ORIGINAL ARTICLE

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

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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.

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

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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

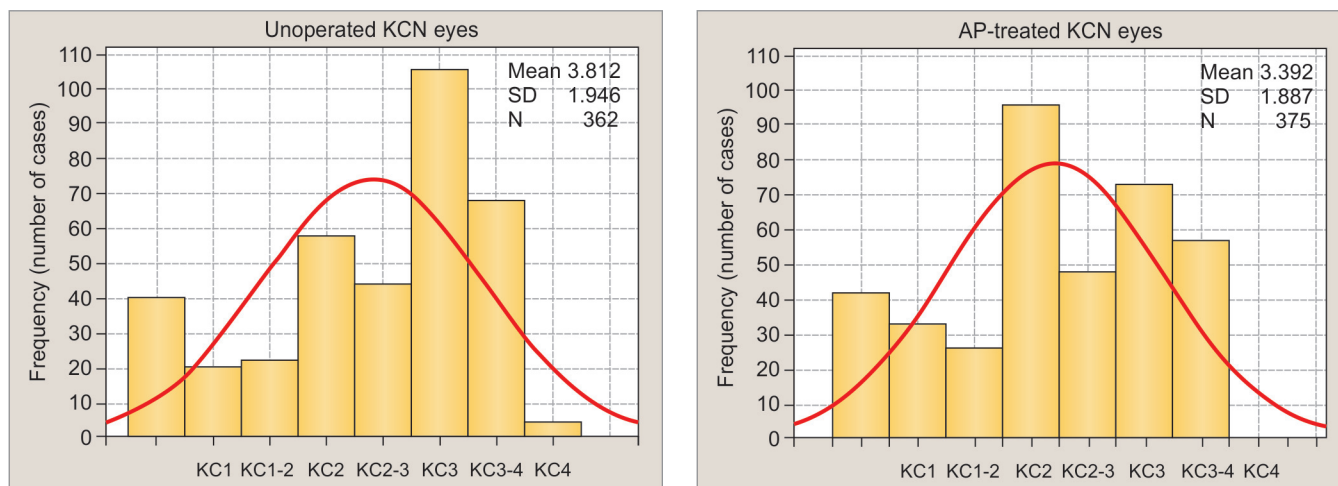Receiver operating characteristics (ROC) curve analysis, area under curve (area), standard error (Std. error),

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
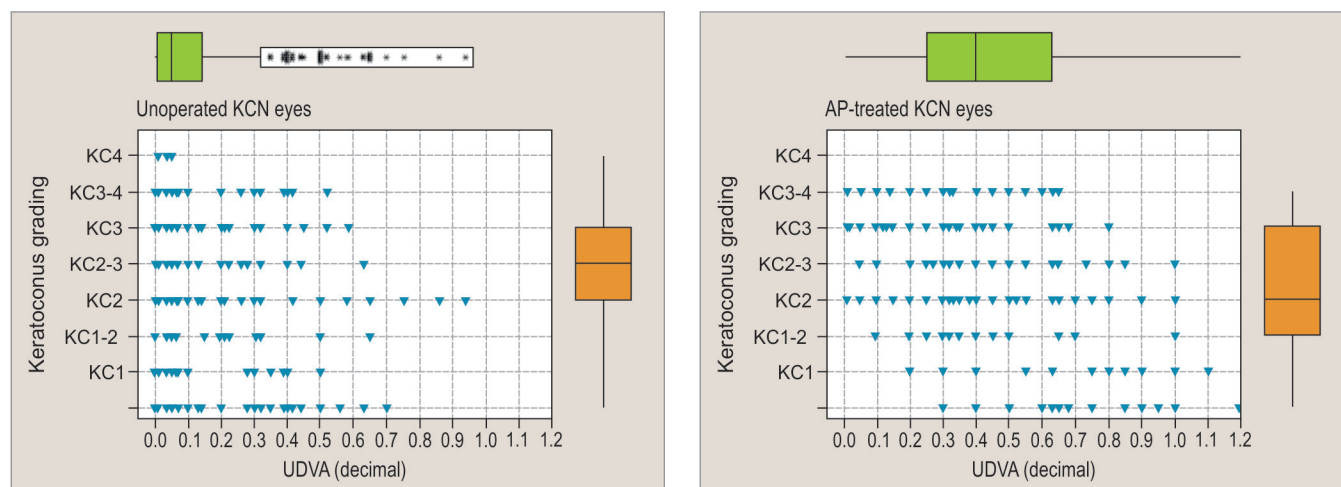

