Keratoconus Diagnosis Using Anterior Segment Polarization-Sensitive Optical Coherence Tomography

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PURPOSE. To investigate the tissue properties of keratoconic and normal corneas in vivo by using polarization-sensitive optical coherence tomography (PS-OCT), and to evaluate early keratoconus by the area under the receiver operating characteristic curve (AUROC) and Mahalanobis distance analysis.

METHODS. Thirty-one eyes of 20 patients with keratoconus, 7 eyes of 7 patients with keratoconus suspect, and 25 eyes of 25 normal subjects were investigated by PS-OCT and corneal and anterior segment (CAS)-OCT. Average of en face phase retardation of the posterior surface of the cornea, curvature, videokeratographic parameters, regular and irregular astigmatism, pachymetry map, and elevation were measured. The AUROC of each parameter was calculated to evaluate the diagnostic power to detect keratoconus and keratoconus suspect.

RESULTS. While in normal controls, the center of the en face phase retardation map showed low and homogeneous birefringence, in keratoconic corneas the birefringence increased with disease severity. Some keratoconus suspects had apparent high birefringence values without displaying morphologic signs of keratoconus in the anterior surface. The phase retardation values for normal, keratoconus suspect, and keratoconus subjects were, respectively, 0.20 ± 0.06, 0.35 ± 0.06, and 0.50 ± 0.14 radians in 3 mm diameter and 0.22, 0.33 ± 0.13, and 0.74 ± 0.45 radians in 6 mm diameter. Outer morphological parameters such as curvature, videokeratographic parameters, regular and irregular astigmatism, and elevation showed high AUROCs for discriminating keratoconus from normal controls. On the other hand, using Mahalanobis distance, the AUROC of phase retardation, which represents microstructural properties of tissue, showed high value (0.989–1.000) for discriminating between keratoconus suspects and normal controls.

CONCLUSIONS. Average of en face phase retardation of the posterior surface of the cornea was increased in keratoconus patients due to changes in the lamellar structure of collagen fibers. Phase retardation was sensitive with regard to discriminating keratoconus suspect and might be useful for detecting very early or even subclinical keratoconus. (Invest Ophthalmol Vis Sci. 2013;54:1384–1391) DOI:10.1167/iovs.12-10979

Keratoconus is a bilateral progressive noninflammatory disease characterized by ectatic thinning of the cornea.1 Only the evaluation of corneal outer morphology is important not only in the diagnosis of keratoconus but also in its management, for example, for intrastromal corneal ring segment implantation, collagen cross-linking procedure, and deep anterior lamellar keratoplasty. Detection of initial and subclinical keratoconus is especially important for preoperative screening for laser refractive surgeries to avoid unpredictable outcomes.2,3 Recently, parameters such as anterior and posterior corneal curvature,1 elevation,6–8 topography mapping,7 corneal regular and irregular astigmatism,9 and pachymetry mapping9 were found to be useful for evaluation of keratoconic cornea morphology. However, these parameters describe the morphological profile of the cornea and consequently are not useful for evaluating the strength of corneal tissue microstructure, such as collagen fibers. Moreover, the relationship between the microstructure of corneal collagen fibers and subclinical keratoconus without any morphological sign has not been clarified. In order to establish a highly sensitive method for keratoconus diagnosis, it is essential to develop a modality that is capable of investigating the corneal microstructure, as well as the relationship between corneal microstructure and subclinical keratoconus.

Polarization-sensitive optical coherence tomography (PS-OCT), which is a variant of the functional extensions of OCT, can enhance contrast of fibrous tissues in biological samples by measuring birefringence.10 PS-OCT has been applied to discriminate several ocular tissue types in the posterior eye by using their birefringence; examples are retinal nerve fibers11,12 and scar tissue in age-related macular degeneration.13,14 Changes in the microscopic organization of fibrous tissues alter their birefringence; thus PS-OCT is useful for studying microscopic structural changes of fibrous tissues. It is well known that corneal birefringence results from highly organized collagen fibrils aggregated in bundles, which give rise to approximately 200 lamellae in the stroma.15–21 Thus, each lamella is composed of parallel collagen fibrils embedded in an optically homogeneous substance. In keratoconic corneas, the arrangement of regular fibril lamellae is altered,22,25,26 with consequent modifications in their birefringence. Although a previous study reported that PS-OCT detected birefringence in keratoconus ex vivo,22 in vivo clinical investigations have not yet been conducted. Thus, in addition to detecting morpho-
logical signs in the cornea by standard-intensity OCT images, PS-OCT is capable of providing qualitative information, such as the degree of organization of the fibrous arrangement in corneal stroma by phase retardation imaging. Moreover, PS-OCT might be able to detect modifications of fibrous arrangement before any morphological sign appears in early keratoconus.

