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Distinguishing Highly Asymmetric Keratoconus Eyes Using Combined Scheimpflug And Spectral Domain OCT Analysis

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Abstract

Purpose—To determine optimal objective, machine derived variables and variable combinations from Scheimpflug and spectral domain ocular coherence tomography (SD-OCT) imaging to distinguish the clinically unaffected eye in patients with asymmetric keratoconus from a normal control population.

Design—Retrospective case-control study

Subjects—Thirty clinically unaffected eyes with no physical findings on slit lamp examination, no definitive abnormalities on corneal imaging, and CDVA of 20/20 or better from 30 patients with highly asymmetric keratoconus (AKC) and 60 eyes from 60 normal control patients who had undergone uneventful LASIK with at least two years of stable follow-up (Controls).

Methods—Scheimpflug and SD-OCT imaging was obtained in all eyes, and receiver operating characteristic (ROC) curves were generated to determine area under the curve (AUC), sensitivity, and specificity for each machine derived variable and variable combination.

Main Outcome Measures—Distinguishing AKC eyes from Controls as determined by AUC, sensitivity, and specificity.

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Results—No individual machine derived metric from Scheimpflug or SD-OCT technology yielded an AUC higher than 0.75. Combining 5 Scheimpflug metrics (index height decentration (IHD), index vertical asymmetry (IVA), pachymetry apex, inferior-superior (IS) value, ARTmax) yielded the best Scheimpflug results (AUC 0.86, Sensitivity 83%, Specificity 83%). Combining 11 SD-OCT thickness metrics (minimum-median, temporal outer, superior nasal outer, minimum, epithelium Min-Max, epithelial standard deviation, superior inner, superior outer, superior temporal outer, superior nasal inner, central) yielded the best SD-OCT results (AUC 0.96, Sensitivity 89%, Specificity 89%). Combining 13 total Scheimpflug/SD-OCT metrics yielded the best results overall (AUC 1.0, Sensitivity 100%, Specificity 100%). The most impactful variables in combined models included epithelial thickness variability and total focal corneal thickness variability from SD-OCT and anterior curvature and topometric indices from Scheimpflug technology. No posterior corneal metrics were impactful in modeling.

Conclusions—Individual machine derived metrics from Scheimpflug and SD-OCT imaging poorly distinguished normal eyes from minimally affected eyes from patients with highly asymmetric keratoconus. Combined SD-OCT metrics performed better than combined Scheimpflug metrics. Combining anterior curvature and asymmetry indices from Scheimpflug with regional total thickness and epithelial thickness variability metrics from SD-OCT clearly distinguished the two populations. Posterior corneal indices were not useful in distinguishing populations.

Keywords

Keratoconus; Subclinical; Scheimpflug; Pentacam; Pachymetry; Screening; Epithelial thickness; Ocular coherence tomography; OCT

Corneal morphologic imaging (topography and tomography) is critical to identify corneal ectatic disorders such as keratoconus and to appropriately screen patients to determine suitability for corneal refractive surgery.^{1–5} A variety of devices and strategies have been used with varying degrees of success, but discrepancy exists in terms of the relative importance of various screening technologies and variables to identify the earliest manifestations of keratoconus.^{6–14}

Placido based corneal topography evaluation of anterior corneal surface curvature has been the mainstay of keratoconus diagnosis for more than 30 years.^{2,4,5,15–18} While a variety of objective metrics have been proposed, the mainstay of optimal Placido analysis has been subjective pattern analysis. While this subjective analysis is critical for best discriminative capacity, there can be significant variation in subjective pattern analysis and screening for both Placido based topography and Scheimpflug based tomography, particularly for anterior curvature pattern analysis.^{5,8,17,19,20}

More recently, Scheimpflug imaging has allowed for evaluation of regional corneal thickness and both anterior and posterior curvature and elevation.^{9,11–14,21–30} Spectral domain anterior segment optical coherence tomography (SD-OCT) has also shown promise in identifying keratoconic eyes in earlier stages.^{31–40} Epithelial thickness profiles have been found to vary significantly between ectatic and normal corneas^{20,31,32,34,41} and have improved screening protocols.^{20,31,32,41–43} Reinstein et al.^{20,42} demonstrated the

effectiveness of epithelial measurements of very-high frequency digital ultrasound (VHFUDU) in differentiating fellow eyes of keratoconic patients, albeit with limited accuracy. Epithelial measurements in SD-OCT have shown similar promising but limited results in identifying subclinical keratoconus, suggesting a need for multifactorial models in screening for keratoconus.^{31,32,34,35}