Fig. 2: Marginal plot of UDVA (expressed decimally) and TKC grading with overlying box plots showing mean levels and outliers. Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes
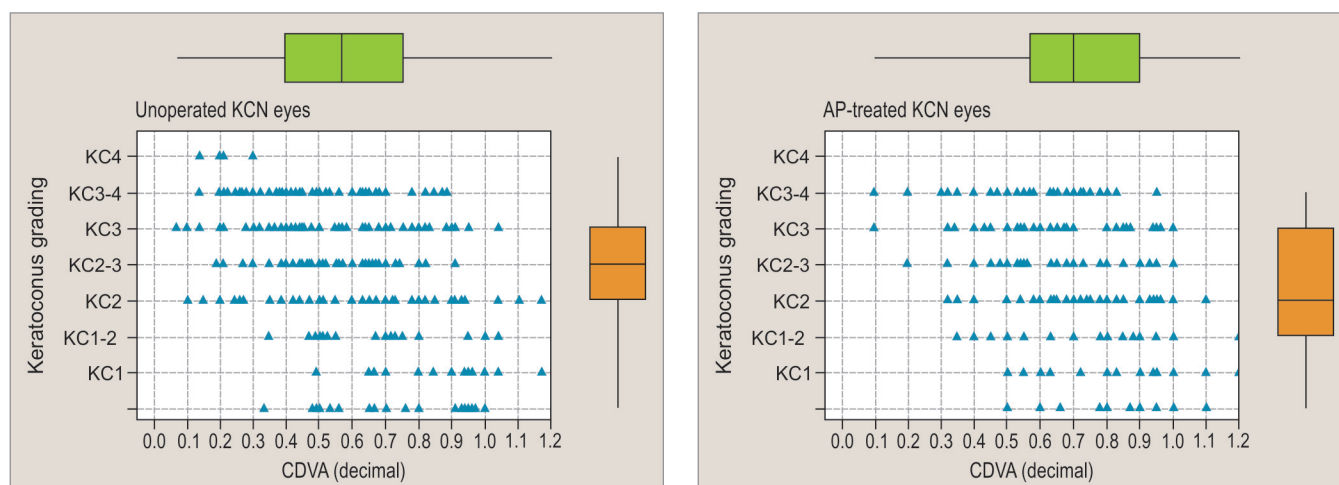
Fig. 3: Marginal plot of CDVA (expressed decimally) and TKC grading with overlying box plots showing mean levels and outliers. Left — group A, unoperated KCN eyes and, right — group B Athens-protocol (AP) treated KCN eyes

