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Keratoconus Diagnosis with Optical Coherence Tomography Pachymetry Mapping

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Abstract

Objective—To detect abnormal corneal thinning in keratoconus using pachymetry maps measured by high-speed anterior segment optical coherence tomography (OCT).

Design—Cross-sectional observational study.

Participants—Thirty-seven keratoconic eyes from 21 subjects and 36 eyes from 18 normal subjects.

Methods—The OCT system operated at a 1.3 μm wavelength with a scan rate of 2000 axial scans per second. A pachymetry scan pattern (8 radials, 128 axial scans each; 10 mm diameter) centered at the corneal vertex was used to map the corneal thickness. The pachymetry map was divided into zones by octants and annular rings. Five pachymetric parameters were calculated from the region inside the 5 mm diameter: minimum, minimum–median, inferior–superior (I-S), inferotemporal–superonasal (IT-SN), and the vertical location of the thinnest cornea. The 1-percentile value of the normal group was used to define the diagnostic cutoff. Placido-ring–based corneal topography was obtained for comparison.

Main Outcome Measures—The OCT pachymetric parameters and a quantitative topographic keratoconus index (keratometry, I-S, astigmatism, and skew percentage [KISA%]) were used for keratoconus diagnosis. Diagnostic performance was assessed by the area under the receiver operating characteristic (AROC) curve.

Results—Keratoconic corneas were thinner. The pachymetric minimum averaged $452.6 \pm 60.9 \mu\text{m}$ in keratoconic eyes versus $546 \pm 23.7 \mu\text{m}$ in normal eyes. The 1-percentile cutoff was $491.6 \mu\text{m}$. The thinnest location was inferiorly displaced in keratoconus ($-805 \pm 749 \mu\text{m}$ vs $-118 \pm 260 \mu\text{m}$; cutoff, $-716 \mu\text{m}$). The thinning was focal (minimum–median: $-95.2 \pm 41.1 \mu\text{m}$ vs $-45 \pm 7.7 \mu\text{m}$; cutoff, $-62.6 \mu\text{m}$). Keratoconic maps were more asymmetric (I-S, $-44.8 \pm 28.7 \mu\text{m}$ vs $-9.9 \pm 9.3 \mu\text{m}$; cutoff, $-31.3 \mu\text{m}$; and IT-SN, $-63 \pm 35.7 \mu\text{m}$ vs $-22 \pm 11.4 \mu\text{m}$; cutoff, $-48.2 \mu\text{m}$). Keratoconic eyes had a higher

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KISA% index (2641 ± 5024 vs 21 ± 19). All differences were statistically significant (t test, $P < 0.0001$). Applying the diagnostic criteria of any 1 OCT pachymetric parameter below the keratoconus cutoff yielded an AROC of 0.99, which was marginally better ($P = .09$) than the KISA% topographic index (AROC, 0.91).

Conclusions—Optical coherence tomography pachymetry maps accurately detected the characteristic abnormal corneal thinning in keratoconic eyes. This method was at least as sensitive and specific as the topographic KISA.

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Keratoconus is a bilateral progressive ectatic corneal disease characterized by thinning and apical protrusion.^{1,2} The clinical diagnosis of moderate to advanced keratoconus is not difficult because of the characteristic topographic pattern and the classic clinical signs.² However, diagnosing early keratoconus in patients with normal best spectacle-corrected visual acuity and minimum or no clinical signs can be challenging.³ This identification is especially important in preoperative screening for laser refractive surgeries because undetected corneal ectatic disorders can result in accelerated, progressive keratoectasia and unpredictable outcomes after LASIK and photorefractive keratectomy.^{1,4-8}

Currently, Placido-disk-based corneal topography is regarded as the most sensitive measurement for detecting ectatic corneal disorders such as keratoconus and pellucid marginal degeneration.⁹⁻¹³ Topographic analyses have revealed characteristic features of these diseases before biomicroscopic signs or symptoms.^{14,15} Normal, suspicious, and abnormal topography patterns of these diseases had been classified.^{8,16} Quantitative topographic indices, such as the Rabinowitz-McDonnell index,¹⁷ the keratoconus prediction index,¹⁸ the Z3 index,¹⁹ the keratometry, inferior-superior (I-S), astigmatism, and skew percentage (KISA%) index,²⁰ and the mean curvature,^{21,22} have been developed to help diagnose keratoconus, and these indices are highly sensitive for keratoconus detection.^{2,20,23,24} However, topography screening methods have shortcomings. First, satisfactory topography maps may not be available owing to cornea irregularity or tear film breakup. Second, topography may not detect all patients at risk for keratoectasia; Randleman et al⁸ reported a meta-analysis in which 27% of 93 postrefractive surgery ectasia cases had normal preoperative topography, and 22% have an equivocal pattern (asymmetric bowtie). The asymmetric bowtie pattern is overrepresented in fellow eyes and relative eyes of keratoconus, but also occurs in normal eyes.²⁵ Third, it is difficult for these topography-based methods to distinguish keratoconus from contact lens-induced warpage, subepithelial deposits or scarring, uneven tear film, lid artifact, or other causes of corneal distortion.²⁶⁻²⁸ These causes of topographic distortion may cause a false-positive diagnosis of keratoconus or mask a true diagnosis of keratoconus.