Despite multiple available technologies, there remains a gap in identifying ectatic corneal disease at its earliest manifestation, and there remains significant controversy and discrepancy in the literature about the relative value of different evaluations (thickness vs. curvature, curvature vs. elevation, anterior vs. posterior elevation, total vs. epithelial thickness) in distinguishing keratoconus suspect eyes from normal populations. A recent consensus statement stated that abnormal posterior ectasia and abnormal corneal thickness distribution changes were mandatory to diagnose keratoconus and that posterior corneal elevation abnormalities must be present to diagnose subclinical keratoconus, despite a paucity of data to support these opinions.¹⁰ In contrast, a variety of authors have found that posterior elevation and relational thickness values poorly distinguish between normal control eyes and the less affected eye of patients with asymmetric keratoconus (AKC).^{6,9,11,12,14}

While a variety of studies have evaluated the relative efficacy of individual metrics from the same technology^{6,11,12,22,32,34–36} or the comparative efficacy of different technologies,^{7,20,30} there are sparse reports on combining metrics from different imaging technologies to improve overall screening sensitivity and specificity.^{29,37} None of these combinations have performed particularly well to date at distinguishing asymmetric/subclinical keratoconus from normal populations.

The purpose of this study was to evaluate objective, machine derived metrics from Scheimpflug and SD-OCT imaging and determine their relative value individually and in combination in distinguishing between normal control eyes and the minimally affected eye of patients with highly asymmetric keratoconus.

METHODS

This was a retrospective case-control study approved separately from Emory University (Atlanta, GA, USA) and the University of Southern California (Los Angeles, CA, USA) Institutional Review Boards. The study and control populations presented to one author's practice (JBR) from 2014 to 2017. Patients were included in the study group if they had highly asymmetric keratoconus disease presentation. Specifically, all study patients had clear evidence of keratoconus in one eye and no clear evidence of disease in the clinically unaffected eye. For the clinically involved eye, all patients had abnormal focal anterior corneal steepening, focal corneal thinning, clinical evidence of disease at the slit lamp, scissoring on retinoscopy, subjectively impaired visual acuity, and best corrected distance acuity (CDVA) worse than 20/20. For the unaffected asymmetric keratoconus eye (AKC), there was no clinical evidence of disease, no physical findings on slit lamp examination, no definitive abnormalities on corneal imaging, and CDVA of 20/20 or better. Scheimpflug imaging from the study population is available for review as online supplemental material. These images were produced at different time points, so output was not standardized across

cases. The specific maps and output were not used for any analysis; only data directly derived from the devices was used.

The control population presented contemporaneously and sequentially, with normal clinical evaluations, normal imaging with Scheimpflug, Dual Scheimpflug, and SD-OCT technology with automated epithelial thickness mapping as determined by one author (JBR) and had undergone uneventful LASIK with at least two years of stable follow-up.

All patients had both eyes evaluated with Scheimpflug imaging (Pentacam HR, Oculus, Inc.) and Spectral-Domain OCT (RT-Vue-100, Optovue, Inc.). A single scan that passed all specified quality metrics for each eye was used for evaluation. All Scheimpflug variables were directly downloaded from the Pentacam software using the “CALL-ALL” function, while SD-OCT variables were manually recorded from the Optovue software. Only objective, machine derived variables were used for analysis and classifications; no subjective image evaluation was performed beyond the initial identification of subjects. Representative study population images (AKC patients and controls) are shown in Figure 1. For the AKC group the clinically keratoconic eye was only used to identify the population but not otherwise evaluated or analyzed for this study.

Scheimpflug Parameters

Scheimpflug-based tomography with a rotating camera to take 500 measurement points from a total of 50 single slit images, totaling 25,000 measurement points, was used to assess the anterior and posterior surfaces of the cornea and generate a 3-dimensional image of the cornea. A quality score is provided for each scan, with an ‘OK’ given for acceptable scans. Objective, machine derived variables evaluated included keratometry values (front and back surface astigmatism), anterior curvature (asphericity coefficients of front and back, inferior-superior value (IS value), sagittal steepest K and steepest K zonal means at 3mm, 4mm and 5mm), machine-derived topometric screening indices (index of surface variation (ISV), index of vertical asymmetry (IVA), keratoconus index, central keratoconus index, index of height asymmetry (IHA), and index of height decentration (IHD)), regional pachymetry values (minimum thickness and thickness measurements at the center of the pupil and apex), cornea densitometry, ART-Max, and BAD scores.