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
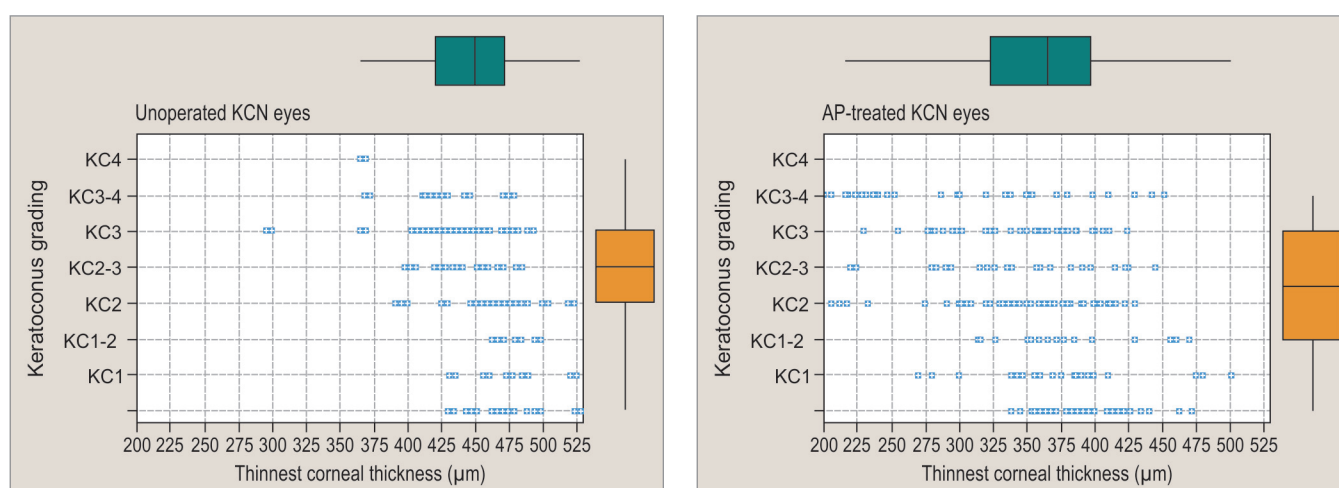

