuity or pachymetry in early diagnosis and possible progression in keratoconus and corneal ectasia. These indices may become a novel benchmark for future studies, and may aid in the development of new keratoconus diagnostic and follow-up criteria.

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Secondary Ectasia Due to Forceps Injury at Childbirth: Management With Combined Topography-guided Partial PRK and Collagen Cross-linking (Athens Protocol) and Subsequent Phakic IOL Implantation

To the Editor:

A 23-year-old man, previously diagnosed with "progressive keratoconus" in his left eye, presented with uncorrected distance visual acuity (UDVA) of 20/20 in the right eye and counting fingers in the left eye, with 20/100 pinhole refraction. Refraction in the left eye was −9.50 −5.00 × 155° with corrected distance visual acuity (CDVA) of 20/100. Keratometry was 43.00/43.50 @ 95° and 51.00/56.80 @ 60° in the right and left eyes, respectively. Potential acuity measurement in the left eye (used to exclude severe amblyopia in that eye) was 20/60. Slit-lamp microscopy examination of the cornea revealed an oblique Descemet membrane split just temporal to the corneal center (Fig, image A), suggesting forceps injury at childbirth as the etiology of the ectasia.[1]

Tomographic pachymetry evaluation (Oculyzer; Wavelight AG, Erlangen, Germany) was normal in the right eye with thinnest cornea of 530 μm, and severe inferior steepening in the left eye with thinnest cornea of 438 μm. Endothelial cell counts were 2242 cells/mm^2 and 1628 cells/mm^2 in the right and left eyes, respectively. Corneal cross-linking (CXL) was recommended for the left eye, but the patient opted to wait.

Over the next 2 years, without intervention, the right eye remained stable. The left eye demonstrated progression of the ectasia and refraction changed to −11.50 −7.00 × 155° with CDVA of 20/150 and keratometry of 56.60/51.20 @ 147.5°.

Tomography showed significant deterioration in the left eye in inferior steepening (Fig, image D). The patient denied any eye rubbing during this interval.

The Athens Protocol (combined topography-guided partial photorefractive keratectomy [PRK] and CXL)[2] was applied in the left eye. This technique has been reported previously.[2-5] The treatment plan with the WaveLight excimer laser platform is demonstrated in the Figure (image F). One year postoperatively, the cornea appeared to be stable with refraction of −9.00 −2.00 × 160° and CDVA of 20/40 (soft contact lens of −9.50 diopters [D]). As the patient became contact lens–intolerant, phakic intraocular lens (PIOL) implantation was performed in the left eye. A single-piece, polymethylmethacrylate, −11.50-D lens with a 6-mm optical zone and 8.5-mm total diameter (Verisyse; AMO, Dublin, Ireland) was chosen. The endothelial cell count at the time of implantation was 1628 cells/mm^2.

The patient was followed for an additional 3 years after PIOL implantation with UDVA of 20/25, pin-

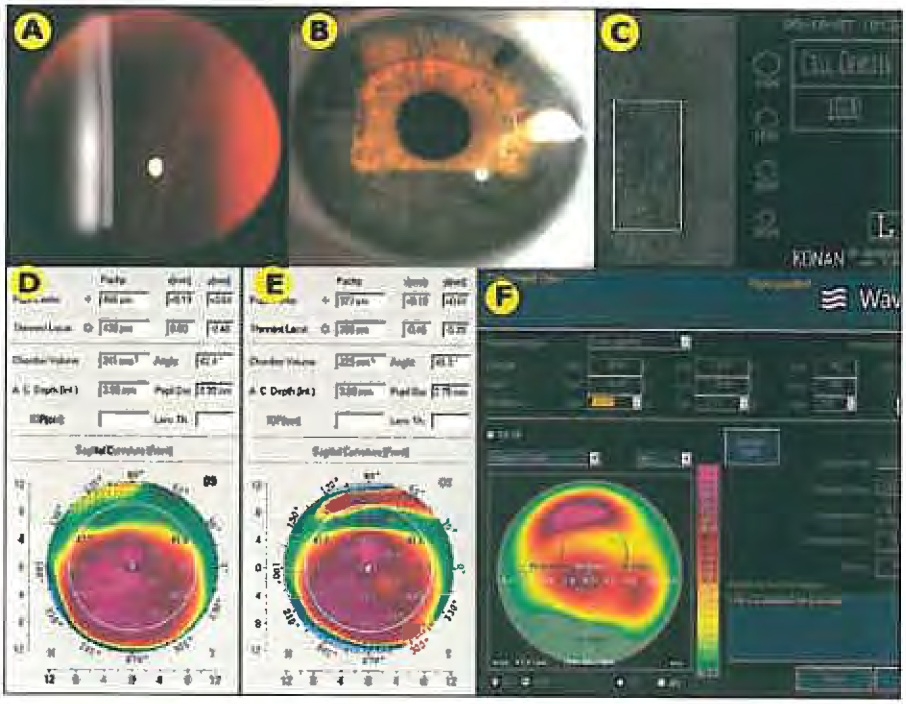

Figure. **A)** Slit-lamp retroillumination of the left eye at presentation shows the Descemet membrane split consistent with history of forceps injury at childbirth. **B)** Slit-lamp photograph of the left eye 3 years after the Athens protocol and 2 years after phakic intraocular lens (IOL) implantation. **C)** Corneal clarity, phakic IOL, and surgical peripheral iridectomy can be seen. Endothelial cell count at the time of image B (last follow-up) is also shown. **D)** Pentacam of the left eye before undergoing the Athens protocol. **E)** Pentacam of the left eye at the time of image B. Improvement of the corneal curvature and regularity can be seen compared to image D. **F)** Treatment plan using the WaveLight excimer platform for topography-guided partial photorefractive keratectomy. The treatment plan, which is pivotal to the application of the Athens protocol, combines a myopic ablation over the cone and a partial hyperopic application superiorly. This treatment combination enhances normalization of the ectasia with a small ablation amount over the cone.

hole to 20/20. Slit-lamp photography of the anterior segment of the left eye is seen in the Figure (image B). Keratometry in the left eye is 55.30/48.80 @ 162° and tomography stable (Fig, image D). The right eye has not changed over 6-year follow-up. Refraction is +0.50 −2.00 × 145°, with UDVA of 20/15. Corneal optical coherence tomography shows hyper-reflective lines in the anterior cornea, suggesting the depth of the CXL effect.[2] Endothelial cell counts remain at 1600 cells/mm^2 (Fig, image C).

The management sequence in this case may provide an effective alternative to other surgical options.

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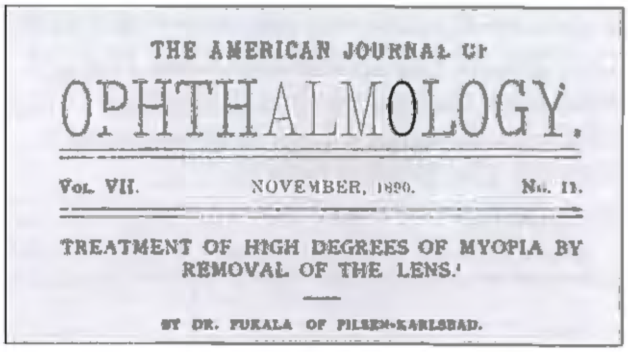
Vincenz Fukala (1847-1911) and the Early History of Clear-lens Surgery in High Myopia

To the Editor:

Vincenz (Wincenty) Fukala was an important pioneer in systematically performing clear-lens extraction in patients with high myopia. Due to his thorough knowledge of theory and positive experiences in many patients, he demonstrated the benefit of clear-lens removal in young patients with high myopia.

Fukala was born in 1847 in a Polish family in Zóllkiew near Lviv at Galicia. He studied medicine in Vienna and specialized in ophthalmology in 1871. He demonstrated the benefit of clear-lens removal in young persons with high degrees of myopia. He persisted despite opposition of several authorities, including Donders, Fuchs, and von Graefe. Thanks to this determination, he convinced the skeptics of the efficacy of lens discission. Ophthalmologists gradually began to carry out surgery in high myopic patients worldwide.



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TREATMENT OF HIGH DEGREES OF MYOPIA BY
REMOVAL OF THE LENS.[1]

BY DR. FUKALA OF PILSEN-KARLSBAD.

Figure. Fukala's translated publication appeared in the November 1890 issue of *The American Journal of Ophthalmology*.

Fukala's procedure consisted of discission of the clear lens with subsequent needling and extraction of swollen lens material. Postoperatively, most patients had good visual acuity and enjoyed working for the first time in their lives. The surgical goal was to observe a clear pupil at the end of surgery. Casey A. Wood translated Fukala's publication from *Graefe's Archive of Ophthalmology* for the *American Journal of Ophthalmology*.[1] In this comprehensive article, Fukala reported having treated 19 eyes with myopia ≥13.00 diopters during the previous 3 years. Fukala only treated young people aged ≤24 years whose fundus revealed no retinal or choroidal disease. Patients had relatively good visual acuity. Patients on whom Fukala operated showed at least a four-fold improvement in vision.

In 1894, Fukala reported 44 patients who successfully underwent surgery from 1887 to 1894. In 1896, Fukala reported that several surgeons had also routinely operated on highly myopic patients, namely Schweigger in Berlin, Pflüger in Bern, Thier in Aachen (each approximately 100 patients), and v. Hippel in Halle and Sattler in Leipzig (each approximately 80 patients).[2]

Barnes wrote: "Up to this writing, there have been about 2500 of the operations reported from abroad...."[3] However, after statistical evaluation of surgical results in the first decades of the 20th century, ophthalmologists no longer performed clear-lens extraction because they feared complications. Retinal detachment was recognized as a major sight-threatening complication of the surgery. Fischer indicated an 11-fold higher risk of blindness in patients who underwent clear-lens surgery.[4] Other complications of clear-lens surgery in high myopia included corneal opacifications after secondary cataract surgery, incarceration of parts of the capsule or vitreous in the corneal wound, vitreous prolapse, and increased intraocular pressure.

At the end of the 20th century, clear-lens excision in high myopes was rediscovered, likely due to the fact that the risk of complications decreased significantly compared to 100 years prior. A more detailed review is available elsewhere.[5]

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The authors have no proprietary interest in the materials presented herein.

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ORIGINAL RESEARCH

Long term results of a prospective randomized bilateral eye comparison trial of higher fluence, shorter duration ultraviolet A radiation, and riboflavin collagen cross linking for progressive keratoconus

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Purpose: To evaluate the safety and efficacy of higher fluence cornea collagen cross linking (CXL).

Methods: Twenty-one patients with bilateral keratoconus had randomized CXL in one eye (group A) with 7 mw/cm^2 for 15 minutes; the other eye (group B) had the standard 3 mw/cm^2 for 30 minutes; 50 um PTK with the Eye-Q 400 Hz Excimer laser (Wavelight, Erlagen, Germany) was used for epithelial removal. The patients were evaluated postoperatively at the following intervals: day 1, day 4, month 1, month 3, and then every 6 months.