SD-OCT Parameters

Spectral-domain OCT running on report software version A6, 8, 0, 27, with a scan rate of 26,000 axial scans per second was used to assess regional total corneal and epithelial thickness. Objective, machine derived variables evaluated included total corneal measurements obtained from the routine display of single average thickness values divided into the following zones (per the device output), where “inner” represents the 2 to 5 mm diameter area and “outer” represents the 5 to 6 mm diameter area: central (C), superior outer (SO), superior inner (SI), superotemporal outer (STO), superotemporal inner (STI), temporal outer (TO), temporal inner (TI), inferotemporal outer (ITO), inferotemporal inner (ITI), inferior outer (IO), inferior inner (II), inferonasal outer (INO), inferonasal inner (INI), nasal outer (NO), nasal inner (NI), superonasal outer (SNO), superonasal inner (SNI). Additional values obtained from this routine display included minimum thickness (Min), difference

between minimum thickness and averaged thickness from central 5mm diameter (Minimum-Median), difference between minimum thickness and averaged maximum thickness from central 5mm diameter (Minimum-Maximum), vertical location of the central 5mm zone (5mm Zone Y), average thickness of the SN quadrant minus that of IT quadrant (SN-IT) and the average thickness of superior quadrant minus that of the inferior quadrant (S-I). The epithelial measurements were obtained from the same routine display, with single average epithelial thickness values divided into the same octants as the total corneal measurements. Additional epithelial measurements obtained included average thickness in a 5mm zone in superior and inferior quadrants, minimum and maximum thickness in 5mm zone, standard deviation of epithelial thickness (Epi Std Dev) and difference between minimum and maximum epithelial thickness (Epi Min-Max).

Statistical Methods

The mean, standard deviation (SD), and range were calculated for each variable. An unpaired t-test was used to compare the means of control eyes and AKC eyes to determine significant differences between the two populations. P-values less than 0.05 were considered significant. Receiver operating characteristic (ROC) analysis was conducted for each significant variable in each device to determine predictive capability of each variable in isolation, as quantified by the area under the curve (AUC). Sensitivity, specificity, and cut off values were calculated from these ROC curves with Youden's index. A multivariable logistic regression analysis was conducted for all significant variables within and between both devices. For each multivariable analysis, Wald's chi-squared test was used to remove the least influential variable in a step-wise manner to produce maximal AUC values using minimal number of variables. The effect of each variable on the model was calculated by transformation into a LogWorth scale. All analyses were performed with SPSS (SPSS version 23, IBM) and JMP (Version 8.0, SAS Institute Inc.) software.

RESULTS

There were 30 highly asymmetric, clinically normal fellow eyes from 30 patients with definitive keratoconus in the contralateral eye (AKC group) and 60 clinically normal eyes from 60 bilaterally normal control patients (Control group) evaluated. There were no significant differences between groups for age (31.8 ± 13.4 years (14 to 61 years) AKC vs. 35.4 ± 9.3 years (20 to 56 years) Controls, $p = 0.15$) or sex distribution (56.6% males AKC vs. 56.7% males Controls, $p = 0.91$). There was no significant difference in frequency of unaffected right or left eyes in the AKC group (53.3% left vs 46.7% right, $p = 0.79$).

Descriptive statistics of significant Scheimpflug variables are displayed in Table 1. Compared to controls, pachymetry variables (apex, pupil, minimum) were significantly thinner, ARTmax was significantly lower, and topometric screening indices (IVA, ISV, IHD), IS-value, and BAD-D score were significantly higher in the AKC eyes. ROC analysis found that BAD-D score had the highest individual metric AUC value (0.754), followed by ISV (0.746). Neither these nor any other individual Scheimpflug metrics performed well at differentiating populations (Table 1).

Descriptive statistics of statistically significant SD-OCT variables are displayed in Table 2. The AKC eyes had significantly lower total corneal thickness than control eyes in multiple regions. Among epithelial variables, Epi Std Dev. was significantly higher, and Epi Min-Max was significantly lower in AKC eyes. No significant difference in any of the epithelial thickness quadrants was found between the two populations. ROC analysis found that Min (0.739) and superior outer thickness (0.724) had the highest individual AUC values. Neither these nor any other individual SD-OCT metrics performed well at differentiating populations (Table 2).