In this study, we first compared the phase retardations between patients with keratoconus and healthy control subjects in vivo. We evaluated whether PS-OCT could perform early detection of disorganization of the fibrous arrangement before morphological changes occur. We also investigated the diagnostic power of the phase retardations and the parameters with three-dimensional corneal and anterior eye segment OCT (3D CAS-OCT) to detect keratoconus and keratoconus suspect by the area under the receiver operating characteristic curve (AUROC) and Mahalanobis distance analysis.

** Patients and Methods **

We examined 31 eyes of 20 patients with keratoconus (18 men and 2 women), 7 eyes of 7 patients with keratoconus suspect (7 men), and 25 eyes of 25 normal subjects (17 men and 8 women) without ocular abnormalities, other than refractive errors, at Tsukuba University between March 2010 and July 2011. The mean ages of patients with keratoconus, those with keratoconus suspect, and normal subjects were 33.7 ± 13.4 years (mean ± standard deviation, range 20–60 years), 38.9 ± 14.6 years (mean ± standard deviation, range 23–59 years), and 29.7 ± 6.5 years (mean ± standard deviation, range 21–49 years), respectively. For normal subjects, only the right eye was examined. The research followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from each participant. The study was approved by the Institutional Review Board of Tsukuba University.

Measurements were performed by experienced examiners using CAS-OCT (SF, SH, SB) and PS-OCT (YL, MY). Besides the topographic appearance of the map, keratoconic eyes included in this study were diagnosed by evidence of one or more of the following clinical findings using a slit-lamp microscope: corneal stromal thinning, corneal protrusion at the apex, apical scar, Fleischer ring, and Vogt striae. Inclusion criteria were absence of other preexisting corneal diseases and no history of ocular surgery. The severity of keratoconus was graded according to Amsler-Krumeich classification (2 eyes with grade 1; 13 eyes with grade 2; 13 eyes with grade 3; and 3 eyes with grade 4). The contralateral eye of a patient with unilateral keratoconus was included in the keratoconus suspect group if it had no clinical abnormalities on the slit-lamp exam. The anterior segment PS-OCT device used in this study was described in our previous paper. In brief, anterior segment PS-OCT is a swept-source OCT based on the fiber-based Mach-Zehnder interferometer. The light source was a wavelength swept laser that sweeps over 110 nm across a center wavelength of 1.3 μm with a scanning rate of 30 kHz. These properties of the light source determine the depth resolution of the system, which measured 9.2 μm in tissue, with the refractive index of the sample assumed to be 1.38. The system is capable of obtaining several parameters simultaneously from measured volumetric Jones matrices: intensity; phase retardation, which is a phase shift introduced by birefringence of the sample; and axis orientation of the sample.

Keratoconus and normal corneas were scanned with a horizontal fast raster pattern on scanning ranges of 4 × 4 and 8 × 8 mm²; each scanning range included 512 horizontal × 128 vertical A-lines. After the scanning, an annular area from 0.4 to 3.0 mm diameter was cropped from the 4 × 4 mm² scan. An en face phase retardation map was created from the cropped scan, which is denoted as 3 mm diameter phase retardation. Similarly, annular areas from 0.4 to 6.0 mm diameter and from 3.0 to 6.0 mm diameter were cropped from the 8 × 8 mm² scan. The en face phase retardation maps created from these cropped scans are denoted, respectively, as 6 mm diameter phase retardation and 3 to 6 mm phase retardation. Note that the central 0.4 mm region was excluded because strong specular reflection from the corneal apex created a flare at this region. Examples of the en face maps are shown in Figure 1A. These maps were utilized for quantitative phase retardation analysis.

To calculate en face phase retardation maps, the following method was used. First, Jones matrices were moving averaged with a kernel sized 30.6 μm (axial) × 93.6 (horizontal) × 85.9 (vertical), which was used for the 4 × 4 mm² scan, or a kernel sized 30.6 μm (axial) × 187.5 μm (horizontal) × 171.9 μm (vertical), which was used for the 8 × 8 mm² scan. Second, the moving-averaged Jones matrices were multiplied by an inverse Jones matrix at the front surface of the cornea in order to cancel the fiber birefringence of the OCT interferometer. Third, the Jones matrices at the posterior surface of the cornea were extracted, and matrix diagonalization was applied to obtain the round-trip phase retardation of the cornea at each transversal location. In the phase retardation maps, we mapped the phase retardation that ranges from 0 to π using a hue color map as
shown in Figure 1. This color map was used consistently for all phase retardation maps.