Results: For groups A and B respectively, in mean values: uncorrected distance visual acuity (UDVA) improved from 20/60 to 20/38, and 20/62 to 20/40; best corrected visual acuity (BCVA) from 20/30 to 20/25 in both groups; mean sphere was reduced by 2.5 and 2.1 diopters; mean cylinder was reduced by 2.9 and 2.5 diopters on average; Steepest K was reduced from 49.5 to 46.1, and from 48.7 to 45.8 diopters. There was no ectasia progression in any of the cases during the follow-up time studied. There was no change in the endothelial cell count. All patients returned to full activities postoperatively within a month. Four cases from group A and five cases from group B had delayed epithelial healing (completed by postoperative day 9). No other adverse effects were noted in any of the cases studied. Mean follow-up was 46 months (18–56). Corneal optical coherence tomography (OCT) revealed diffused light scattered in anterior two-thirds of the cornea stroma, which was more intense and much broader in diameter in group A than in group B.

Conclusion: This novel technique offers similar clinical results in ectasia stabilization without any adverse effects noted.

Keywords: cornea collagen cross linking (CXL), ectasia management, keratoconus management, higher fluence ultraviolet light

Introduction

The management of keratoconus (KCN) with collagen cross linking (CXL), utilizing UV irradiation and simultaneous topical riboflavin administration, has been studied at length. This has taken place both in laboratory work as well as clinical work,[1–14] and received the CE mark of approval, in December 2006, for clinical use in countries in the European Union. The standard technique described by Wollensak et al involves partial or complete central epithelial removal, followed by topical administration of riboflavin 0.1% solution in order to achieve intra-stromal penetration.[1]

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We theorized that by increasing the UV light fluence we targeted the following: (1) a faster procedure, as the fluence time is shortened, and (2) shorter keratocyte exposure time and potentially less fibrocyte cornea damage caused.

Methods

Twenty-one patients with bilateral progressive keratoconus were studied. The study is a prospective randomized comparative case series. These patients were selected with the following criteria:

1. Topographic and tomographic evidence of keratoconus ($K > 45$ and/or inferior steepening greater than 1 diopter to the superior half of the cornea, and 1 diopter of tomographic cylinder progression over 1 year.)
2. Minimum cornea thickness at or over 450 microns.
3. Age at or over 18 years.
4. Refer to Table 1 for pre-op and post-op: refraction, corrected distance visual acuity (CDVA), UDVA, IOP, corneal endothelial cell count, and the figures for ultrasound cornea pachymetry (UCP), cornea tomography (Oculyzer; Wavelight, Erlangen, Germany), and OCT cornea imaging (Optovue Inc, Fremont, CA), with a minimum of 28 months follow-up.

Surgical technique

Phototherapeutic keratectomy (PTK) epithelial removal: under topical 1% proparacaine anesthesia (Alcaine, Alcon, Fort Worth, Texas), the Wavelight 400 Hz Excimer laser was used for PTK with the parameters of 6.5 mm optical zone, 50 um depth of tissue removal. This mode was used instead of manual epithelial removal for several reasons: (1) to avoid ethanol-related cornea toxicity, and (2) to use the epithelium as a masking agent in epithelial removal, anticipating that this mode would perhaps remove Bowman's membrane and possibly some stroma over the area of the cone, as the epithelium there is usually significantly thinner.

Collagen cross-linking: 0.1 ml of 0.1% of riboflavin solution was administered every 30 seconds for 5 minutes (10 drops) until the de-epithelialized cornea was a bright yellow color, due to the presence and stromal infiltration of the riboflavin solution. The preceding removal of Bowman's membrane at the cone area facilitated rapid riboflavin solution diffusion within the stroma within 5 minutes. The cornea was then exposed to UV light: group A with 7 mW/cm^2 for 15 minutes and group B for the standard 3 mW/cm^2 for 30 minutes.

A UV irradiation source of an average 370 nm wavelength (365–375 nm) was used to irradiate the corneal surface. The effective fluence at the corneal surface was calibrated at 7 mW/cm^2 and lasted 15 minutes. The total amount of UV irradiation delivered at an 8 mm-diameter corneal plane was calculated to be 6.3 joules (in comparison to 5.4 joules for group B).

Post-op medicines included topical ofloxacin four times daily for 1 week, and a combination of chlorampenicol and 1% prednisolone acetate (Dispersadron C, Alcon) four times daily for a month and twice daily for another month. Vitamin C – 1000 mg per day – was administered orally for 2 months, and patients were encouraged to avoid direct sunlight. The patients were evaluated at postoperative day 1, day 4, month 1, month 3, and then every 6 months.

Results

Table 1 documents the pre- and post-UDVA, CDVA, Steepest K, Min K, endothelial cell count (ECC), Pentacam thickness, OCT thickness and hyper-reflectivity. The results for groups A and B in mean values respectively are: UDVA improved from 20/60 to 20/40, BSCVA from 20/30 to 20/25, mean sphere was reduced by 2.4 diopters, mean cylinder was reduced by 2.9 diopters on average, Steepest K was reduced from 49.5 to 46.1 diopters. There was no ectasia progression in any of the cases during the follow-up time studied and there was no change in the endothelial cell count.

There was an initial reduction of cornea pachymetry at 1 month, at about 20% of the preoperative pachymetry measurement. The mean thinnest cornea pachymetry appeared to increase at 18 months follow-up by 25%, on average, when compared to postoperatives in the first month, and by 5% when compared to the preoperative pachymetry measurement. All patients returned to full activities postoperatively within a month. Four cases from group A and five cases from group B had delayed epithelial healing (completed in day nine). No other adverse effects were noted in any of the cases studied. Mean follow-up was 46 months (18–56).

Representative pre- and postoperative tomographies for two eyes from group A, along with their topographic

Table 1 Summary of perioperative data

Variable	7 mW/cm^2 – group A	3 mW/cm^2 – group B
UDVA pre-op	20/60	20/62
UDVA post-op	20/38	20/40
CDVA pre-op	20/30	20/30
CDVA post-op	20/25	20/25
Spherical equivalent change	–2.5D (1.4–3.1)	–2.3D (1.3–2.9)
Refractive cylinder change	–2.9D (1.5–3.4)	–2.8D (1.6–3.3)
Topometric cylinder change (steepest K)	–3.4D (1.6–4.1)	–2.9D (1.7–3.8)
Endothelial cell change	–100	–250
Delayed epithelial healing	4	5
Complications	0	0

Abbreviations: UDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; D, diopter.

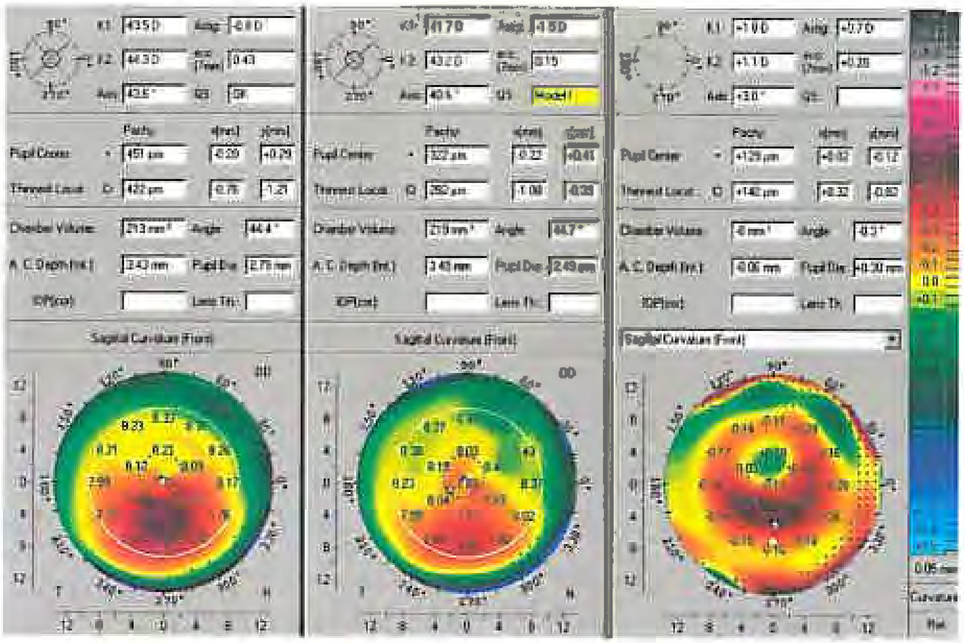

Figure 1 Pre (left), post (center), and difference (right) topography maps from an indicative case of Group A.

difference, are displayed in Figures 1 and 2. Slit lamp biomicroscopy revealed no long term epithelial defects, and diffuse light scattering in anterior 2/3 of the cornea stroma, consistent with our clinical findings from the standard CXL technique, was more intense and much broader in diameter in group A (Figures 3 and 4).

Discussion

We have clinically applied CXL, utilizing ultraviolet A irradiation and riboflavin solution in cornea ectasia, keratoconus and bullous keratopathy over the last 6 years.[12–16,18–24] We have previously presented and reported the employment of higher fluence CXL with riboflavin

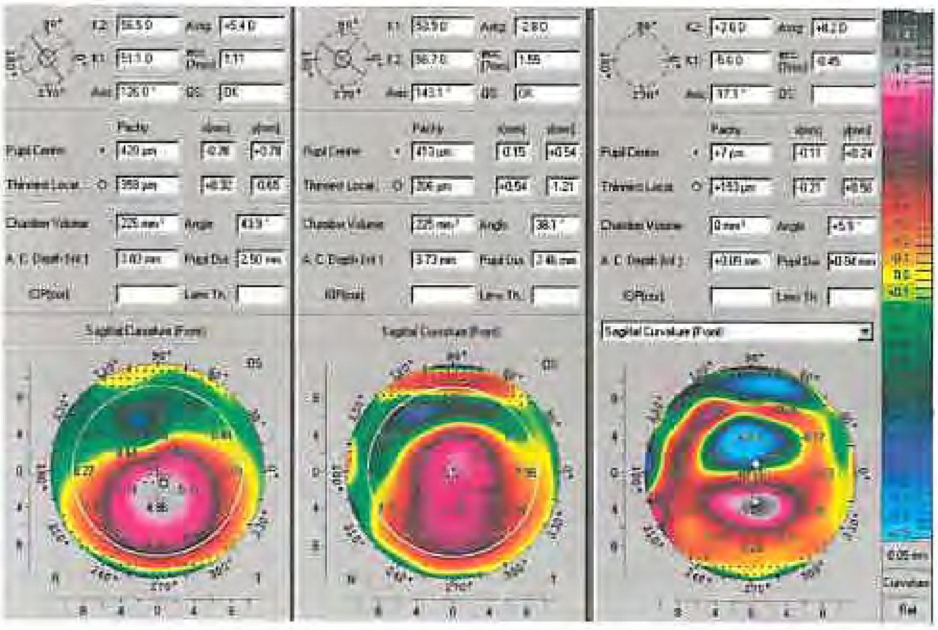

Figure 2 Pre (left), post (center), and difference (right) topography maps and keratometric data of an additional indicative case of Group A.