Multivariable analysis using significant variables from each device was conducted to identify the best combination of variables. When using only Scheimpflug variables, the highest AUC value attained was 0.857 (83% Sensitivity and 83% Specificity) with 5 variables (Figure 2). When using only SD-OCT variables, the highest AUC value attained was 0.955 (89% Sensitivity and 89% Specificity) with 11 variables (Figure 2). In multivariable analysis using variables combined from both Scheimpflug and SD-OCT devices, the highest possible AUC value was 1.0 (100% Sensitivity and 100% Specificity) with 13 variables. Variable rank by order of importance for each model is shown in Table 3, while comparative analysis of ROC curves for each combined model is shown in Figure 2. The most important metric categories were various focal total thickness measurements and epithelial thickness variability from SD-OCT, and anterior curvature and surface asymmetry indices from Scheimpflug. No posterior corneal metrics, elevations, or regional thickness progression metrics were impactful in combined variable modeling.

DISCUSSION

The results of this study demonstrate that while individual objective, machine derived metrics from Scheimpflug and SD-OCT technology had limited capacity in distinguishing normal control eyes from the fellow, clinically unaffected eyes of patients with highly asymmetric keratoconus, using a combination of these objective variables from either device yielded improved models for differentiating these groups. The primary findings from this paper are the following:

1. No single objective variable from either Scheimpflug or SD-OCT technology performed well at distinguishing between the clinically unaffected affected eye of patients with asymmetric keratoconus eyes from normal controls
2. Combined SD-OCT metrics performed better than combined Scheimpflug metrics in distinguishing the study populations
3. A combination of variables from SD-OCT and Scheimpflug technologies performed optimally at distinguishing study populations
4. The most significant machine derived variables across models included total corneal thickness measures and variability from SD-OCT and to a lesser extent Scheimpflug imaging, anterior asymmetry and anterior curvature metrics from Scheimpflug imaging, and epithelial thickness variability from SD-OCT.

In comparing our results to literature reports, the first challenge encountered was unclear nomenclature regarding less severe manifestations of keratoconus in other publications. Clarifying this nomenclature was beyond the scope of this project; as such, we took multiple terms (asymmetric keratoconus, keratoconus suspect, forme fruste keratoconus, subclinical keratoconus, clinically and topographically normal fellow eyes, among others) to be more or less interchangeable as it related to comparisons with our study population. While not endorsing any of these terms specifically, we attempted to use the authors' own wording for these comparisons.

Shajari and colleagues²³ reported findings similar to ours regarding individual Scheimpflug metrics in asymmetric keratoconus patients. The authors found that IHD (AUC 0.788) and IVA (AUC 0.772) were best in detecting subclinical keratoconus, followed by KI (AUC 0.743), while BAD-D (AUC 0.622) and ARTmax (AUC 0.613) performed worse in differentiating populations. In our study, we found a similar range of results for IHD, ISV, IVA, BAD-D, and ARTmax, while IHD, ISV, IVA, and IS value had the strongest impact on our combined Scheimpflug model (Table 3). Our findings agree in part with other recent studies,^{12,21,22,30} which found that ARTmax and BAD-D metrics were the most effective among individual metrics in distinguishing forme fruste keratoconus eyes from normal eyes but did not perform well enough in isolation or together to accurately distinguish subclinical keratoconus from a normal cohort.

Our findings also agree with studies evaluating SD-OCT, which found that epithelial thickness measurements from SD-OCT have value in early diagnosis of forme fruste keratoconus.^{20,31,32,35} Li et al.³² found epithelial thickness standard deviation (pattern standard deviation) to be a strong predictor of early keratoconus, while Temstet et al.³⁵ found epithelial thickness in the thinnest location to be useful in diagnosis of early subclinical keratoconus. Epithelial thickness metrics (Epi Min-Max and Epi Std Dev) had a significant impact on our models that included SD-OCT metrics and combined Scheimpflug/SD-OCT metric models in our study.