Corneal thinning is a key pathologic feature of keratoconus¹; therefore, a keratoconus diagnosis based on corneal thickness measurement may offer additional information not available on topography.^{3,29} Corneal thickness has been proposed to be a useful parameter for the clinical identification of keratoconus.³⁰⁻³⁴ Studies using ultrasound or slit-scanning technologies have found that the difference (or ratio) between the peripheral and the thinnest (or central) corneal thickness was significantly greater in eyes with keratoconus than in normal eyes.^{3,35-38} However, to the best of our knowledge, corneal focal thinning and asymmetric thinning have not been evaluated together to detect corneal abnormality in keratoconus.

Optical coherence tomography (OCT) has micron-level high resolution and can accurately map the corneal thickness of normal, postoperative, and opacified corneas.³⁹⁻⁴¹ In this study, we developed a keratoconus screening method using a high-speed anterior segment OCT

prototype. We compared the OCT pachymetry-based method with a topography-based KISA % method for categorized diagnosis of keratoconus.

Methods

Subjects

Thirty-seven keratoconic eyes of 21 patients (12 men and 9 women) were recruited for this cross-sectional observational study at the Cleveland Clinic Cole Eye Institute, Cleveland, Ohio. Thirty-six eyes of 18 normal subjects (10 men and 8 women) were also included as a control group. This study followed the tenants of the Declaration of Helsinki, was in accord with the Health Insurance Portability and Accountability Act of 1996, and was approved by the Institutional Review Board of Cleveland Clinic. Written informed consent was obtained from all the subjects.

Keratoconic eyes included in this study were diagnosed clinically; each had ≥ 1 clinical sign other than the topographic appearance of the map, including slit lamp findings of Munson's sign, hydrops, Vogt's striae, Fleischer's ring, apical scar, apical thinning, or Rizutti's sign. None of the eyes had signs or history of other cornea disease, and none had undergone previous ocular surgery.

Optical Coherence Tomography Imaging

The OCT pachymetry map scans (Fig 1) were acquired with a high-speed anterior segment OCT prototype (Carl Zeiss Meditec Inc., Dublin, CA) as previous described.³⁹ Each eye was scanned 3 times within a single visit and the pachymetry maps were calculated. The maps (Fig 2) were divided into zones by octants: superior (S), superotemporal (ST), temporal (T), inferotemporal (IT), inferior (I), inferonasal (IN), nasal (N), superonasal (SN), and annular rings (2, 5, 7, and 10 mm diameters).

Optical Coherence Tomography Pachymetric Parameters

We constructed several diagnostic parameters from the OCT pachymetric map with the aim of capturing the focal and asymmetric nature of keratoconic corneal thinning. The parameters were calculated from the central 5 mm diameter of the pachymetry map. The octant values were averaged in the 2- to 5-mm diameter zone. The 5 pachymetric diagnostic parameters were as follows:

1. Minimum-median.
2. The I-S: The average thickness of the inferior (I) octant minus that of the superior (S) octant.
3. The IT-SN: The average thickness of the IT octant minus that of the SN octant.
4. Minimum.
5. Vertical location of the minimum. Locations superior to the corneal vertex had positive values and locations inferior to the vertex had negative values.

Focal thinning was captured by the minimum–median and minimum parameters. Asymmetric thinning was captured by the I-S and IT-SN parameters, and by the vertical location of the minimum.

Videokeratography-Derived KISA% Index

Topography maps of the corneas were obtained with a Placido-ring corneal topography system (Atlas 995, Carl Zeiss Meditec). The average keratometry reading (Sim-K) was calculated by

taking the average of the flat K and steep K readings from Atlas. The KISA% index was calculated using a previously published method for all subjects.²⁰ The published threshold value for a classification keratoconus is KISA% > 100.⁴²

Statistical Analysis

The repeatability of the OCT pachymetry map was evaluated by the root-mean-square deviation from the average corneal thickness map. The repeatability of each OCT pachymetric parameter was calculated by pooled standard deviation (SD) of repeated measurements.⁴³ The mean value $\pm$ SD of each pachymetric parameter was calculated for both the keratoconus and normal groups. The normality of the OCT diagnostic parameters was confirmed by a Kolmogorov–Smirnov test on the dataset, in which 1 eye was randomly selected from each normal subject. The generalized estimating equation⁴⁴ was used to account for the inter-eye correlation in the variance of t test.