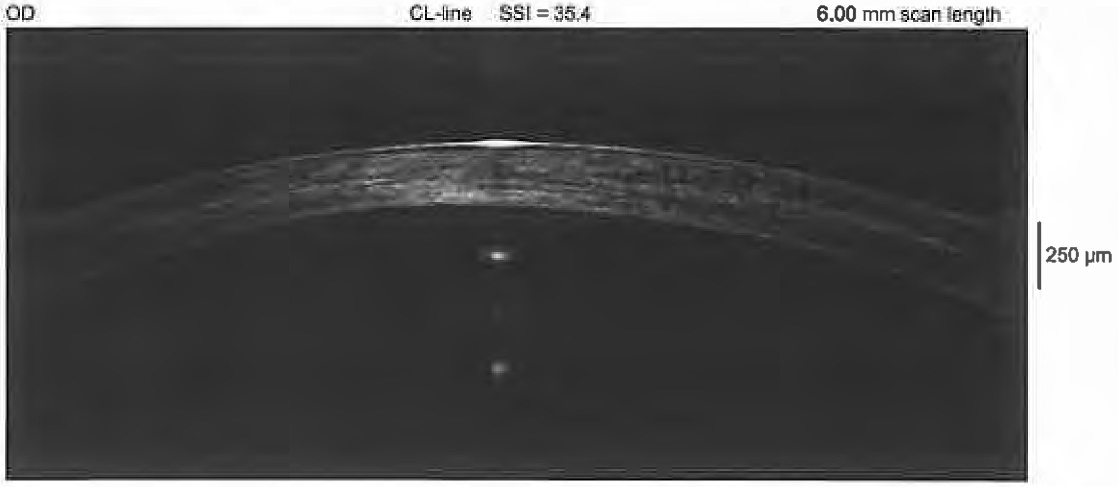

Figure 3 A 1 year postoperative cornea OCT from a case from Group A (also studied in Figure 1). There is very wide and deep stromal hyper-reflectivity representing effective large stromal volume cross-linking.

solution administration via a femtosecond created intracorneal pocket.[22]

CXL was shown to have a documented benefit to corneal ectatic disorders. One of the shortcomings with the standard Dresden protocol are lengthy exposure duration (30 minutes). Post-operative pain, delayed epithelial healing, and delayed visual rehabilitation for 1 to 2 weeks postoperatively are some of the other shortcomings.

The contributing elements in the CXL photo-oxidative and biochemical reactions are riboflavin, UVA light, oxygen, and stromal collagen. There is a potential limit of oxygen availability and absorption by riboflavin within the stroma during the length of standard cross-linking procedure. If the riboflavin was already present in the cornea stroma, a larger portion of UVA light may pass through the cornea epithelium and produce the photochemical reaction in the cornea stroma instead of the eye's surface, therefore facilitating more efficient intra-stromal cross-linking and potentially less collateral toxicity to the cornea surface.

In the standard technique, the riboflavin-soaked cornea stroma absorbs the UVA light and, with oxygen, produces a photo-oxidative reaction (type 2). The product is a free radical oxygen molecule, which facilitates a biochemical reaction within stromal collagen. We speculate that it generates fiber to fiber bonds, or bonds between proteoglycans and collagen fibrils,[25] leading to higher stromal rigidity.

The novel method described herein, where higher fluence UV light is used with shorter exposure, appears to be safe and effective in stabilizing keratoconus.

Figure 4 This is an 18 month postoperative cornea OCT of a case from Group A (same case shown in Figure 2). The extreme cornea thinning is evident, along with deep stroma hyper-reflectivity representing effective large stromal volume cross-linking.

This technique appears to be similar but more comfortable for the patients. It requires half UV exposure time, has similar first night discomfort, and all patients returned to pre-op visual function with no epithelial defect by week one (on average).

Would there be a reduced stromal keratocyte loss, compared to that reported with the standard technique,[17] because there is a shorter duration of UV exposure with higher fluence? Most human cells are believed to be more resistant to short or pulsed exposure to UV light, rather than longer and continuous exposure. Does this procedure pose less risk for postoperative infectious keratitis, again due to the shorter duration and the higher fluence providing a "dis-infective effect"?

In our early clinical experience, this new technique has been very rewarding in regard to the cross-linking effect.

This technique may become an alternative CXL technique for the prevention and stabilization of cornea ectasia. In our opinion, it may become an effective application as an adjunct prophylactic treatment in routine 'Laser Assisted In-Situ Keratomileusis' (LASIK) cases, when cornea ectasia may be a possible concern. Further studies and longer follow-up are needed to validate these data.

Disclosure

The authors report no conflicts of interest in this work.

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Chapter 8

THE ATHENS PROTOCOL: PRK AND CXL

Anastasios John Kanellopoulos, MD

A second procedure for visual rehabilitation may sometimes be needed after cornea collagen cross-linking (CXL) for treatment of progressive keratoconus or post-LASIK ectasia. Following many years of employing CXL for ectasia cases, we introduced the "Athens Protocol": same-day topography-guided partial PRK and CXL.

Our findings support that simultaneous topography-guided partial PRK with cornea collagen cross-linking (CXL) offers a safe and effective approach for normalizing the cornea and enhancing visual function in eyes with ectatic conditions. The core importance of combining CXL in this technique is to address highly irregular astigmatism in the management of eyes with keratoconus and post-LASIK ectasia.

Our theoretical and clinical evidence supports the use of this "Athens protocol" where CXL and topography-guided surface ablation are performed in the same session rather than sequentially over time.

It is our experience that surface ablation using the topography-guided excimer laser platform (Allegretto, Alcon/WaveLight) effectively and predictably normalizes the corneal surface and improves functional vision, and we believe there is a synergistic effect when this procedure is performed simultaneously with CXL.

Safety with our combination approach has been favorable as well. Although postoperative haze and delayed epithelial healing have occurred, these have been minor complications in a small number of eyes within our large series. Out of the 400 eyes studied, just two required repeat CXL, and none needed to have a cornea transplant.

Meeting Visual Rehabilitation Needs

Although the efficacy of CXL for stabilizing keratectasia is well-established and the procedure also causes some corneal flattening, significant residual astigmatism limiting contact lens wear may be a persistent problem for some patients. This situation creates an indication to perform topography-guided PRK.

While surface ablation in a keratoconic eye may sound unorthodox, the goal of our treatment using the topography-guided software is to normalize the corneal surface and improve best-corrected acuity. This is a therapeutic procedure, not a refractive one. In fact, some eyes turn out more myopic postoperatively, but have significant regularity and best spectacle-corrected visual acuity. We use surface ablation to remove no more than 50 μm of stroma and typically treat only 2 D to 2.5 D of astigmatism and up to 1 D of myopia.

Buratto L
PRK: Present, Past, and Future. (pp. 85-88)

Figure 8-1. The basic steps of the Athens Protocol: Top left, The PTK treatment is planned on the Alcon/WaveLight platform. Top right, Following the PTK, areas of Bowman's have been ablated by the PTK, confirming that the epithelium over the cone is thinner. Bottom left, The treatment plans of the topography-guided partial PRK that is the core concept of this protocol. Bottom right, MC application prior to the riboflavin and CXL.

Figure 4.1: Epithelium removed with 50 micron PTK

Figure 4.3: Topography-guided PRK to correct part of the refractive error (*TCAT treatment plan*) maximal thickness removal 50 *microns*

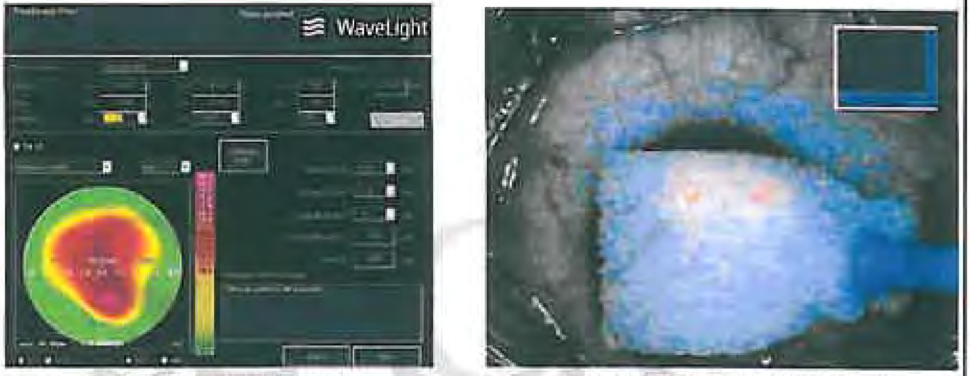

Figure 4.2: TCat treatment plan

Figure 4.4: MMC solution 0,02% for 20 seconds

The protocol begins with a 6.5-mm phototherapeutic keratectomy (PTK) to remove 50 µm of epithelium. Then, the topography-guided partial PRK is performed followed by mitomycin C application (0.02% for 20 seconds) and the CXL procedure. The excimer laser ablation resembles part of a hyperopic treatment. It is performed using a 5.5-mm effective optical zone and targets steepening of the area adjacent to the cone in an attempt to regularize the corneal surface (Figure 8-1).

We believe our rationale for performing the two procedures simultaneously with the ablation first has several advantages. We have reported data showing that the corneal epithelium and Bowman's membrane can act as barriers to UVA light penetration into the stroma. As these tissues are removed with the PTK/PRK procedure, it seems intuitive that the efficacy of the CXL procedure would be increased. This concept is supported by clinical findings outlined below.

For example, in a patient who had CXL alone in one eye and the Athens protocol in the other, inspection of OCT maps for hyper-reflectivity, which we recently described as a sign of the extent of cross-linking, shows the area of cross-linking is much broader and denser in the latter eye.

We additionally introduced the theory that the PRK-treated eye represents a better biomechanical model for performing the CXL procedure. In theory, an eye with a more regularized surface from CXL as opposed to an irregular untreated cornea would be better able to handle ongoing strain from IOP and eye rubbing over the cone peak and would more likely remain more stable.

We believe redistribution of corneal strain by remodeling the cornea with surface ablation is a significant factor in the synergistic effect achieved when performing the two procedures together. The simultaneous procedure also avoids removing cross-linked cornea, which occurs when performing CXL first followed by the laser treatment.