We used a logistic regression analysis combining variables from Scheimpflug and SD-OCT imaging, which was highly effective in distinguishing the minimally affected asymmetric keratoconus eyes from normal eyes. To our knowledge, our study is the first to successfully combine objective variables from these two imaging modalities to effectively discriminate between normal controls and the clinically unaffected eye of patients with highly asymmetric keratoconus. Silverman et al.⁴⁴ used a combined multivariable discriminate analysis with Artemis-1 and Scheimpflug imaging to distinguish normal eyes from clinically evident keratoconic eyes (97.3% sensitivity, 100% specificity) and Qin et al.³⁶ combined OCT variables in a logistic regression to separate normal eyes from clinically evident keratoconic eyes (90.5% sensitivity, 95.0% specificity). Rabinowitz et al.³⁷ correctly identified 87.5% of suspect keratoconus eyes by combining OCT total thickness variables with Placido-based topography variables derived from the Tomey device; however, the authors defined a more advanced form of "suspect keratoconus" by including patients with clear inferior steepening.

A recent consensus position paper stated that posterior corneal elevation abnormalities are mandatory to diagnose subclinical keratoconus.^{10,45} Our findings refute that opinion. The combination of variables from Scheimpflug and SD-OCT, which included anterior curvature metrics, total corneal and epithelial thickness measurements, distinguished AKC eyes from normal eyes effectively, while adding relational thickness or posterior elevation data reduced model accuracy. Further studies with posterior curvature and elevation data from other imaging modalities may identify alternate discriminative parameters. Based on available data, it appears that neither posterior elevation nor regional thickness abnormalities as determined by Scheimpflug technology are mandatory to diagnose subclinical keratoconus.

Our results highlight the complexity of distinguishing the clinically unaffected eye from patients with asymmetric keratoconus from normal populations. Multiple variables from different technologies were necessary to fully distinguish groups. Even given the strict parameters applied in this study, the less involved eye from highly asymmetric keratoconus patients still represent a highly heterogeneous population. Anterior curvature, asymmetry indices, focal total thickness, regional total thickness variability, and epithelial thickness were all necessary to correctly distinguish all eyes. Given the heterogeneity of these populations, we anticipate that other samples similar to ours may find different combinations of variables that best discriminate groups. Nevertheless, we anticipate that most of the variables and variable categories identified as critical in our study will prove important in other analyses, albeit possibly to varying extents. Despite this likely limitation for our analysis, we felt that publishing these findings would represent a positive first step to direct future studies towards the best variables to assess in greater detail.

There are limitations to this study. The AKC population was defined using subjective image pattern analysis of by one author (JBR) to identify patients with highly asymmetric keratoconus. While this induced subjectivity into the initial identification of the study population, no further subjective analysis was utilized at any step of data analysis or multivariable analysis. Subjective pattern analysis is a fundamental part of routine clinical practice, but the literature has shown that this is fraught with challenges, given the potential variability between reviewers when using Placido based topography or Scheimpflug based tomography for anterior curvature.^{5,8,17,19,20} We therefore selected to evaluate only metrics that were directly machine derived for this analysis.

The primary limitations in this study include small sample size and lack of long-term follow-up. Our sample size was limited by our inclusion criteria; we felt it best to evaluate a truly subclinical population, with the less affected eyes being ones that were not readily identifiable subjectively or from any single technology, since identifying more advanced stages of keratoconus and corneal ectasias are already straightforward using a variety of technologies. Lack of follow-up or intervention in these eyes limits our ability to identify parameters that best indicate a higher risk of progression. Further, while we utilized two specific devices in this study, other devices using similar technology may perform as well or better than these specific instruments. In future studies, we plan to assess different technologies in highly asymmetric keratoconus groups and apply our modeling to populations that developed ectasia after corneal refractive surgery.

None of the metrics identified directly measure corneal biomechanics; rather, they all describe corneal morphology. We anticipate there will remain a gap in our optimal identification of corneal ectasias in their earliest manifestations until we are able to accurately assess corneal biomechanics directly. Recent work to directly measure corneal biomechanics has shown promise but remains to be robustly validated⁴⁶ and/or developed for clinical use.⁴⁷

In conclusion, our findings demonstrate that the clinically unaffected fellow eye in patients with highly asymmetric keratoconus remains difficult to identify using individual metrics from Scheimpflug or SD-OCT alone; however, using a combination of these metrics with logistic regression modeling yielded excellent discriminative power. A model that incorporated anterior curvature, anterior surface asymmetry, total pachymetry in various locations, and epithelial thickness variability demonstrated highest ability in discriminating these populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Precis (Highlights)

Individual Scheimpflug and SD-OCT metrics poorly distinguish normal and asymmetric keratoconic eyes; however, combining Scheimpflug anterior curvature and asymmetry indices with SD-OCT regional total thickness and epithelial thickness variability metrics clearly distinguished the two populations.