The 1-percentile value (mean – 2.33 SD) of the normal group was used to define the cutoff value of each pachymetry parameter. Two criteria, “1 abnormal” or “2 abnormal,” were used to screen keratoconus. With the “1 abnormal” criterion, if any of the pachymetric parameter values exceeded the cutoff value, the eye was considered to be keratoconic. Similarly, with the “2 abnormal” criterion, if any 2 of the parameters were abnormal, the eye was keratoconic.

Receiver operating characteristic (ROC) curve analyses were performed to compare the diagnostic performance of OCT pachymetry and KISA%. The ROC curves of the “1 abnormal” and “2 abnormal” criteria were generated by “composite scores” based on the standardized deviation of the 5 pachymetric diagnostic parameters. The ROC curve generated by the composite scores had been used in other ophthalmology studies.⁴⁵ The composite scores for “1 abnormal” and “2 abnormal” criteria were calculated as follows: The mean and SD of the normal group were denoted by $mean_N$ and SD_N . Then the standardized deviation of a OCT pachymetry parameter value (denoted by OCT_{score}) was defined by:

$$OCT_{score} = \frac{OCT - mean_N}{SD_N}.$$

The composite score of the “1 abnormal” criterion was the most negative among the 5 standardized deviations (the parameters were defined so that more negative values are indicative of keratoconus). The composite score of the “2 abnormal” criterion was the second lowest of 5 standardized deviations. Moreover, the AROC values were computed based on the formula in Obuchowski⁴⁶ extending the nonparametric method of Delong et al⁴⁷ to clustered data. The standard error of sensitivity and specificity was computed based on the formula for clustered binary data derived by Rao and Scott.⁴⁸ The same method was already used in previous studies in ophthalmology^{45,49} to handle the intereye correlation appropriately.

We set the level of significance at $P < 0.05$. The AROC, sensitivity, and specificity analyses were performed with MATLAB 7.0 (The MathWorks, Inc., Natick, MA) and the other analyses were done in SAS 9.1 (SAS Institute Inc., Cary, NC).

Results

Keratoconus cases had an average spherical error of -8.0 ± 6.1 diopters (D; mean $\pm$ SD; range -22.5 to 0). The average astigmatism in these eyes was 3.2 ± 2.2 D (range, 0 – 7.0). The average keratometry reading (Sim-K) was 49.2 ± 5.2 D (range, 40.8 – 60.9). For the normal group, the mean spherical error was -3.7 ± 2.2 D (range, -8.75 to 1.25). The mean astigmatism was 0.8

± 0.7 D (range, 0–2.75). The average recorded keratometry reading was 43 ± 1.4 D (range, 41–47).

The repeatability of the OCT pachymetry map inside the central 5-mm zone was $3.0 \mu\text{m}$ for the normal eyes and $5.0 \mu\text{m}$ for the keratoconic eyes. The repeatability of the individual OCT pachymetric parameters are given in Table 1. In general, the parameters were more reproducible in normal eyes than in keratoconic eyes. The I-S and the IT-SN asymmetric parameters were more repeatable in the 2- to 5-mm diameter zone than in the outer zones (>5 mm).

The average OCT pachymetric measurements are listed in Table 2. The pachymetric parameters of the keratoconus eyes were all significantly smaller than those of the normal eyes ($P < 0.0001$ by 2-sided generalized estimating equation *t* test).

The 1-percentile cutoff values for the OCT pachymetric diagnostic parameters are listed in Table 3. The cutoff values were $491.6 \mu\text{m}$ for minimum; $-62.6 \mu\text{m}$ for minimum–median; $-31.3 \mu\text{m}$ for I-S; $-48.2 \mu\text{m}$ for IT-SN; and $-716 \mu\text{m}$ for the vertical location of the thinnest corneal region.

The sensitivity, specificity, and AROC of the individual OCT parameters are listed in Table 4. All OCT parameters had good diagnostic power to detect keratoconus eyes with AROC (0.868–0.954) and good sensitivities (0.622–0.757) at the 1-percentile cutoff. The minimum parameter has the best AROC (0.954); however, there is no statistical difference among the 5 parameters. The minimum–median parameter had the second highest AROC (0.929) and the best sensitivity (0.757).

The KISA% indices were 2641 ± 5024 for the keratoconus group and 21 ± 19 for the normal group. The cutoff value of the KISA% was 100, reflecting a previously published method.⁴²

The sensitivity and the specificity of the OCT method and KISA% methods are compared in Table 5. The ROC curves of the OCT keratoconus screening method with the “1 abnormal” rule and the KISA% method are plotted in Figure 3. Both methods provided excellent discrimination between normal and keratoconic eyes. The AROC was 0.99 ± 0.01 for the OCT method and 0.91 ± 0.05 for the KISA% method. The difference between the AROC values was not statistically significant ($P = 0.09$).