Results from a comparison of two large, consecutive series of eyes treated at the same session or with CXL first followed 1 year later by a topography-guided surface ablation showed statistically significant differences in a number of outcome parameters favoring the same-day procedure. The study, which

Figure 8-2. A clinical picture of the right eye of a 27-year-old man with advanced KCN. Preop BSCVA was 20/50 with -2.5 -5 @80. The patient underwent the Athens Protocol and is now UCVA 20/30 and BSCVA 20/20 with -1 -1.5 @85. The slit-lamp photo shows the corneal clarity and the ground-glass appearance typical of CXL.

Figure 8-3. Cornea OCT of the same eye 7 months postop Athens Protocol. One can appreciate the anterior cornea hyper-reflectivity consistent with CXL and the demarcation line at about 300 μm depth depicting (as we have introduced and published) the depth of effective CXL. Those clinicians familiar with findings following CXL alone may appreciate the enhanced depth and diameter of the CXL effect noted on OCT supporting the advantage on the eye with the Athens Protocol.

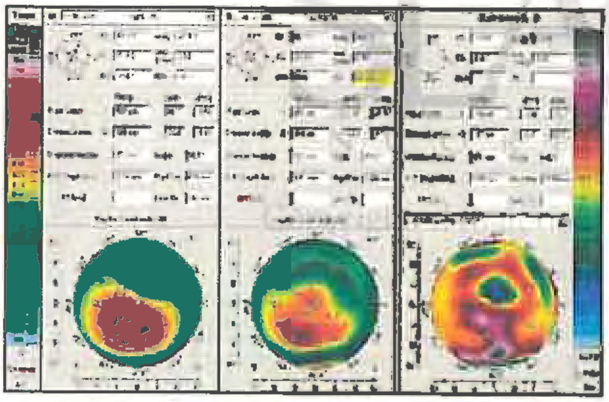

Figure 8-4. A comparison of preoperative and 7 months postoperative of Pentacam images showing the significant normalization of the cone and keratometric flattening and better symmetry.

has been published,[1] included 127 eyes in the sequential group and 198 eyes treated with the Athens protocol (Figure 8-2).

For the eyes in the sequential group, mean logMAR uncorrected visual acuity (UCVA) improved from 0.9 to 0.49, mean logMAR best spectacle-corrected visual acuity improved from 0.41 to 0.16, mean K decreased by 2.75 D and mean MRSE by 2.5 D, and the mean haze score was 1.2. For the eyes in the simultaneous group, there was a significantly greater improvement in mean logMAR UCVA (from 0.96 to 0.3) and mean logMAR BSCVA (from 0.39 to 0.11) as well as a significantly greater mean reduction in MRSE (-3.2 D) and keratometry (-3.5 D) (Figures 8-3 and 8-4). The mean haze score in the simultaneous group was 0.5, and that was significantly lower than in the controls. Central corneal thickness decreased by 70 μm after both procedures, and there was no significant change in endothelial cell count in either group. These findings demonstrate that performing the two procedures together offers advantages of less PRK-associated scarring and better riboflavin and UVA penetration to achieve a wider and deeper CXL effect with greater corneal flattening.

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The Athens Protocol

The management of keratoconus and post-LASIK ectasia by means of combined, same-day, topography-guided partial PRK and collagen cross-linking.

BY A. JOHN KANELLOPOULOS, MD

Progressive, asymmetrical corneal steepening associated with an increase in myopic and astigmatic refractive errors, combined with midperipheral and/or peripheral corneal thinning, represents a constellation of findings in ectatic corneal disorders (eg, keratoconus and pellucid marginal degeneration).

These entitites are associated with asymmetry upon presentation, unpredictability of progression, and myriad abnormal topographic findings. Similar observations after LASIK surgery have been described as *post-LASIK ectasia*.[1-3] Analyses of series of eyes that have developed post-LASIK ectasia have suggested that certain preoperative and/or operative features may be associated with this adverse outcome of LASIK or PRK.[4] The fact that ectasia can occur in the absence of these features, or that it may not occur in spite of them, has confounded surgeons' understanding of this complication.[5] Nevertheless, post-LASIK ectasia is a visually disabling complication whose ultimate surgical treatment is penetrating keratoplasty when glasses or contact lenses can no longer provide patients with visual quality that allows them to perform their activities of daily living.

During the past 10 years, the use of topical riboflavin combined with ultraviolet-A (UVA) irradiation to increase collagen cross-linking (CXL) has demonstrated the potential for retarding or eliminating the progression of keratoconus and post-LASIK ectasia. My colleagues and I have previously reported on the application of CXL in post-LASIK ectasia.[6] We have found that once the progression has stabilized, it is possible to treat the surface of the eye with customized PRK to normalize the corneal surface by reducing irregular astigmatism. After using CXL for cases of ectasia, my colleagues and I introduced the Athens Protocol, which consists of same-day, topography-guided partial PRK and CXL.

EFFECTIVE AND SAFE

My colleagues and I at the LaserVision.gr Institute for Laser in Athens have found that simultaneous topography-guided partial PRK with corneal CXL is a safe and effective approach for normalizing the cornea and enhancing the visual function of eyes with ectatic conditions. Combined CXL with topography-guided, partial PRK can address high amounts of irregular astigmatism in these eyes.

Our theoretical and clinical evidence supports the use of the Athens Protocol, in which the surgeon performs CXL and topography-guided surface ablation in the same session rather than sequentially.

We have found that surface ablation using the topography-guided Allegretto Wave Eye-Q 400-Hz and recently the WaveLight EX500 (500-Hz) laser systems (Alcon Laboratories, Inc, Fort Worth, TX; the EX500 is not yet available in the United States) effectively and predictably normalizes the corneal surface and improves patients' functional vision. We believe there is a synergistic effect when this procedure is performed simultaneously with CXL. Our combined approach also has a favorable safety profile. Although postoperative haze and delayed epithelial healing have occurred, these have been minor complications in a small number of eyes within a very large series.

MEETING PATIENTS' NEEDS FOR VISUAL REHABILITATION

The efficacy of CXL for stabilizing keratectasia has been well established.[6] The procedure does, however, cause some corneal flattening. Significant residual astigmatism limiting contact lens wear may be a persistent problem for some patients. In these cases, topography-guided partial PRK can be indicated.

Surface ablation on a keratoconic eye may sound unorthodox, but the goal of our treatment using the topography-guided software is to normalize the corneal surface and improve BCVA. This is a therapeutic procedure, not a refractive one; some eyes experience an increase in myopia postoperatively but also a significant improvement in surface regularity and BSCVA. We use an ablation pattern that removes no more than 50 µm of stroma and treats, at most, 2.00 to 2.50 D of astigmatism and up to 1.00 D of myopia.

THE PROTOCOL

Using the Athens Protocol, we begin with a 6.5-mm phototherapeutic keratectomy to remove 50 µm of epithelium. We perform the topography-guided partial PRK, apply mitomycin C (0.02% for 20 seconds), and then do the CXL procedure. The excimer laser ablation resembles that employed in a hyperopic treatment. Laser energy is applied using a 5.5-mm effective optical zone, and it targets the steepening of the area adjacent to the cone in an attempt to

Figure 1. A clinical photograph (OD) of a 27-year-old man with advanced keratoconus. His preoperative BSCVA was 20/50 with -2.50 -5.00 X 80. He underwent treatment according to the Athens Protocol and now has a UCVA of 20/30 and a BSCVA of 20/20 with -1.00 -1.50 X 85. The slit-lamp photograph shows the corneal clarity and ground-glass appearance typical of CXL.

Figure 2. Corneal optical coherence tomography of the same eye as in Figure 1 taken 7 months after the Athens Protocol. Note the anterior corneal hyper-reflectivity consistent with CXL and the demarcation line at a depth of about 300 µm depicting effective CXL.

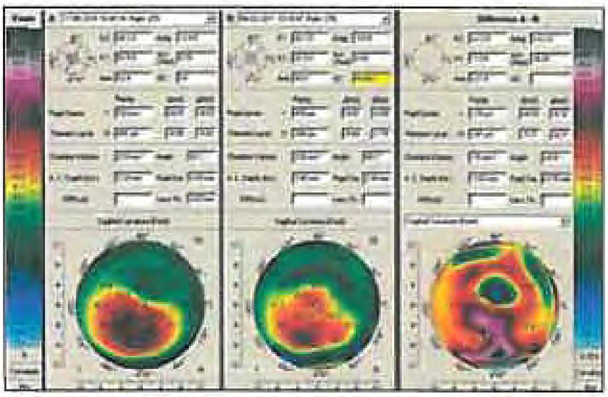


Figure 3. A comparison of the preoperative (left) and 7-month postoperative (middle) Pentacam Comprehensive Eye Scanner (Oculus, Inc., Lynnwood, WA) images showing significant normalization of the cone, keratometric flattening, and improved symmetry. The difference map is on the right.

normalize the corneal surface. In support of our rationale for performing the two procedures simultaneously with the ablation first, data have shown that the corneal epithelium and Bowman membrane can act as barriers to the penetration of UVA light into the stroma.[7] Because phototherapeutic keratectomy/PRK removes the epithelium and Bowman membrane, it seems intuitive that the efficacy of the CXL procedure would increase. This concept is supported by clinical findings.[8-10]

Looking for signs of hyper-reflectivity, we inspected the optical coherence tomography of a patient who had CXL alone in one eye and the Athens Protocol in the other. We recently described hyper-reflectivity as a sign of the extent of cross-linking.[10] The area of CXL in this patient was much more broad and dense in the eye treated according to the Athens Protocol.

We also introduced the theory that the PRK-treated eye represents a better biomechanical model on which to perform CXL.[8-10] Hypothetically, an eye with a more regular surface would be better strengthened using CXL and would be more likely to remain stable after the procedure. This is in comparison to an eye that has ongoing strain from raised IOP and localized eye rubbing over the cone's peak. We believe that the redistribution of corneal strain through remodeling using surface ablation is a significant factor in the synergistic effect achieved when the two procedures are performed together. The simultaneous technique also avoids the removal of cross-linked corneal tissue, which occurs when CXL is performed before the laser treatment.

CLINICAL RESULTS

We reported our results from a comparison of two large, consecutive series of eyes treated at the same session or with CXL first followed 1 year later by a topography-guided surface ablation (Figures 1-3). Our data showed statistically significant differences in several parameters favoring the same-day procedure.[10] The published study included 127 eyes in the sequential group and 198 eyes treated according to the Athens Protocol.

For the eyes in the sequentially treated group, the mean logMAR UCVA improved from 0.90 to 0.49, the mean logMAR BSCVA improved from 0.41 to 0.16, the mean keratometry values decreased by 2.75 D, the mean manifest refraction spherical equivalent decreased by 2.50 D, and the mean haze score was 1.20. For the eyes in the simultaneous group, there was a significantly greater improvement in both mean logMAR UCVA (from 0.96 to 0.30) and mean logMAR BSCVA (from 0.39 to 0.11) as

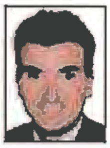
(Continued on page 34)

well as a significantly greater mean reduction in the manifest refraction spherical equivalent (-3.20 D) and keratometry value (-3.50 D). The mean haze score in the simultaneous group was 0.5—significantly lower than in the sequentially treated group. Central corneal thickness decreased by 70 µm in both treatment arms, and there was no significant change in endothelial cell count in either group.