Figure 1.

Representative image of patients in this study, including both eyes from one patient with asymmetric keratoconus, showing the clinically affected eye (1A), unaffected eye (1B), and a normal control eye (1C). Each figure shows baseline Scheimpflug and SD-OCT imaging, with Scheimpflug anterior curvature and anterior elevation (top row), Scheimpflug total thickness and posterior elevation (middle row), and SD-OCT total corneal thickness and SD-OCT epithelial thickness (bottom row). For the unaffected eye (1B), IS Value = 0.78, Pachymetry Apex & Pupil = 535 microns, ARTmax = 446, and BAD-D = 1.14

Figure 2.

Comparative ROC Curves for Scheimpflug imaging only (Blue line, AUC = 0.857, 83% Sensitivity and 83% Specificity), SD-OCT imaging only (Green line, AUC = 0.955, 89% Sensitivity and 89% Specificity), and 13 variable combined Scheimpflug/SD-OCT imaging (Orange, AUC = 1.0, 100% Sensitivity and 100% Specificity).

Table 1

Significant Scheimpflug Variables Used to Differentiate Study Populations

Variable	Control	AKC	P-Value	AUC	95% CI	Cut off	Sens	Spec
BAD-D	0.875 ± 0.55 (-0.15 – 2.20)	1.56 ± 0.79 (0.31 – 3.42)	<0.001	0.754	0.647–0.861	1.01	80.0	66.7
ISV	14.9 ± 4.34 (8 – 29)	19.83 ± 6.18 (11 – 34)	<0.001	0.746	0.638–0.855	18.5	53.3	86.7
IVA	0.098 ± 0.04 (0.03 – 0.19)	0.13 ± 0.053 (0.06 – 0.28)	<0.001	0.722	0.613–0.830	0.115	70.0	66.7
ARTmax	447.6 ± 69.2 (319 – 610)	374.7 ± 87.7 (229 – 554)	<0.001	0.739	0.617–0.861	363.5	56.7	88.3
Pachymetry Min	541.8 ± 27.3 (491 – 598)	515.5 ± 27.6 (459 – 579)	<0.001	0.740	0.631–0.849	514.5	53.3	86.7
Pachymetry Apex	546.8 ± 26.9 (495–607)	523.4 ± 25.8 (473–585)	<0.001	0.732	0.621–0.843	531.0	66.7	75.0
Pachymetry Pupil	545.9 ± 27.3 (493–606)	522.3 ± 24.7 (475–579)	<0.001	0.731	0.620–0.841	529.5	66.7	75.0
IHD	0.0089 ± 0.005 (0.001 – 0.03)	0.0102 ± 0.004 (0.003 – 0.02)	0.210*	0.604	0.484–0.725	0.0075	76.7	51.7
IS Value	0.22 ± 0.53 (-0.99 – 1.41)	0.32 ± 0.73 (-2.2 – 1.49)	0.420*	0.599	0.469–0.730	0.51	53.3	75.0

BAD-D = Belin-Ambrosio Deviation Score

ISV = index surface variance

IVA = index vertical asymmetry

ARTmax = Ambrosio's Relational Thickness Maximum

Min = minimum

IHD = index height decentration

IS Value = inferior-superior value

AKC = asymmetric keratoconus

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AUC = area under curve
CI = confidence interval
Cut off = cut off value
Sens = sensitivity
Spec = specificity
* p value not significantly different, but variable was significant in grouped variable modeling