In addition to the en face phase retardation maps, the following processing provided representative phase retardation values at eight octants: superior-superior-temporal (SST), superior-temporal-temporal (STT), inferior-temporal-temporal (ITT), inferior-inferior-temporal (IIT), inferior-nasal-nasal (INN), inferior-nasal-superior (INS), superior-nasal-nasal (SNN), and superior-nasal-superior (SSN). These octants are illustrated in Figure 1. In order to obtain the phase retardation values at the eight octants, the Jones matrix volume was first moving averaged as for the en face phase retardation maps. With the posterior surface of the cornea extracted, a raw Jones matrix map of the cornea was obtained. The raw Jones matrix map was divided into eight octants, and averaged Jones matrices of each octant were obtained using the complex Jones matrix averaging method. The Jones matrices were multiplied by an inverse Jones matrix at the front surface of the cornea to cancel the fiber birefringence of the OCT interferometer. Finally, diagonalization was applied to obtain representative phase retardation values at each octant. The standard deviation of the eight phase retardation values in the eight octants was also calculated.

It has been demonstrated that 3D CAS-OCT based on swept-source OCT technology provides anterior and posterior corneal surfaces and pachymetric information simultaneously. In this study, we employed commercially available 3D CAS-OCT (CASIA; Tomey Corp., Nagoya, Aichi, Japan). The following values were evaluated: anterior mean simulated steep K (Ks) and flat K (Kf), average K (AveK), anterior and posterior elevation, videokeratographic parameters, pachymetry map, and regular and irregular astigmatism. In 3D CAS-OCT, anterior and posterior corneal elevations were measured in the same manner as in a previous study using a rotating Scheimpflug camera. A best-fit sphere was used as reference surface. The sphere that best fit the posterior corneal surface was automatically determined by built-in 3D CAS-OCT software with the float option over a 9 mm fit. Anterior and posterior elevations were measured as the maximum value above the best-fit sphere in the central 5 mm of the posterior cornea.

Videokeratographic parameters such as different sector index (DSI), opposite sector index (OSI), and center/surround index (CSI) were measured according to a previous study. The DSI is defined as the greatest difference in average power between any two sectors, while the OSI is the greatest difference in average power between two opposite sectors of an image divided into eight pie-shaped sectors. CSI is the difference in the average area-corrected corneal power between the central area and an annulus surrounding the central area. The OCT pachymetry map scans were acquired with the 3D CAS-OCT. The five pachymetric diagnostic parameters were calculated using the ocular values of the averaged 2 to 5 mm diameter zone. The five pachymetric parameters were defined as minimum (Min), minimum-median (Min-Med), inferior-superior (I-S), inferotemporal-supernasal (ITSN), and the vertical location of the thinnest cornea (Location) according to a previous study. Using the 3D CAS-OCT, 16 images of the anterior segment were obtained in less than 0.3 seconds. A total of 512 points were evaluated in each anterior segment image. This represents pseudo-256 mire rings with 32 detection points. Using the Fourier series harmonic analysis and higher-order astigmatism; posterior Fourier indices (posterior spherical, regular, asymmetry, and higher-order astigmatism); pachymetry (Location, Min, Min-Med, I-S, and IFSN); and elevation (anterior and posterior elevation).

In a previous study, linear discriminant analysis was used to distinguish keratoconus from normal corneas. However, this analysis required predefined rules, and thus the algorithm was elaborated and its performance was defined by arbitrarily selected predefined rules. In contrast, Mahalanobis distance analysis does not require any arbitrary parameters. In addition, since the Mahalanobis distance is a scalar value, it can be compatible with standard single-parameter analysis, such as t-test or ROC analysis. These properties of Mahalanobis distance make our method robust and portable.

Receiver operating characteristic (ROC) analysis was performed using SPSS (version 19.0; SPSS, Inc., Chicago, IL). All other statistical analyses were performed using StatView software (version 5.0; SAS Institute, Inc., Cary, NC). ROC curve analyses were performed to compare the diagnostic capability of parameters obtained by 3D CAS-OCT and PS-OCT. The AUROC values were computed as in previous studies. The AUROCs of Mahalanobis distances were also calculated. In addition, for each evaluated parameter, sensitivity and specificity were assessed according to the formula mean + 2 SD standard deviations for the normal group, and the first percentile value.
was calculated to indicate the cutoff point. In order to evaluate the repeatability, 23 eyes with keratoconus and 20 eyes with normal corneas were measured twice by PS-OCT, and the intraclass correlation coefficients (ICCs) were assessed. The results of all association tests were considered statistically significant when the $P$ value was less than 0.05.