These findings demonstrate that performing the two procedures together offers the advantages of less PRK-associated scarring and better penetration of riboflavin and UVA to achieve a wider and deeper CXL effect with greater corneal flattening.

CONCLUSION

Our findings suggest potentially promising results with same-day, simultaneous topography-guided PRK and collagen CXL (Athens Protocol) as a therapeutic intervention in highly irregular corneas with keratoconus and progressive post-LASIK ectasia. We have reported for the first time effective CXL treatment in cases with minimal thickness (< 350 µm). It is unfortunate that topography-guided ablations are not yet available in the United States. The future FDA approval of this technology and its potential to normalize highly irregular corneas—along with CXL—may significantly reduce the need for further inventions such as intracorneal rings or keratoplastic procedures in these cases. This treatment has definitely done so in European practices during the past 10 years. ■



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ORIGINAL ARTICLES

Management of Corneal Ectasia After LASIK With Combined, Same-day, Topography-guided Partial Transepithelial PRK and Collagen Cross-linking: The Athens Protocol

Anastasios John Kanellopoulos, MD; Perry S. Binder, MS, MD

ABSTRACT

PURPOSE: To evaluate a series of patients with corneal ectasia after LASIK that underwent the Athens Protocol: combined topography-guided photorefractive keratectomy (PRK) to reduce or eliminate induced myopia and astigmatism followed by sequential, same-day ultraviolet A (UVA) corneal collagen cross-linking (CXL).

METHODS: Thirty-two consecutive corneal ectasia cases underwent transepithelial PRK (WaveLight ALLEGRETTO) immediately followed by CXL (3 mW/cm^2) for 30 minutes using 0.1% topical riboflavin sodium phosphate. Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction spherical equivalent, keratometry, central ultrasonic pachymetry, corneal tomography (Oculus Pentacam), and endothelial cell counts were analyzed. Mean follow-up was 27 months (range: 6 to 59 months).

RESULTS: Twenty-seven of 32 eyes had an improvement in UDVA and CDVA of 20/45 or better (2.25 logMAR) at last follow-up. Four eyes showed some topographic improvement but no improvement in CDVA. One of the treated eyes required a subsequent penetrating keratoplasty. Corneal haze grade 2 was present in 2 eyes.

CONCLUSIONS: Combined, same-day, topography-guided PRK and CXL appeared to offer tomographic stability, even after long-term follow-up. Only 2 of 32 eyes had corneal ectasia progression after the intervention. Seventeen of 32 eyes appeared to have improvement in UDVA and CDVA with follow-up >1.5 years. This technique may offer an alternative in the management of iatrogenic corneal ectasia. [*J Refract Surg.* 2011;27(5):323-331.] doi:10.3928/1081597X-20101105-01

Progressive, asymmetrical corneal steepening associated with an increase in myopic and astigmatic refractive errors, combined with midperipheral and/or peripheral corneal thinning, represents a constellation of findings in ectatic corneal disorders, such as keratoconus and pellucid marginal degeneration. Asymmetry in presentation and unpredictability of progression associated with a myriad of abnormal topographic findings describe these entities. Similar findings following LASIK have been described as corneal ectasia.[1-3] Analysis of different series of eyes developing corneal ectasia after LASIK has suggested that certain preoperative and/or operative features may be associated with this adverse outcome of LASIK or photorefractive keratectomy (PRK).[4] The fact that corneal ectasia can occur in the absence of these features, or that it does not occur despite the presence of these features,[5] has confounded our understanding of this entity. Nevertheless, corneal ectasia after LASIK is a visually disabling complication with an ultimate surgical treatment of penetrating keratoplasty when spectacles or contact lenses can no longer provide patients with the quality of vision to permit activities of daily living.

Over the past 10 years, the use of topical riboflavin combined with ultraviolet A (UVA) irradiation to increase collagen cross-linking (CXL) has demonstrated the potential for retarding or eliminating the progression of keratoconus and corneal ectasia after LASIK. The application of CXL in corneal ectasia after LASIK has been reported previously.[6] Once

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the progression has stabilized, it is possible to treat the surface of the eye with customized PRK to normalize the corneal surface by reducing irregular astigmatism and potentially reducing the refractive error as well as providing improved visual outcomes in addition to stabilizing the disease process.[7,8] We have subsequently introduced the combined, same-day use of these two intervention modalities in the management of keratoconus.[9-11]

We present a series of patients with corneal ectasia after LASIK who have undergone combined, same-day, topography-guided PRK and subsequent UVA collagen CXL to achieve stabilization of corneal ectasia and enhance visual rehabilitation.

PATIENTS AND METHODS

PATIENT SELECTION

Patients entered into this study were seen by one of the authors (A.J.K.) in his private practice, either through individual patient referral, referral from other eye care practitioners, or were his own patients. Once a diagnosis of corneal ectasia after LASIK was confirmed (see below), patients were presented with the options of contact lens fitting, intracorneal ring segment implantation, or, in advanced cases, penetrating keratoplasty. If these modalities did not serve the needs of the patient, he/she was then presented with the option of undergoing topography-guided PRK and UVA collagen CXL as a possible technique to prolong or prevent the need for penetrating keratoplasty. Patients provided verbal and written consent prior to undergoing the combined topography-guided PRK/CXL procedure.

A diagnosis of corneal ectasia was made when patients developed progressive corneal steepening associated with an increasing myopic and/or astigmatic refractive error 2 or more months after LASIK surgery. These findings were combined with increasing inferior corneal steepening and thinning based on videokeratography and ultrasound pachymetry. Preoperative LASIK clinical data and topography were requested from the referring physician or primary LASIK surgeon for analysis. Progression of the myopic refractive error with or without progression of the manifest astigmatism, decreasing uncorrected distance visual acuity (UDVA), loss of corrected distance visual acuity (CDVA), progressive inferior corneal steepening on topography, and/or decreasing inferior corneal thickness were findings in all cases.

CLINICAL EXAMINATION

Each patient underwent manifest refraction as well as measurement of UDVA and CDVA, which was recorded in a 20-foot lane using high-contrast Snellen visual acuity testing. Cycloplegic refractions were performed using 1% tropicamide solution (Alcon Laboratories Inc, Ft Worth, Texas). Slit-lamp microscopy confirmed the presence of a LASIK flap. Keratometry readings were obtained by videokeratography (Topolyzer; WaveLight AG, Erlangen, Germany) and/or manual keratometry (model 71-21-35; Bausch & Lomb, Rochester, New York). Pachymetry was performed using at least one of the following devices/instruments: Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany), Orbscan II (Bausch & Lomb), or EchoScan US-1800 (NIDEK Co Ltd, Gamagori, Japan). Specular microscopy was performed using the Konan specular microscope (Konan Medical, Boston, Massachusetts). Topography was performed using the Orbscan II or Pentacam.

SURGICAL TECHNIQUE—THE ATHENS PROTOCOL

We have reported this technique in the management of keratoconus.[9-11]

Step 1. The (Partial, Spherically Corrected) Topography-guided Transepithelial PRK Technique. We devised this technique based on the proprietary WaveLight customized platform. As noted above, we previously described the use of the topography-guided platform with this device to normalize irregular corneas as well as corneal ectasia.

This customized excimer laser treatment is guided by topographic images and is different from wavefront-guided treatments. It received CE mark for clinical use in the European Union in 2003; however, it has yet to receive US Food and Drug Administration approval.

This proprietary software utilizes topographic data from the linked topography device (Topolyzer). By default, it permits the consideration of eight topographies (of predetermined threshold accuracy), averages the data and enables the surgeon to adjust the desired postoperative cornea asphericity (chosen as zero in all cases), provides the option of including tilt correction (no tilt was chosen in all cases), as well as the adjustment of sphere, cylinder, axis, and treatment zone (optical zone of 5.5 mm was chosen in all cases). The image of the planned surgery is generated by the laser software.

We used topography-guided PRK to normalize the cornea by reducing irregular astigmatism while treating part of the refractive error. To remove the minimum possible tissue, we decreased the effective optical zone diameter to 5.5 mm in all cases (compared to our usual treatment diameter of at least 6.5 mm in routine PRK and LASIK). We also planned ~70% treatment of cylinder and sphere (up to 70%) so as not to exceed 50 µm in planned stromal removal. We chose the value of 50 µm as the maximum ablation depth effected, based on our experience of treating irregular corneas with this platform.[7-10]

Following the placement of an aspirating lid speculum (Rumex, St Petersburg, Florida), a 6.5-mm, 50-µm phototherapeutic keratectomy (PTK) was performed to remove the corneal epithelium. Partial topography-guided PRK laser treatment was applied. A cellulose sponge soaked in mitomycin C (MMC) 0.02% solution was applied over the ablated tissue for 20 seconds followed by irrigation with 10 mL of chilled balanced salt solution.

Step 2. Collagen CXL Procedure. For the next 10 minutes, the proprietary 0.1% riboflavin sodium phosphate ophthalmic solution (Priavision, Menlo Park, California) was applied topically every 2 minutes. The solution appeared to "soak" into the corneal stroma rapidly, as it was centrally devoid of Bowman layer. Following the initial riboflavin administration, 4 diodes emitting UVA light of mean 370-nm wavelength (range: 365 to 375 nm) and 3 mW/cm^2 radiance at 2.5 cm were projected onto the surface of the cornea for 30 minutes (Keracure prototype device, Priavision). The Keracure device, which has a built-in beeper, alerts clinicians every 2 minutes during the 30-minute treatment to install the riboflavin solution in a timely fashion. A bandage contact lens was placed on the cornea at the completion of the combined procedures.

Postoperatively, topical ofloxacin (Ocuflox 0.3%; Allergan Inc, Irvine, California) was used four times a day for the first 10 days and prednisolone acetate 1% (Pred Forte, Allergan Inc) was used four times a day for 60 days. Protection from all natural light with sunglasses was encouraged, with administration of oral 1000 mg vitamin C daily for 60 days postoperative. The bandage contact lens was removed at or around day 5 following complete re-epithelialization.

EVALUATION

The following evaluations were completed before and after both treatments: age, sex, UDVA, CDVA, refraction, keratometry, tomography, pachymetry, endothelial cell count, corneal haze on a scale of 0 to 4 (0=clear cornea, 1=mild haze, 2=moderate haze, 3=severe haze, and 4=reticular haze [obstructing iris anatomy]), and corneal ectasia stability as defined by stability in mean keratometry and tomography.