Case Reports

Case 1 (Fig 4A) was an keratoconic eye with Munson’s sign, Vogt’s striae, Fleisher’s ring, apical scar, apical thinning, and Rizutti’s sign. The topographic KISA% value was calculated to be 49.647. The OCT pachymetric parameters were: minimum–median = $-161.6 \mu\text{m}$; I-S = $-60.8 \mu\text{m}$; IT-SN = $-104 \mu\text{m}$; minimum = $380.1 \mu\text{m}$; and vertical location of the minimum = $-921 \mu\text{m}$. All the parameters exceeded the keratoconus thresholds. Both topographic and OCT pachymetric analysis accurately classified this eye as keratoconic. In contrast with the loss of data in the topography map, OCT was able to measure the pachymetry map over a wide area of central cornea.

Case 2 (Fig 4B) was an keratoconic eye with Munson’s sign and Rizutti’s sign. The topographic KISA% value was 9. The OCT pachymetric parameters were as follows: minimum–median = $-37.3 \mu\text{m}$; I-S = $-42 \mu\text{m}$; IT-SN = $-37.3 \mu\text{m}$; minimum = $496.9 \mu\text{m}$; and vertical location of the minimum = $-1470 \mu\text{m}$. The KISA% method misclassified this eye as normal. The OCT pachymetric analysis accurately identified the eye as keratoconic, based on 2 abnormal parameters: I-S and the vertical location of the minimum. Inspection of the topography map indicated a skewed and asymmetric bow-tie astigmatism pattern that could be due to

keratoconus. However, the skew and asymmetry were not picked up by automated topography analysis (I-S and skewed radial axis were normal) because of masking by what seems to be an upper lid artifact.

Case 3 (Fig 4C) was a keratoconic eye with Munson's and Rizutti's signs. The KISA% value was 23. The OCT pachymetric parameters were as follows: minimum-median = $-84.3 \mu\text{m}$ (below the cutoff of $-63 \mu\text{m}$); I-S = $-25 \mu\text{m}$; IT-SN = $-29.4 \mu\text{m}$; minimum = $429.9 \mu\text{m}$ (below the cutoff of $492 \mu\text{m}$); and vertical location of the minimum = $-2503 \mu\text{m}$ (below the cutoff of $-716 \mu\text{m}$). The KISA% index misclassified this eye as normal. The OCT pachymetric analysis accurately identified the eye as keratoconic, based on 3 abnormal parameters: minimum-median, minimum, and the vertical location of the minimum. Inspection of the topography map showed possible asymmetry in the bow-tie astigmatism pattern that could indicate keratoconic inferotemporal steepening. However, this possibility was difficult to assess, owing to irregular variations in the inferotemporal region of the topography map that might be due to an irregular poor tear film. The asymmetry was not picked up by automated topography analysis (I-S was within normal limits).

Discussion

The OCT pachymetry maps are highly repeatable: Our study showed a pooled root-mean-square repeatability of $3 \mu\text{m}$ (normal) or $5 \mu\text{m}$ (keratoconus). We applied keratoconus analysis to the central 5-mm area of the OCT pachymetry maps, because we had previously found the repeatability to be better in the 0- to 5-mm diameter zones than in larger diameter zones.³⁹ This was confirmed for keratoconus parameter calculations (I-S and IT-SN) in this study (Table 1). Another rationale for applying the analysis to the central 5-mm region is that the cone peak of a keratoconic eye is most likely located inside this region.²²

Minimum (or central) corneal thickness is the most frequently cited pachymetric parameter to evaluate keratoconus. Rabinowitz et al,³³ Pflugfelder et al,³ and several other research groups^{29,31,32,34} reported that keratoconic corneas were significantly thinner than normal corneas (Table 6). Minimum corneal thickness was the best parameter in our study (highest AROC value, 0.954). However, a low "minimum corneal thickness" value could also be due to generalized corneal thinning, focal thinning, or both; it might not specifically indicate keratoconus. Binder's study⁵⁰ showed that a thin cornea may not necessarily lead to ectasia after refractive surgeries. Furthermore, the normal corneal thickness range has a wide distribution: The average central corneal thickness of normal eyes is $536 \pm 31 \mu\text{m}$ (median $\pm$ SD), as determined by a metaanalysis.⁵¹ The smaller population SD of $23.7 \mu\text{m}$ found in our study might be due to the relatively small sample size; the $492\text{-}\mu\text{m}$ cutoff value derived from our normal reference data might be too high and might result in lower specificity when applied to larger populations. In the future, larger studies will more firmly establish the diagnostic cutoff values and diagnostic performance of OCT pachymetric map analysis.

Focal corneal thinning is possibly a more specific indicator of keratoconus.² We designed a new parameter—"minimum-median"—to detect focal thinning. The AROC of this difference parameter was not higher than the minimum, but we considered these 2 parameters to be complementary, because they measured different aspects of corneal thinning (focal and general).