Fig. 5: Marginal plot of ISV, index of surface variance, and TKC grading with overlying box plots showing mean levels and outliers Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes
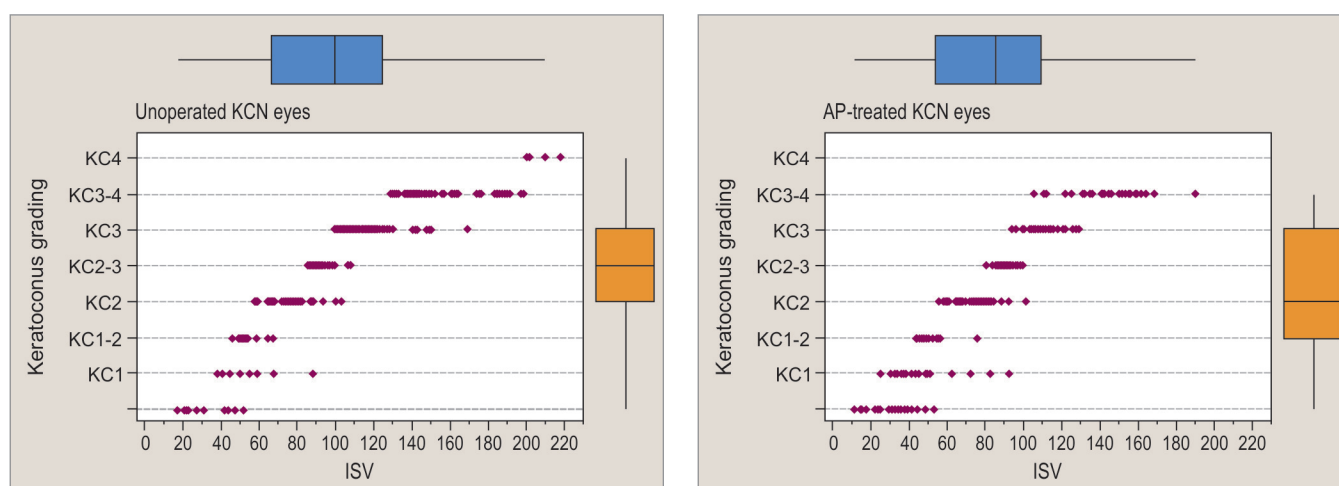
Fig. 6: Marginal plot of IHD, index of height decentration, and TKC grading with overlying box plots showing mean levels and outliers. Left — group A, unoperated KCN eyes and, right — group B, Athens-protocol (AP) treated KCN eyes
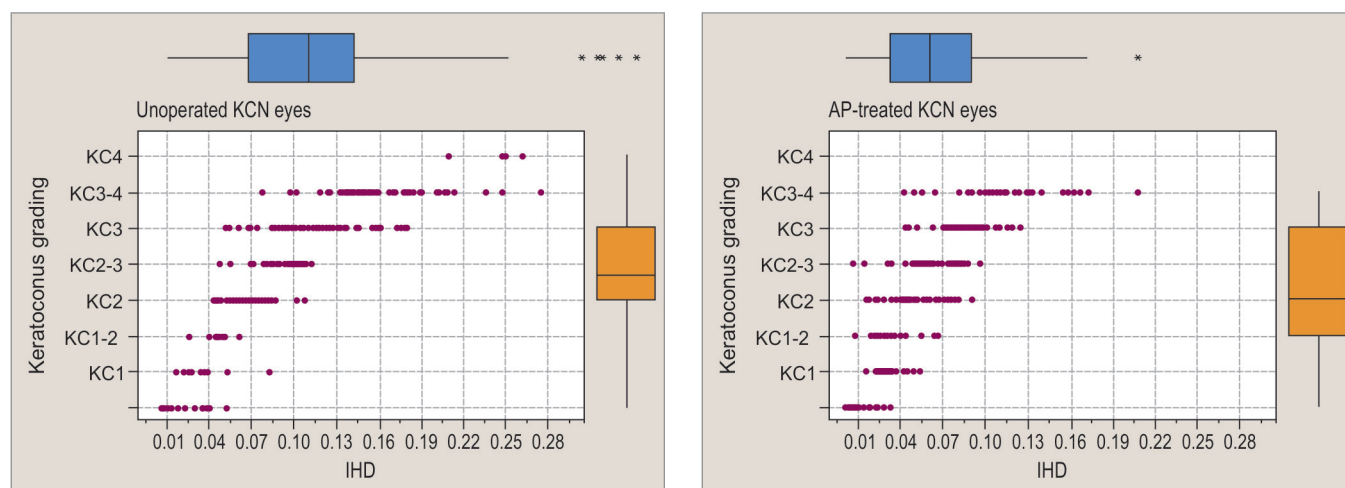
Test result variable(s)	Area under curve	Std. error [a]	Asymptotic signature [b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
CDVA	0.550	0.039	0.000	0.524	0.677
TCT	0.596	0.070	0.009	0.535	0.621
ISV	0.876	0.035	0.000	0.808	0.944
IHD	0.887	0.036	0.000	0.817	0.957

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

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
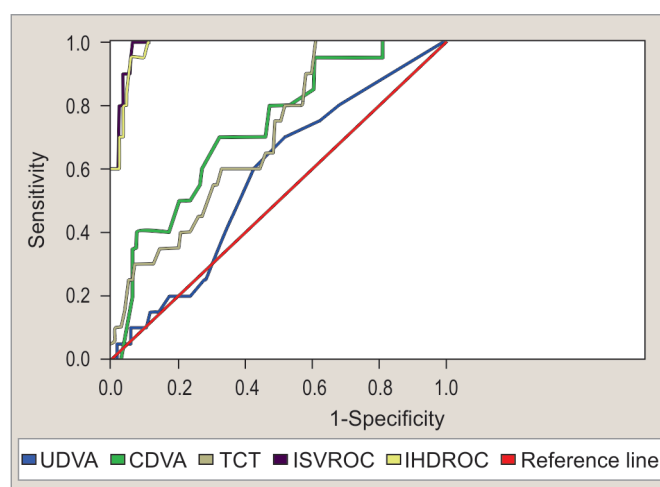

Fig. 7: Receiver operating characteristics plot for the four variables, CDVA, TCT, ISV and IHD. (CDVA: best-spectacle corrected distance visual acuity; TCT: thinnest corneal thickness; ISV: index of surface variance; IHD: index of height decentration)

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

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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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