CASE REPORTS

CASE 1

A 39-year-old man had undergone LASIK in May 2004 at another institution. At that time, according to patient history, UDVA was counting fingers in both eyes. Manifest refraction was −6.50 −0.50 × 020 (20/20) in the right eye and −6.00 −0.50 × 165 (20/20) in the left eye. Preoperative keratometry and corneal thickness readings were not available. No surgical data were available. The patient achieved UDVA of 20/20 in each eye, and reportedly plano refraction in both. In October 2005, he complained of progressively decreasing vision in both eyes. At that time, UDVA was 20/50 in the right eye and 20/40 in the left eye and he was told that "astigmatism was developing."

The patient presented in March 2006, 26 months after LASIK, with a manifest refraction of +2.25 −1.75 × 090 (20/20) in the right eye and −1.25 −0.75 × 010 (20/20) in the left eye. Uncorrected distance visual acuity was 20/40 in the right eye and 20/30 in the left eye. Keratometry was 38.75@90/35.62@180 in the right eye and 40.65@05/39.55@95 in the left eye. Central corneal thickness (measured with Pentacam and ultrasound) was 495 µm in the right eye and 505 µm in the left eye, respectively. A diagnosis of bilateral corneal ectasia was made.

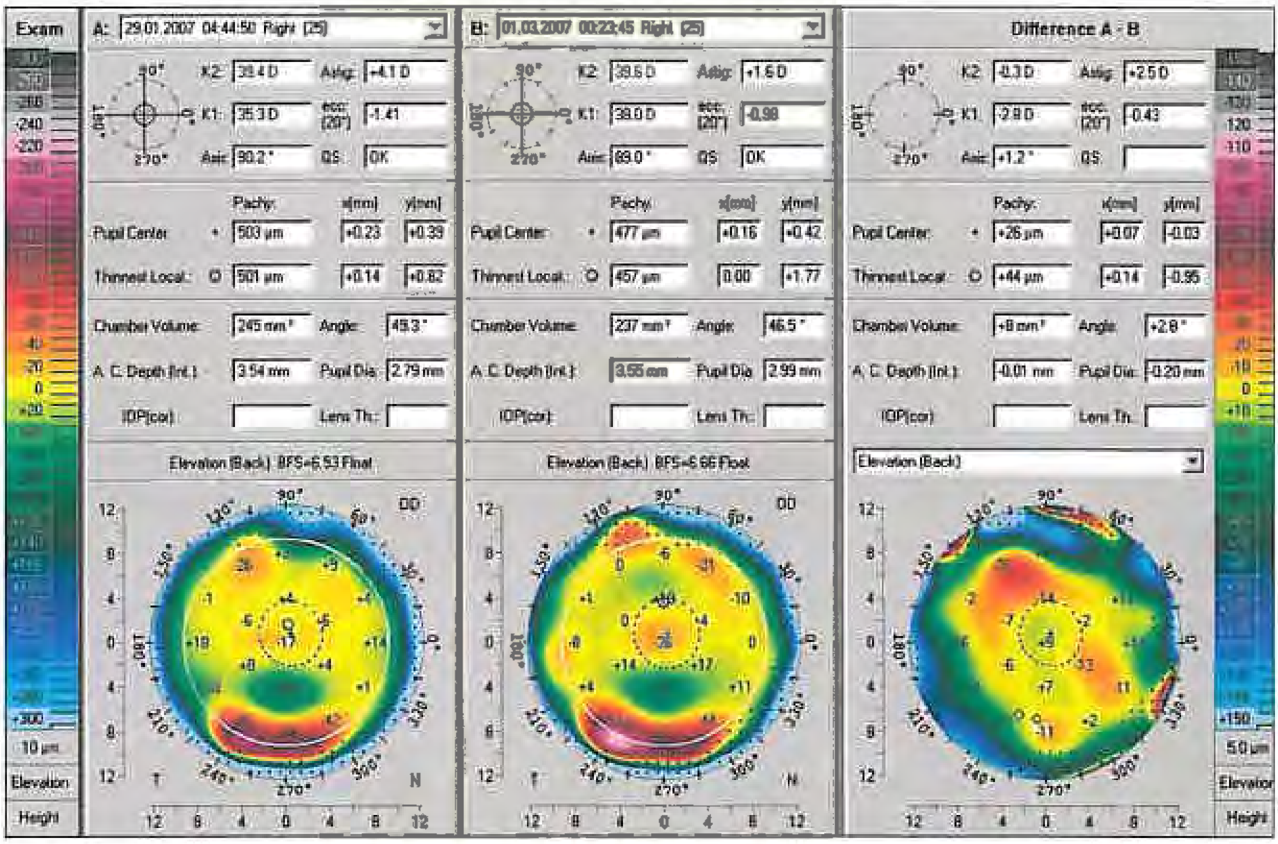
Because of the decrease in UDVA and the presence of corneal ectasia, the patient was informed of the risks, benefits, and alternatives of the combined topography-guided PRK/CXL technique. This procedure was performed on both eyes in January 2007, 32 months after LASIK. Based on the clinical manifest refraction of right (+2.25 −1.75 × 90 [20/20]) and left (−1.25 −0.50 × 005 [20/20]) eyes, the attempted correction was reduced to +1.75 −1.50 × 90 and −0.75 −0.50 × 005 for the right and left eyes, respectively. (The goal in the treatment was modified to anticipate the possible long-term flattening effect that CXL may have on these corneas.)

In February 2010, 37 months after topography-guided PRK/CXL, UDVA improved to 20/40 in the right eye and 20/20 in the left eye with a manifest refraction of −0.75 (20/20) in the right eye and +0.25 −0.25 × 95 (20/20) in the left eye. Keratometry was 37.50@85/36.62@175 in the right eye and 37.75@79/37.87@169 in the left eye. Ultrasound pachymetry was 440 µm and 414 µm in the right and left eyes, respectively. Figure 1 demonstrates the pre- and postoperative topographies of the right eye as well as the difference map after treatment with the Athens Protocol.

CASE 2

A 33-year-old woman reportedly had a manifest refraction of −4.00 −2.50 × 90 (20/20) in the right eye and −1.50 −2.00 × 100 (20/20) in the left eye. No other preoperative data were available. The patient had a history of eye rubbing.

Sometime in 2002, the patient underwent bilateral



Exam	A: 29.01.2007 04:44:50 Right (25)	B: 01.03.2007 00:23:45 Right (25)	Difference A - B
K2	39.4 D	39.6 D	-0.3 D
K1	35.3 D	38.0 D	-2.8 D
Axis	90.2 °	89.0 °	+1.2 °
Astig	-4.1 D	+1.6 D	+2.5 D
ecc (20°)	-1.41	-0.98	-0.43
QS	OK	OK	
Pupil Center: Pachy	503 µm	477 µm	+26 µm
Pupil Center: x[mm]	+0.23	+0.16	+0.07
Pupil Center: y[mm]	+0.39	+0.42	-0.03
Thinnest Local: Pachy	501 µm	457 µm	+44 µm
Thinnest Local: x[mm]	+0.14	0.00	+0.14
Thinnest Local: y[mm]	+0.82	+1.77	-0.95
Chamber Volume	245 mm³	237 mm³	+8 mm³
Angle	45.3 °	46.5 °	+2.8 °
A. C. Depth (Int.)	3.54 mm	3.55 mm	-0.01 mm
Pupil Dia	2.79 mm	2.99 mm	-0.20 mm
IOP(cor)			
Lens Th.			
	Elevation (Back) BFS=6.53 Float	Elevation (Back) BFS=6.66 Float	Elevation (Back)

Figure 1. *Case 1.* Clinical course of the right eye. Topography on the left shows marked central inferior corneal steepening consistent with corneal ectasia. The center image shows the final topography 2 years after initial LASIK, which is flatter and normalized. The image on the right demonstrates the comparison between preoperative and postoperative.

LASIK (the exact date is unknown and the surgical data were unavailable). Initially, the patient recovered excellent UDVA, but in December 2005, approximately 3 years postoperatively, she presented with slowly decreasing vision in both eyes. At that time, UDVA was 20/800 in each eye. Manifest refraction was −10.50 −6.00 × 105 (20/40) in the right eye and −7.75 −2.50 × 110 (20/30) in the left eye. Central corneal thickness measured by ultrasound was 395 µm in the right eye and 410 µm in the left eye. Keratometry was 52.87@103/46.12@13 in the right eye and 47.12@111/45.00@021 in the left eye. Corneal topography revealed bilateral corneal ectasia after LASIK, which was more pronounced in the right eye.

On December 19, 2005, >3 years after LASIK, the patient underwent topography-guided PRK/CXL in the right eye only, with no treatment in the left eye. At this time, manifest refraction was −10.50 −6.00 × 105 (20/30) in the right eye and −7.75 −4.50 × 130 (20/40) in the left eye. In June 2007, 18 months after topography-guided PRK/CXL, UDVA was 20/800 in each eye. Manifest refraction in the treated right eye had worsened to −12.00 −2.50 × 100 (20/40). Keratometry was 48.00@29/47.30@119 in the right eye and 47.87@20/46.20@110 in the left eye, and ultrasound pachymetry was 424 µm in the right eye and 388 µm in the left eye. Corneal topography revealed flattening in the difference map in the right eye (Fig 2). The patient was unhappy with this result and is currently uncomfortable with her anisometropia. She decided not to proceed with treatment in the fellow eye because she was unconvinced she had benefited from the topography-guided PRK/CXL procedure. She is currently wearing rigid gas permeable contact lenses in both eyes.

CASE 3

A 26-year-old male helicopter pilot underwent LASIK in both eyes in June 2004. No operative data were available. The only data available from the initial LASIK procedure was that he had "about" −3.00 diopters (D) of myopia in both eyes prior to LASIK. Uncorrected distance visual acuity during the initial 2 years after LASIK was "good" but then deteriorated in his right eye. He was subsequently diagnosed with corneal

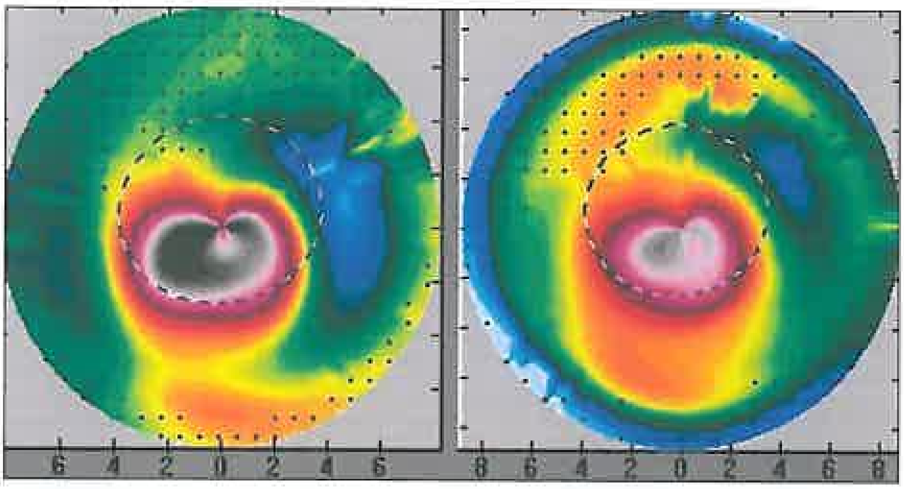


Figure 2. *Case 2.* Topography on the left shows marked inferior steepening before topography-guided PRK/CXL treatment. The topography on the right shows the same cornea 18 months after topography-guided PRK/CXL with marked flattening of the corneal ectasia and normalization of the cornea.