In addition to focal thinning, Vinciguerra and Camesasca⁵² and Binder et al⁵ summarized that asymmetric and eccentric corneal thinning were also characteristics of keratoconus. To evaluate the asymmetry of the map, we calculated the difference between the average corneal thicknesses from all possible pairs of 4 opposite octants: I-S, IT-SN, T-N, and IN-ST. We found that only the I-S and IT-SN parameters yielded significant differences between the keratoconus

and the normal groups ($P < 0.0001$). The correlation coefficient between I-S and IT-SN was 0.74; therefore, we considered them to have some complementary information and used both octant differences as asymmetry parameters. To evaluate the eccentricity of the corneal thinning, we calculated 2 parameters: the distance from the thinnest corneal point to the corneal vertex, and the vertical location of the thinnest corneal point. We found that the vertical location of the thinnest corneal point had better discriminative power (AROC values, 0.92 vs 0.86), and we therefore selected it as the eccentricity parameter.

Our results suggested that the 5 OCT pachymetric diagnostic parameters we selected were highly complementary. The “1 abnormal” criterion improved the diagnosis power for keratoconus and provided an excellent combination of sensitivity (0.97) and specificity (0.97). And with “2 abnormal” criterion, the specificity of keratoconus diagnosis was very high (1.00). Of course, larger studies are necessary to validate our findings. Moreover, our study is a preliminary study consisting only of keratoconus cases that had been confirmed by clinical (slit lamp) signs. Therefore, the sensitivity of OCT in the detection of forme fruste keratoconus (those without clinical signs) has yet to be established.

An OCT pachymetry map analysis can provide decisive diagnostic information in cases where topography is ambiguous. In case 1, part of the topography map was lost owing to poor corneal reflex. In contrast, OCT was able to provide pachymetry map over a wide area of central cornea. In cases 2 and 3, KISA% analysis identified the topography maps as within normal range, because asymmetry or skew in the bowtie astigmatism pattern were masked by irregularities that might be due to a lid artifact or tear film disturbance. Performance of OCT was not affected by these conditions. It is an important advantage that OCT can reliably map the corneal thickness of normal, postoperative, and opacified corneas.³⁹⁻⁴¹

One limitation of the current OCT technology is that interpolation is used in the central 0.5- to 1.0-mm diameter and among the 8 radial scans. Thus, small areas of corneal thickness variation might be missed.³⁹ Another limitation of the OCT system used in this study was that it was not fast enough to measure the corneal topography; therefore, it could not completely replace a Placido-ring topography system. In a previous study, we found the repeatability of anterior corneal power by this OCT system to be 0.79 D,⁵³ significantly worse than the repeatability of standard keratometry (0.2 D) or Placido-ring topography (0.1 D).⁵⁴ These findings suggested that the scan speed of 2000 a-scans/sec might not be sufficient to overcome the motion error for surface contour measurements. Thickness measurement was much more robust, because axial eye motion moved the anterior and posterior surface equally and had little effect on the thickness measurement. Therefore, we concentrated on pachymetry map analysis in this study. However, the speed limitation is not intrinsic to OCT; new Fourier-domain OCT technology is capable of >10-fold higher scan speeds.⁵⁵ We are currently evaluating Fourier-domain OCT as a method to map both pachymetry and topography.

A commercially available OCT instrument similar in performance (wavelength, scan range, speed, signal) to the anterior segment OCT prototype used in this study, the Visante anterior segment OCT system (Carl Zeiss Meditec Inc.), was approved by the US Food and Drug Administration in October 2005. Thus, the keratoconus screening method presented in this study can now be applied by other researchers and clinicians. Because the Visante software uses different image processing algorithms and has a slightly different parameter output format, we are performing another study to confirm our findings using the commercial unit.

In summary, we showed that OCT pachymetry map-based analysis could detect abnormal corneal thinning in keratoconus eyes. We provide a set of 5 diagnostic parameters and cutoff values that performed well together in our small study.