Table 2

Significant SD-OCT Variables Used to Differentiate Study Populations

Variable (microns)	Control	AKC	P-Value	AUC	95% CI	Cut off	Sens	Spec
Epi Min-Max	-6.14 ± 2.13 (-13 – -3)	-8.0 ± 3.71 (-19 – -4)	0.003	.676	0.543–0.809	-6.5	68.4	65.5
Epi Std Dev	1.39 ± 0.53 (0.6 – 3.2)	1.85 ± 1.05 (0.9 – 5.7)	0.005	.671	0.537–0.805	1.35	73.7	58.2
Minimum	532.3 ± 27.3 (479 – 597)	508.0 ± 21.7 (453 – 547)	<0.001	.739	0.630–0.848	517.5	73.1	70.0
Min-Median	-19.4 ± 5.7 (-41 – -9)	-22.3 ± 5.42 (-33 – -14)	0.025	.663	0.541–0.784	-16.5	88.5	36.7
Central	538.5 ± 28.3 (483 – 601)	515.8 ± 21.4 (469 – 555)	<0.001	.721	0.608–0.834	525.5	73.1	65.0
Sup. Outer	608.2 ± 38.3 (542 – 690)	578.3 ± 29.3 (526 – 646)	<0.001	.724	0.613–0.834	611.5	92.3	46.7
Sup. Inner	571.7 ± 33.6 (510 – 642)	548.9 ± 24.3 (498 – 595)	0.002	.688	0.572–0.803	587.5	96.2	33.3
Sup. Nasal Outer	597.9 ± 36.3 (532 – 669)	573.8 ± 24.0 (519 – 629)	0.002	.689	0.576–0.802	607.5	96.2	38.3
Sup. Nasal Inner	567.1 ± 32.6 (505 – 635)	546.7 ± 23.2 (493 – 587)	0.005	.673	0.556–0.790	588.5	100	30.0
Inf. Temporal Outer	562.6 ± 31.3 (506 – 633)	539.5 ± 24.2 (485 – 581)	0.001	.705	0.590–0.820	550.5	69.2	65.0
Inf. Temporal Inner	544.2 ± 29.0 (490 – 607)	520.7 ± 23.5 (462 – 561)	<0.001	.721	0.609–0.833	533	73.1	66.7
Temporal Outer	568.3 ± 34.1	542.6 ± 28.7			0.599–0.828	550.5	69.2	65.0

<u>Variable (microns)</u>	<u>Control</u>	<u>AKC</u>	<u>P-Value</u>	<u>AUC</u>	<u>95% CI</u>	<u>Cut off</u>	<u>Sens</u>	<u>Spec</u>
	(512 – 637)	(486 – 616)	0.001	.714				
Temporal Inner	547.6 ± 30.3 (492 – 610)	523.0 ± 24.3 (467 – 570)	<0.001	.718	0.606–0.830	536	69.2	65.0
Sup. Temporal Outer	590.6 ± 38.1 (528 – 662)	562.2 ± 25.8 (513 – 617)	<0.001	.715	0.605–0.824	568.5	69.2	68.3
Sup. Temporal Inner	560.8 ± 32.5 (503 – 624)	536.5 ± 24.0 (490 – 581)	<0.001	.708	0.595–0.820	542	61.5	73.3

Min-Median = Minimum-Median

Sup = Superior

Inf = Inferior

Epi = Epithelium

Std = Standard Deviation

$$\text{Min-Max} = \text{Minimum} - \text{Maximum}$$

AKC = asymmetric keratoconus

AUC = area under curve

CI = confidence interval

Cut off = cut off value

Sens = sensitivity

Spec = specificity

Table 3

Variable Rank by Impact on Combined Models to Distinguish Study Populations

Variable Rank	Scheimpflug (n=5)	SD-OCT (n=11)	Combined 13 Variable
1	IVA	Min-Median	Temp. Outer (O)
2	Pachymetry Apex	Epi Min-Max	Pachymetry Min (S)
3	IHD	Minimum	Temp. Inner (O)
4	ARTmax	Temp. Outer	IVA (S)
5	IS Value	Sup. Nasal Outer	Central (O)
6		Epi Std	Epi Std (O)
7		Sup. Outer	Min-Median (O)
8		Central	ISV (S)
9		Sup. Inner	Inf. Temp. Inner (O)
10		Sup. Nasal Inner	Epi Min-Max (O)
11		Sup. Temp. Outer	Minimum (O)
12			Sup. Outer (O)
13			Sup. Inner (O)
AUC	0.86	0.96	1.0
Sensitivity	83%	89%	100%
Specificity	83%	89%	100%

AUC = area under curve

ISV = index surface variance

IVA = index vertical asymmetry

IHD = index height decentration

IS Value = inferior-superior value

ARTmax = Ambrosio's Relational Thickness Maximum

BAD-D = Belin-Ambrosio Deviation Score

Min = Minimum

Max = Maximum

Min-Median = Minimum-Median

Sup = Superior

Temp = Temporal

Inf = Inferior

Epi = Epithelium

Std = Standard Deviation

O = SD-OCT

S = Scheimpflug