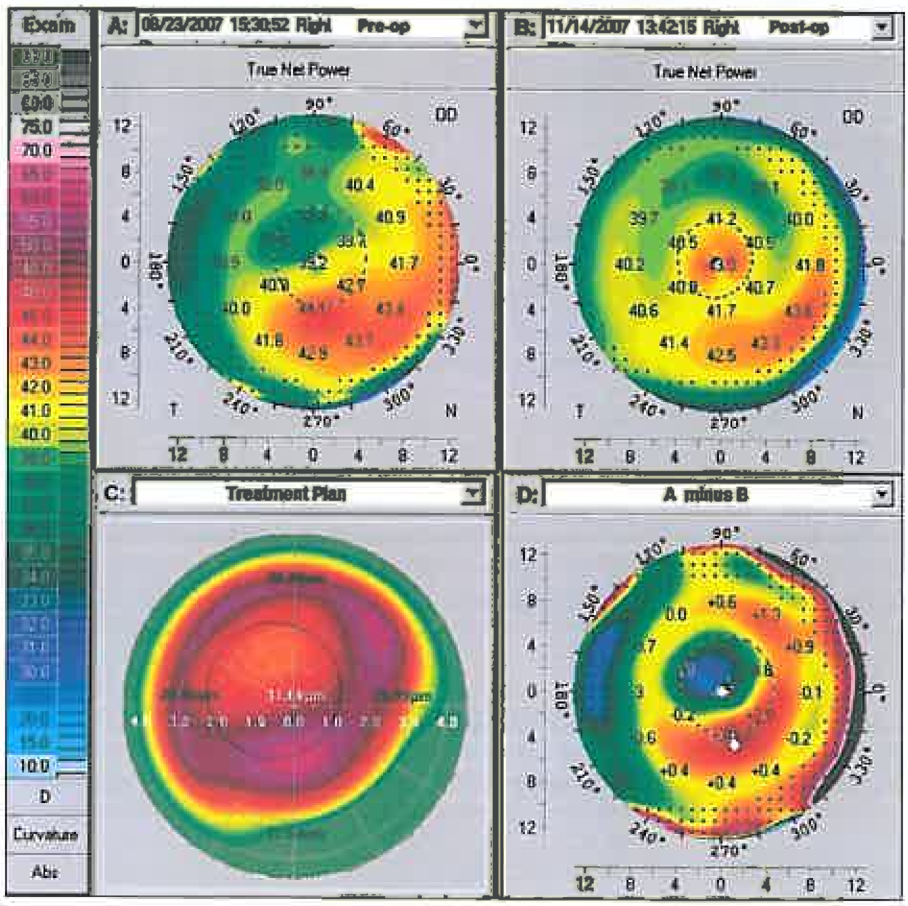
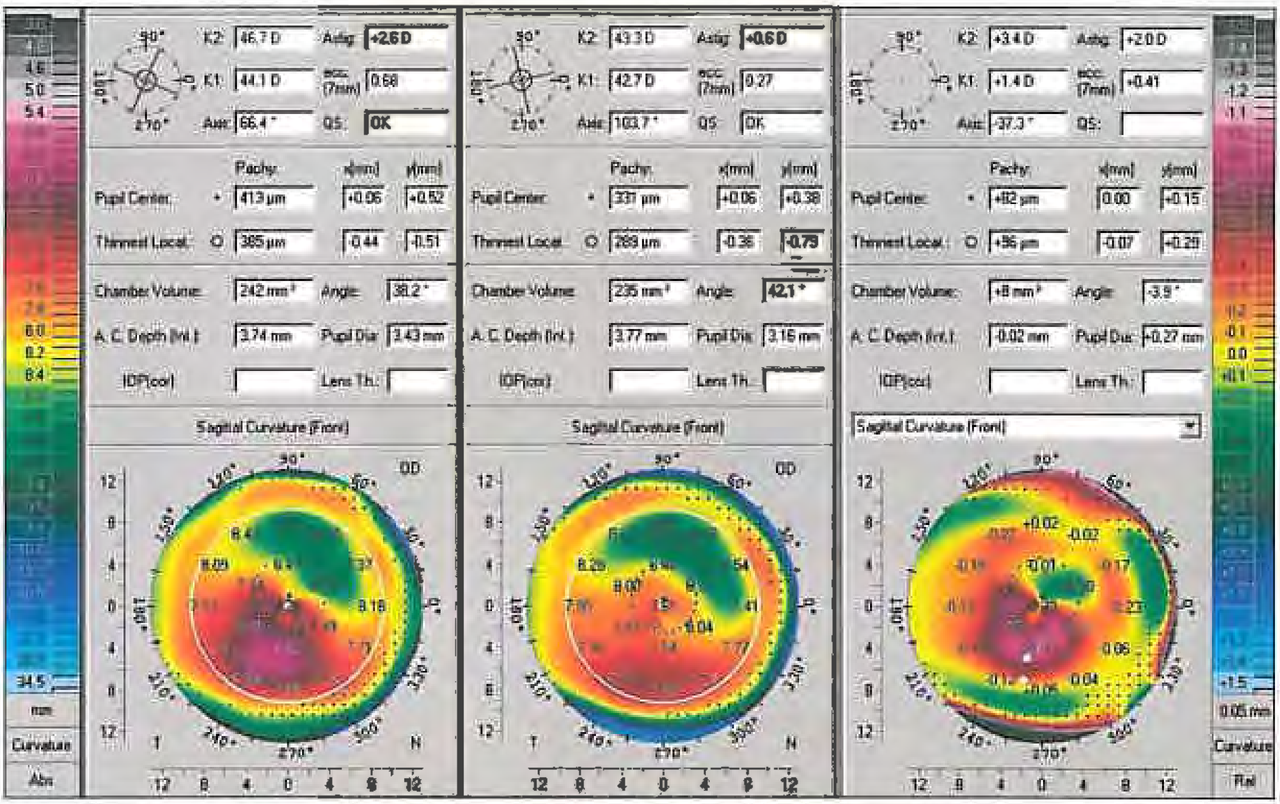


Figure 3. *Case 3.* Clinical course of the right eye. **A)** Topography 3 years after LASIK demonstrates irregular astigmatism and marked inferior corneal steepening. Uncorrected distance visual acuity was 20/40 and corrected distance visual acuity was 20/20 with refraction of +1.50 −2.00 × 65. **B)** Topography 3 months after topography-guided PRK/CXL procedure demonstrates a flatter and normalized cornea. Uncorrected distance visual acuity was 20/15. **C)** Topographic reproduction of the topography-guided PRK treatment plan with the WaveLight platform. This platform plans to remove tissue in an irregular fashion to normalize the corneal ectasia seen in Figure 3A. **D)** Comparison map, derived from subtracting image B from A, represents the topographic difference in this case 3 months after the combined treatment. The paracentral flattening is self-explanatory, as the PRK and CXL have flattened the cone apex. The superior nasal arcuate flattening represents the actual part-hyperopic correction, which the topography-guided treatment has achieved, to accomplish steepening in the area central to this arc. Thus, the topography-guided treatment has normalized the ectatic cornea by flattening the cone apex and at the same time by "steepening" the remainder of the central cornea.

ectasia and was offered Intacs (Addition Technology Inc, Des Plaines, Illinois) or a corneal transplant.

He presented to our institution in September 2007, 3 years after LASIK. Uncorrected distance visual acuity was 20/40 in the right eye and 20/15 in the left eye. Manifest refraction was +1.50 −2.00 × 65 (20/20) in the right eye and plano (20/15) in the left eye. Keratometry was 41.62@65/43.62@155 in the right eye and 41.75/42.12@10 in the left eye. Central ultrasound pachymetry was 476 µm in the right eye and 490 µm in the left eye.

On September 13, 2007, 39 months after LASIK,



K2: 46.7 D Astig: +2.6 D
K1: 44.1 D ecc (7mm): 0.68
Axis: 66.4° QS: OK
Pupil Center: Pachy 413 µm x(mm) +0.06 y(mm) +0.52
Thinnest Local: Pachy 385 µm x(mm) -0.44 y(mm) -0.51
Chamber Volume: 242 mm³ Angle: 38.2°
A. C. Depth (Int.): 3.74 mm Pupil Dia: 3.43 mm
IOP(cor): Lens Th.:

K2: 43.3 D Astig: +0.6 D
K1: 42.7 D ecc (7mm): 0.27
Axis: 103.7° QS: OK
Pupil Center: Pachy 331 µm x(mm) +0.06 y(mm) +0.38
Thinnest Local: Pachy 289 µm x(mm) -0.36 y(mm) -0.79
Chamber Volume: 235 mm³ Angle: 42.1°
A. C. Depth (Int.): 3.77 mm Pupil Dia: 3.16 mm
IOP(cor): Lens Th.:

K2: +3.4 D Astig: +2.0 D
K1: +1.4 D ecc (7mm): +0.41
Axis: -37.3° QS:
Pupil Center: Pachy +82 µm x(mm) 0.00 y(mm) +0.15
Thinnest Local: Pachy +96 µm x(mm) -0.07 y(mm) +0.29
Chamber Volume: +8 mm³ Angle: -3.9°
A. C. Depth (Int.): -0.02 mm Pupil Dia: +0.27 mm
IOP(cor): Lens Th.:

Figure 4. *Case 4.* Pentacam comparison of the right eye. The left column shows the data and topography before topography-guided PRK/CXL. The center column shows the postoperative data and topography. The right column shows the difference (pre- minus postoperative).

combined topography-guided PRK and immediate CXL was performed in the right eye for +0.50 −1.50 × 60. The planned laser resection was 35 µm. Prior to treatment, manifest refraction was +1.50 −2.00 × 65; we reduced the attempted sphere and cylinder, anticipating a subsequent flattening effect of the sequential CXL procedure. Within 6 months, UDVA improved to 20/25 and 24 months later in September 2009, UDVA improved to 20/15 and the manifest refraction improved to plano −0.25 × 05 (20/10). Keratometry in the right eye was 43.00@97/43.25@07 and ultrasound pachymetry was 441 µm. The difference maps (Pentacam) before topography-guided PRK/CXL and 2 years postoperative are shown in Figure 3. At 3-year follow-up, UDVA remains at 20/10.