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References

1. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. *Surv Ophthalmol* 1984;28:293–322. [PubMed: 6230745]
2. Rabinowitz YS. Keratoconus. *Surv Ophthalmol* 1998;42:297–319. [PubMed: 9493273]
3. Pflugfelder SC, Liu Z, Feuer W, Verm A. Corneal thickness indices discriminate between keratoconus and contact lens-induced corneal thinning. *Ophthalmology* 2002;109:2336–41. [PubMed: 12466180]
4. Amoils SP, Deist MB, Gous P, Amoils PM. Iatrogenic keratectasia after laser in situ keratomileusis for less than -4.0 to -7.0 diopters of myopia. *J Cataract Refract Surg* 2000;26:967–77. [PubMed: 10946186]
5. Binder PS, Lindstrom RL, Stulting RD, et al. Keratoconus and corneal ectasia after LASIK. *J Cataract Refract Surg* 2005;31:2035–8. [PubMed: 16412891]
6. Randleman JB, Russell B, Ward MA, et al. Risk factors and prognosis for corneal ectasia after LASIK. *Ophthalmology* 2003;110:267–75. [PubMed: 12578766]
7. Seiler T, Quurke AW. Iatrogenic keratectasia after LASIK in a case of forme fruste keratoconus. *J Cataract Refract Surg* 1998;24:1007–9. [PubMed: 9682124]
8. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal refractive surgery. *Ophthalmology* 2008;115:37–50. [PubMed: 17624434]
9. Avitabile T, Franco L, Ortisi E, et al. Keratoconus staging: a computer-assisted ultrabiomicroscopic method compared with videokeratographic analysis. *Cornea* 2004;23:655–60. [PubMed: 15448489]
10. Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes in unilateral keratoconus patients. *Ophthalmology* 2004;111:440–6. [PubMed: 15019316]
11. Maguire LJ, Bourne WM. Corneal topography of early keratoconus. *Am J Ophthalmol* 1989;108:107–12. [PubMed: 2757091]
12. Rabinowitz YS, Garbus J, McDonnell PJ. Computer-assisted corneal topography in family members of patients with keratoconus. *Arch Ophthalmol* 1990;108:365–71. [PubMed: 2310336]
13. Wilson SE, Lin DT, Klyce SD. Corneal topography of keratoconus. *Cornea* 1991;10:2–8. [PubMed: 2019102]
14. Maeda N, Klyce SD, Tano Y. Detection and classification of mild irregular astigmatism in patients with good visual acuity. *Surv Ophthalmol* 1998;43:53–8. [PubMed: 9716193]
15. Ambrosio JR, Klyce SD, Smolek MK, Wilson SE. Pellucid marginal corneal degeneration. *J Refract Surg* 2002;18:86–8. [PubMed: 11828914]
16. Demirbas NH, Pflugfelder SC. Topographic pattern and apex location of keratoconus on elevation topography maps. *Cornea* 1998;17:476–84. [PubMed: 9756441]
17. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. *J Refract Surg* 1995;11:371–9. [PubMed: 8528916]
18. Maeda N, Klyce SD, Smolek MK, Thompson HW. Automated keratoconus screening with corneal topography analysis. *Invest Ophthalmol Vis Sci* 1994;35:2749–57. [PubMed: 8188468]
19. Schwiegerling J, Greivenkamp JE. Keratoconus detection based on videokeratographic height data. *Optom Vis Sci* 1996;73:721–8. [PubMed: 9002087]
20. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. *J Cataract Refract Surg* 1999;25:1327–35. [PubMed: 10511930]
21. Tang M, Shekhar R, Huang D. Mean curvature mapping for detection of corneal shape abnormality. *IEEE Trans Med Imaging* 2005;24:424–8. [PubMed: 15754992]
22. Tang M, Shekhar R, Miranda D, Huang D. Characteristics of keratoconus and pellucid marginal degeneration in mean curvature maps. *Am J Ophthalmol* 2005;140:993–1001. [PubMed: 16376641]