**RESULTS**

**Birefringence of Normal Controls and Keratoconus Corneas**

Figure 1B shows en face phase retardation maps at the posterior surfaces of representative keratoconus corneas, graded by Amsler-Krumeich classification, and normal controls. In the normal control group, most of the central areas of en face phase retardation maps showed a blue color, which is consistent with low and homogeneous birefringence. On the other hand, in keratoconus corneas, en face phase retardation maps were inhomogeneous and displayed a combination of various colors, such as yellow and pink. Birefringence increased with disease severity. Keratoconus corneas graded 3 and 4 showed strong and inhomogeneous birefringence. The phase retardation of the posterior surface of normal controls, keratoconus suspects, and keratoconus was $0.20 \pm 0.06$, $0.35 \pm 0.06$, and $0.50 \pm 0.14$ radians in 3 mm; $0.29 \pm 0.22$, $0.33 \pm 0.13$, and $0.74 \pm 0.45$ radians in 6 mm; and $0.35 \pm 0.21$, $0.46 \pm 0.35$, and $0.87 \pm 0.77$ radians in 3 to 6 mm, respectively. There were significant differences between normal and keratoconus corneas in 3 mm diameter average and 6 mm diameter average of phase retardation of the posterior surface (Fig. 2, $P < 0.05$, ANOVA). The 3 mm average of birefringence in both keratoconus and normal cornea groups demonstrated good repeatability (ICCs: 0.914 and 0.906) with use of PS-OCT. Phase retardation values at eight octants (SST, STT, ITT, IIT, IN, INN, SNN, and SNN) in keratoconus and normal corneas also showed good repeatability ($0.857 \pm 0.064$ and $0.834 \pm 0.107$).

Contralateral eyes of patients with unilateral keratoconus were recruited for the keratoconus suspect group when there were no clinical findings on the slit-lamp microscope. En face phase retardation maps presented some color variation; however, we could not identify any particular pattern of color changing. Among these subjects, 42.9% had apparent inhomogeneous color changes in en face phase retardation maps without displaying morphologic signs of keratoconus in the anterior surface; 28.5% had apparent color changes in en face phase retardation maps with morphologic signs of keratoconus in the anterior surface; and 28.5% showed neither color change maps nor morphologic signs of keratoconus in the anterior surface. Figure 3 shows results obtained from keratoconus suspect corneas of a 29-year-old male patient (case 1), a 38-year-old male patient (case 2), and a 23-year-old male patient (case 3) with high values of birefringence and no morphologic signs of keratoconus in the anterior surface. Although cases 1 and 2 had a very slight increase of posterior asymmetry, case 3 showed no rise. Birefringence was detected in the keratoconus suspect group but was not observed in normal controls.

**AUROC of Each Parameter**

The AUROCs of the standardized individual 3D CAS-OCT parameters and phase retardation of the posterior surface by PS-OCT are listed in Tables 1 and 2. The 3 mm diameter, 6 mm diameter, and 3 to 6 mm diameter phase retardations of the posterior surface were divided into eight octants. The standard deviation among the octants was calculated. Anterior and posterior curvature, videokeratographic parameters, spherical, regular, asymmetry, higher-order astigmatism, and elevation by...
### Table 1. AUROC of Standardized Phase Retardation by PS-OCT

<table>
<thead>
<tr>
<th>3 mm Diameter Retardation</th>
<th>6 mm Diameter Retardation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SST</td>
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<tr>
<td>Normal vs. suspect</td>
<td>0.971</td>
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<tr>
<td>Normal vs. keratoconus</td>
<td>0.965</td>
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<tr>
<td>Suspect vs. keratoconus</td>
<td>0.673</td>
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</table>

### Table 2. AUROC of Standardized Individual 3D CAS-OCT Parameters

<table>
<thead>
<tr>
<th>Anterior Index</th>
<th>Posterior Index</th>
<th>Anterior Fourier Index</th>
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</thead>
<tbody>
<tr>
<td>Ks</td>
<td>Kf</td>
<td>AvgK</td>
</tr>
<tr>
<td>Normal vs. suspect</td>
<td>0.931</td>
<td>0.840</td>
</tr>
<tr>
<td>Normal vs. keratoconus</td>
<td>1.000</td>
<td>0.979</td>
</tr>
<tr>
<td>Suspect vs. keratoconus</td>
<td>0.995</td>
<td>0.931</td>
</tr>
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</table>