As a result of the improvement and stability in visual function, this patient has joined the United States Air Force as a fighter pilot and is currently serving in active duty.

CASE 4

A 32-year-old woman underwent LASIK in both eyes in December 2006 for a refractive error of −3.75 D in the right eye and −4.00 D in the left eye. No other data were available in regard to the surgery. Her vision was good for 2 years and then started to deteriorate. The treating surgeon made the diagnosis of corneal ectasia after LASIK in December 2008.

The patient presented to our institution in January 2009. Uncorrected distance visual acuity was 20/100 in the right eye and 20/20^{-2} in the left eye. Corrected distance visual acuity was 20/30 with manifest refraction of −3.25 −3.25 × 45 in the right eye and 20/15 with +0.50 −1.25 × 100 in the left eye. Keratometry was 46.70@156/44.10@66 and 39.75@155/41.75@65 in the right and left eyes, respectively. Pachymetry readings were 419 µm and 460 µm in the right and left eyes, respectively. The diagnosis of corneal ectasia after LASIK was confirmed by Pentacam in the right eye (Fig 4, left image). The patient was contact lens–intolerant and opted to undergo topography-guided PRK/CXL despite the informed consent that the estimated residual corneal thickness would be 360 µm. This procedure was performed in February 2009 in the right eye.

The planned correction was −2.50 −2.50 × 45 after 6-mm diameter, 50-µm depth PTK. After ablation, 0.02% MMC in a moistened weck-cell sponge was used on the stroma for 20 seconds. In January 2010

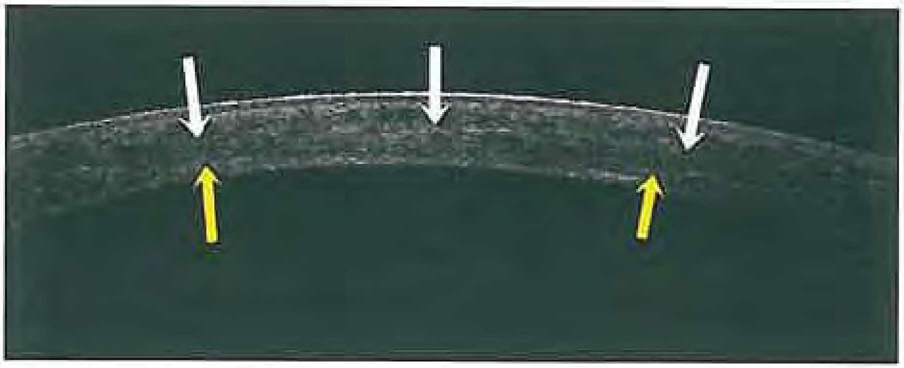


Figure 5. Case 4. Optical coherence tomography of the central cornea in the right eye 11 months after topography-guided PRK/CXL. The hyper-reflectivity of the anterior 2/3 of the cornea suggests (as reported previously[10]) the CXL effect (yellow arrows). The hyper-reflective demarcation in the middle of the cornea (white arrows) suggests a thick LASIK flap calculated to >200 μm.

(11 months following treatment), UDVA was 20/30, and CDVA was 20/20^{-1} with manifest refraction of −0.50 −0.75 × 141. Keratometry was 43.30 and 42.70@103. Central corneal thickness was 330 μm. The pre- and postoperative difference map is shown in Figure 4. Endothelial cell count was unchanged at 20 months (2600 cells/mm^2 from 2650 cells/mm^2 prior to application of the Athen's protocol).

Optical coherence tomography (OCT) of the central cornea in the right eye at 11 months postoperative shows hyper-reflectivity of the anterior 2/3 of the cornea (Fig 5) demonstrating the CXL effect, which we reported previously when applying similar treatment in cases of keratoconus.[10,11] The hyper-reflective demarcation in the middle of the cornea in this case suggests a thick LASIK flap calculated to >200 μm by corneal OCT prior to application of the Athen's protocol.

SUMMARY OF ALL CASES

A total of 32 eyes in 22 patients with corneal ectasia occurring 1 to 4 years after LASIK were treated. Preoperative LASIK data were not available in most cases. In the 5 patients who had available data, no irregularity on topography or tomography was noted and no other factor of the LASIK procedure was evaluated to be high risk (eg, thick flap, residual stromal bed <250 μm). All patients had documented progression of inferior steepening in topography and/or tomography maps. Patient age ranged from 23 to 66 years (mean: 32 years) with gender divided (women:men=11:11). The mean measurements representing values after corneal ectasia were confirmed and preoperative to our technique were as follows. Mean sphere was −7.50 D and mean preoperative astigmatism was −2.40 D in the 32 eyes. Mean preoperative to the original LASIK central corneal thickness was ≥525 μm in 25 of 32 eyes. The original LASIK laser resection data were unavailable in 27 eyes, and flap thickness was assumed or calculated using corneal OCT (Optovue, Fremont, California). The mean residual stromal thickness was 285 μm (range: 210 to 355 μm). Of all 32 ectasia cases, 15 were thought to have resulted from thicker than planned flaps (mean residual stromal bed 230 μm), 10 showed signs of corneal irregularity on preoperative LASIK topography, and 7 had no recognizable risk factor for the development of corneal ectasia.

All topography-guided PRK procedures were planned to reduce corneal thickness by a maximum of 50 μm, despite the existing refractive error, to avoid exacerbation of the ectasia. Most patients (19 patients, 25 eyes) complained of significant pain the first postoperative night whereas others reported minimal discomfort. Mean follow-up after the procedure was 27 months.

Uncorrected distance visual acuity improved in 27 eyes, was unchanged in 4 eyes, and worsened in 1 eye; it was 20/30 or better (+0.18 logMAR) in 11 of 32 eyes and 20/60 or worse (+0.47 logMAR) in 2 eyes. Corrected distance visual acuity was 20/40 or better (+0.30 logMAR) in 27 of 32 eyes and 20/25 or better (+0.10 logMAR) in 14 eyes.

Mean refractive error decreased by more than 2.50 D in 27 of 32 eyes, appeared to increase by 0.75 D in 3 eyes, and remained stable in 2 eyes. Mean final spherical equivalent refraction was −1.75 D, indicating the reduction of cornea irregularity was the target and not emmetropia.

DISCUSSION

Topography-guided PRK flattens some of the cone apex (in a fashion similar to an eccentric partial myopic PRK) but simultaneously flattens an arcuate, broader area of the cornea away from the cone, usually in the superior nasal periphery; this ablation pattern (see Fig 3C) resembles part of a hyperopic treatment and thus will cause some amount of steepening or elevation adjacent to the cone, effectively normalizing the cornea. We have introduced this concept as an effective tissue-sparing ablation pattern in highly irregular corneas such as ectasia in keratoconus.[12] It is this core concept in the topography-guided PRK treatment that makes it, in our opinion, more therapeutic than refractive. We have reported[7-10] that in theory, the new "flatter" and less irregular corneal shape may perform better biomechanically in eyes with corneal ectasia. Specifically, as the corneal apex becomes a flatter and "broader" cone (see Figs 3A and 3B), this may redistribute the biomechanical strain from the eye's intraocular pressure and other external factors (eg, eye rubbing, blinking, etc). This effect may be further enhanced with additional collagen CXL strengthening.

Same-day simultaneous topography-guided PRK and CXL has several advantages: 1) the combination reduces the patient's time away from work, 2) performing both procedures at the same time with topography-guided PRK appears to minimize the potential superficial stromal scarring resulting from topography-guided PRK (unpublished observations, December 2005), and 3) when topography-guided PRK is performed following the CXL procedure, some of the cross-linked anterior cornea is removed, minimizing the potential benefit of CXL (unpublished observations, December 2005). We believe it may be counterintuitive to remove the cross-linked tissue with topography-guided PRK at a later time, as we are potentially removing a beneficial layer of the stiffer, cross-linked cornea, which helps maintain the normalized corneal shape. Lastly, 4) by removing the Bowman layer with topography-guided PRK, this may facilitate riboflavin solution penetration in the corneal stroma and less "shielding" of UVA light in its passage through the cornea, resulting in more effective CXL.

Although a patient with corneal ectasia can have an improved visual result with the addition of the topography-guided PRK, completely removing significant refractive errors was not our goal. We have placed an arbitrary "ceiling" of 50 µm to the amount of tissue that we safely removed centrally, anticipating that further thinning might destabilize the cornea's biomechanical integrity, even following the "stiffening" effect of CXL.

It should be noted that the proprietary riboflavin solution used was a slightly hypotonic (340 mOsm) formulation, resulting in slight "swelling" of the cornea intraoperatively (during CXL). This restored the corneal thickness to approximately 400 µm during CXL to protect the corneal endothelium; we did not encounter any corneal endothelial decompensation in any of the eyes studied herein despite treating cases with corneal thickness less than the theoretical limit of 400 µm[13] prior to CXL (case 4).

In addition, the laser treatment was applied with caution, as the refractive effect of CXL (corneal flattening) had to be anticipated. For this reason, we elected to always attempt a significant undercorrection of both sphere and cylinder by at least 30%. At a later time, we hope to more accurately determine the new ablation rate of CXL stroma.

Simultaneous topography-guided PRK and CXL appears to be effective in the rehabilitation of corneal ectasia after LASIK. The reality of the efficacy of this treatment has been the reduction of penetrating keratoplasty cases performed for the indication of keratoconus and corneal ectasia after LASIK in our practice over the past 4 years. The same-day, simultaneous topography-guided PRK and CXL procedure was easy to perform, but in some cases, the central epithelial surface took up to 1 month to regularize and become lucent. It took from 1 to 4 weeks for us to detect stable changes in keratometry and topography, which seemed to match the visual and refractive changes.

The main goal for all refractive surgeons is to try to eliminate or at least significantly reduce the number of eyes developing corneal ectasia after PRK and LASIK. In some eyes, a preexisting condition that may lead to corneal ectasia with either PRK or LASIK may not be able to be detected, but by eliminating eyes with abnormal preoperative topography and leaving corneas with the maximum clinically acceptable residual stromal thickness, we will be able to reduce the number of eyes that develop corneal ectasia.

Our findings suggest potentially promising results with same-day, simultaneous topography-guided PRK and collagen CXL as a therapeutic intervention in highly irregular corneas with progressive corneal ectasia after LASIK. We have reported herein effective CXL treatment in cases with minimal corneal thickness <350 µm. Our study demonstrates that we now have another means of improving the visual and refractive results of a devastating complication while avoiding or delaying penetrating keratoplasty.

AUTHOR CONTRIBUTIONS

Study concept and design (A.J.K.); data collection (A.J.K., P.S.B.); analysis and interpretation of data (A.J.K., P.S.B.); drafting of the manuscript (A.J.K., P.S.B.); critical revision of the manuscript (A.J.K., P.S.B.); administrative, technical, or material support (A.J.K., P.S.B.); supervision (A.J.K.)

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