23. Klyce SD, Karon MD, Smolek MK. Screening patients with the corneal navigator. *J Refract Surg* 2005;21(suppl):S617–22. [PubMed: 16212291]
24. Smolek MK, Klyce SD. Current keratoconus detection methods compared with a neural network approach. *Invest Ophthalmol Vis Sci* 1997;38:2290–9. [PubMed: 9344352]
25. Levy D, Hutchings H, Rouland JF, et al. Videokeratographic anomalies in familial keratoconus. *Ophthalmology* 2004;111:867–74. [PubMed: 15121361]
26. Cheng HC, Lin KK, Chen YF, Hsiao CH. Pseudokeratoconus in a patient with soft contact lens-induced keratopathy: assessment with Orbscan I. *J Cataract Refract Surg* 2004;30:925–8. [PubMed: 15093665]
27. Wilson SE, Lin DT, Klyce SD, et al. Topographic changes in contact lens-induced corneal warpage. *Ophthalmology* 1990;97:734–44. [PubMed: 2374677]
28. Maeda N, Klyce SD, Smolek MK. Comparison of methods for detecting keratoconus using videokeratography. *Arch Ophthalmol* 1995;113:870–4. [PubMed: 7605277]
29. Ambrosio R Jr, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. *J Cataract Refract Surg* 2006;32:1851–9. [PubMed: 17081868]
30. Haque S, Simpson T, Jones L. Corneal and epithelial thickness in keratoconus: a comparison of ultrasonic pachymetry, Orbscan II, and optical coherence tomography. *J Refract Surg* 2006;22:486–93. [PubMed: 16722488]
31. Gherghel D, Hosking SL, Mantry S, et al. Corneal pachymetry in normal and keratoconic eyes: Orbscan II versus ultrasound. *J Cataract Refract Surg* 2004;30:1272–7. [PubMed: 15177603]
32. Lim L, Wei RH, Chan WK, Tan DT. Evaluation of keratoconus in Asians: role of Orbscan II and Tomey TMS-2 corneal topography. *Am J Ophthalmol* 2007;143:390–400. [PubMed: 17224118]
33. Rabinowitz YS, Rasheed K, Yang H, Elashoff J. Accuracy of ultrasonic pachymetry and videokeratography in detecting keratoconus. *J Cataract Refract Surg* 1998;24:196–201. [PubMed: 9530594]
34. Ucakhan OO, Ozkan M, Kanpolat A. Corneal thickness measurements in normal and keratoconic eyes: Pentacam comprehensive eye scanner versus noncontact specular microscopy and ultrasound pachymetry. *J Cataract Refract Surg* 2006;32:970–7. [PubMed: 16814055]
35. Avitabile T, Marano F, Castiglione F, Reibaldi A. Keratoconus staging with ultrasound biomicroscopy. *Ophthalmologica* 1998;212(suppl):10–2. [PubMed: 9730738]
36. Avitabile T, Marano F, Uva MG, Reibaldi A. Evaluation of central and peripheral corneal thickness with ultrasound biomicroscopy in normal and keratoconic eyes. *Cornea* 1997;16:639–44. [PubMed: 9395873]
37. Gromacki SJ, Barr JT. Central and peripheral corneal thickness in keratoconus and normal patient groups. *Optom Vis Sci* 1994;71:437–41. [PubMed: 7970558]
38. Owens H, Watters GA. An evaluation of the keratoconic cornea using computerised corneal mapping and ultrasonic measurements of corneal thickness. *Ophthalmic Physiol Opt* 1996;16:115–23. [PubMed: 8762772]
39. Li Y, Shekhar R, Huang D. Corneal pachymetry mapping with high-speed optical coherence tomography. *Ophthalmology* 2006;113:792–9. [PubMed: 16650675]
40. Li Y, Netto MV, Shekhar R, et al. A longitudinal study of LASIK flap and stromal thickness with high-speed optical coherence tomography. *Ophthalmology* 2007;114:1124–32. [PubMed: 17320959]
41. Khurana RN, Li Y, Tang M, et al. High-speed optical coherence tomography of corneal opacities. *Ophthalmology* 2007;114:1278–85. [PubMed: 17307254]
42. Twa MD, Parthasarathy S, Roberts C, et al. Automated decision tree classification of corneal shape. *Optom Vis Sci* 2005;82:1038–46. [PubMed: 16357645]
43. Warmke J, Drysdale R, Ganetzky B. A distinct potassium channel polypeptide encoded by the *Drosophila eag* locus. *Science* 1991;252:1560–2. [PubMed: 1840699]
44. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13–22.

45. Lu AT, Wang M, Varma R, et al. Advanced Imaging for Glaucoma Study Group. Combining nerve fiber layer parameters to optimize glaucoma diagnosis with optical coherence tomography. *Ophthalmology* 2008;115:1352–7. [PubMed: 18514318]
46. Obuchowski NA. Nonparametric analysis of clustered ROC curve data. *Biometrics* 1997;53:567–78. [PubMed: 9192452]
47. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45. [PubMed: 3203132]
48. Rao JN, Scott AJ. A simple method for the analysis of clustered binary data. *Biometrics* 1992;48:577–85. [PubMed: 1637980]
49. Tan O, Li G, Lu AT, et al. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. *Ophthalmology* 2008;115:949–56. [PubMed: 17981334]
50. Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. *J Cataract Refract Surg* 2007;33:1530–8. [PubMed: 17720066]
51. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol* 2000;44:367–408. [PubMed: 10734239]
52. Vinciguerra P, Camesasca FI. Prevention of corneal ectasia in laser in situ keratomileusis. *J Refract Surg* 2001;17(suppl):S187–9. [PubMed: 11316017]
53. Tang M, Li Y, Avila M, Huang D. Measuring total corneal power before and after laser in situ keratomileusis with high-speed optical coherence tomography. *J Cataract Refract Surg* 2006;32:1843–50. [PubMed: 17081867]
54. Rabbetts, RB. Bennett & Rabbetts' Clinical Visual Optics. Vol. 4. New York: Butterworth-Heinemann; 2007. p. 395-420.
55. Huang, D.; Izatt, J.; Yasuno, Y.; de Boer, J. Future direction of anterior segment optical coherence tomography. In: Steinert, R.; Huang, D., editors. *Anterior Segment Optical Coherence Tomography*. Thorofare, NJ: SLACK; 2008. p. 165-73.

Figure 1. Cross-sectional optical coherence tomography (OCT) images of a pachymetry map scan from an eye with keratoconus. The anterior and posterior corneal interfaces were overlaid on the image. Arrows indicated the OCT scan orientation.

Figure 2. Pachymetry map of the keratoconic eye in Figure 1. I = inferior octant; IT = inferotemporal; S = superior octant; SN = superonasal octant.

Figure 3.

The receiver operating characteristic (ROC) curves of the optical coherence tomography pachymetric keratoconus screening method ("1 abnormal" criterion) and the topographic keratometry, inferior-superior, astigmatism, and skew percentage (KISA%) method.

Figure 4.

Topography (left panel) and optical coherence tomography (OCT) pachymetry (right panel) maps of 3 keratoconic eyes. **A**, Case 1. Both the KISA% and OCT pachymetric methods correctly classified this eye as keratoconus. **B** and **C**, Cases 2 and 3. The KISA% method misclassified these cases as normal. In contrast, the OCT pachymetric method correctly identified these cases as keratoconus.

Table 1
Repeatability of Optical Coherence Tomography Pachymetric Parameters

Unit: μm	Minimum	Minimum–Median	I-S (mm)			IT-SN (mm)			Vertical Location of the Minimum
			2–5*	5–7	7–10	2–5	5–7	7–10	
Keratoconus	3.9	3.8	8.5	11.7	20.0	8.9	10.6	15.9	301
Normal	1.9	2.3	5.0	8.8	18.6	5.1	8.6	14.9	181

I-S = inferior–superior; IT-SN = inferotemporal–superonasal.

* Diameter of the annular zones.

Table 2
Optical Coherence Tomography Pachymetric Measurements

Unit: μm	Minimum	Minimum–Median	I-S	IT-SN	Vertical Location of the Minimum
Keratocoelus	452.6 $\pm$ 60.9	–95.2 $\pm$ 41.1	–44.8 $\pm$ 28.7	–63.0 $\pm$ 35.7	–805 $\pm$ 479
Normal	546.0 $\pm$ 23.7	–45.0 $\pm$ 7.7	–9.9 $\pm$ 9.3	–22.0 $\pm$ 11.4	–118 $\pm$ 260

I-S = inferior–superior; IT-SN = inferotemporal–superonasal.
Mean values $\pm$ standard deviation are listed.

Table 3
Cutoff Values for Optical Coherence Tomography Pachymetric Parameters

Unit: μm	Minimum	Minimum–Median	I-S	IT-SN	Vertical Location of the Minimum
Cutoff values	491.6	−62.6	−31.3	−48.2	−716.0

I-S = inferior–superior; IT-SN = inferotemporal–superonasal.
Cutoff values were calculated from the 1-percentile pachymetric parameter values (mean − 2.33 standard deviation) of the normal group.

Table 4
Sensitivity, Specificity, and Area under the Receiving Operating Characteristic Curve (AROC) of Individual Optical Coherence Tomography Pachymetric Parameters

	Minimum	Minimum–Median	I-S	IT-SN	Vertical Location of the Minimum
Sensitivity	0.676 (0.092) *	0.757 (0.058)	0.676 (0.092)	0.622 (0.092)	0.730 (0.085)
Specificity	1 (0)	0.972 (0.028)	1 (0)	1 (0)	1 (0)
AROC	0.954 (0.027)	0.929 (0.032)	0.868 (0.052)	0.894 (0.043)	0.920 (0.054)

I-S = inferior–superior; IT-SN = inferotemporal–superonasal.

* Standard errors are listed in parentheses.

Table 5

Sensitivity, Specificity, and Area under the Receiver Operating Characteristic Curve (AROC) for Optical Coherence Tomography (OCT) and Topographic Methods

	OCT Pachymetric Parameters		KISA%
	<i>1 Abnormal</i>	<i>2 Abnormal</i>	
Sensitivity	0.973 (0.027)*	0.838 (0.067)	0.811 (0.081)
Specificity	0.972 (0.028)	1 (0)	1 (0)
AROC	0.999 (0.001)	0.984 (0.012)	0.913 (0.051)

KISA% = keratometry, inferior–superior, astigmatism, and skew percentage.

* Standard errors are listed in parentheses.

Table 6
Average Minimum/Central Corneal Thicknesses of Keratoconic and Normal Eyes Published in the Literature

First Author	Year	Method	Corneal Thickness Measurement	Keratoconus	Normal
Rabinowitz ³³	1998	Ultrasound	Minimum	433±55	522±38
Haque ³⁰	2006	Ultrasound	Central	494±350	531±30
		Orbscan	Central	439±48	513±44
		OCT	Central	434±40	496±29
Pflugfelder et al ³	2002	Orbscan	Central	566±34	442±64
Gherghel ³¹	2004	Ultrasound	Central	503±53	551±37
		Orbscan	Central	459±63	546±48
Ucakhan ³⁴	2006	Ultrasound	Central	463±8	555±7
		Specular microscopy	Central	445±8	536±7
		Pentacam	Central	456±9	558±7
Ambrosio ³⁸	2006	Pentacam	Minimum	428±72	537±37
Lim ³²	2007	Orbscan	Minimum	458±59	554±25

OCT = optical coherence tomography; ultrasound = ultrasound pachymetry.