### Table 2. Extended

<table>
<thead>
<tr>
<th>Posterior Fourier Index</th>
<th>Pachymetry Map</th>
<th>Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical</td>
<td>Regular</td>
<td>Asymmetry</td>
</tr>
<tr>
<td>Location</td>
<td>Min</td>
<td>Min-Med</td>
</tr>
<tr>
<td>Normal vs. suspect</td>
<td>0.966</td>
<td>0.857</td>
</tr>
<tr>
<td>Normal vs. keratoconus</td>
<td>1.000</td>
<td>0.969</td>
</tr>
<tr>
<td>Suspect vs. keratoconus</td>
<td>0.952</td>
<td>0.889</td>
</tr>
</tbody>
</table>
OCT had excellent diagnostic power to distinguish keratoconus eyes from normal controls (normal versus keratoconus, 0.961–1.000). These parameters also showed good diagnostic power to discriminate between keratoconus eyes and keratoconus suspects (suspect versus keratoconus, 0.813–1.000). On the other hand, these parameters showed moderate AUROC values for discriminating between keratoconus suspects and normal controls (normal versus suspect, 0.857–0.977).

In pachymetry analysis, Min-Med showed high AUROC for the detection of keratoconus suspects versus normal controls. Pachymetry map parameters, except location, showed high AUROC values for the detection of keratoconus versus normal controls. However, the AUROC values for distinguishing keratoconus suspect from keratoconus were moderate (0.585–0.945).

In phase retardation of the posterior surface, the AUROC of some octants, such as SST in 3 mm diameter, IIT and SNN in 6 mm diameter, and SST and SNN in 3 to 6 mm diameter, was close to 1.0 (≥0.95) for detecting keratoconus suspects versus normal controls (suspect versus normal). Similarly, some octants showed good diagnostic power to distinguish keratoconus from normal controls (normal versus keratoconus). Diagnostic power to discriminate keratoconus suspect from keratoconus was moderate (suspect versus keratoconus). The standard deviation had the best AUROC for distinguishing keratoconus suspects from normal controls in all parameters by OCT and PS-OCT.

**AUROC of Mahalanobis Distances of Several Parameter Sets**

The evaluation of AUROC with Mahalanobis distance is shown in Table 3. All parameter sets provided very high AUROC values (0.986–1.000) for discriminating keratoconus from normal controls (normal versus keratoconus) when combined with Mahalanobis distance analysis. However, even with Mahalanobis distance analysis, the AUROC values for discriminating keratoconus suspects from normal controls (normal versus suspect) were still moderate for all parameters except phase retardation and pachymetry. In discriminating keratoconus suspects from normal eyes (normal versus suspect), Mahalanobis distance of 6 mm and 3 to 6 mm phase retardation and pachymetry showed the highest AUROC, followed by 3 mm phase retardation and posterior Fourier indices, anterior Fourier indices, anterior elevation indices, and, finally, posterior elevation indices. Sensitivity and specificity of the AUROC with Mahalanobis distance for each combined index are listed in Table 4. Phase retardation and pachymetry showed high sensitivity and specificity.

**DISCUSSION**

The diagnosis of moderate to advanced keratoconus is not overly difficult with currently standard methods due to the characteristic topographic patterns or the classic clinical signs. However, diagnosing early keratoconus in patients with normal best spectacle-corrected visual acuity and no clinical signs is challenging. PS-OCT showed good discrimination ability between the keratoconus suspect group, which included contralateral eyes without clinical findings of patients with keratoconus, and normal controls. In the current study, the normal cornea showed low retardation near the corneal apex that increased toward the periphery as described in a previous ex vivo study. In that study, corneal buttons were obtained from patients after penetrating keratoplasty for keratoconus, and advanced keratoconus corneas showed irregular retardation patterns and locally increased retardation in vitro. We previously reported that with use of PS-OCT, abnormal inhomogeneous birefringence was found in advanced keratoconus, and abnormal birefringence was detected in a region that did not coincide with the thinnest part of the cornea. It was supposed that the presence of abnormal birefringence in those cases was caused by alterations in the lamellar structure of collagen fibers in keratoconus. Such changes in collagen fibers were also reported with the use of X-ray scattering methods. X-ray scattering revealed the distribution of collagen fibril orientations within the tissue volume transmitted by the X-ray beam. Modifications in the lamellar structure of collagen fibers will eventually influence corneal shape and mechanical stability. Since PS-OCT is sensitive to microscopic alterations of collagen fibrils, it might be useful for predicting deformation of corneal shape before any topographic alteration becomes visible.

**Table 3. AUROC with Mahalanobis Distance for Each Combined Index**

<table>
<thead>
<tr>
<th>Parameter Sets</th>
<th>Retardation</th>
<th>Anterior Fourier Indexes</th>
<th>Pachymetry Elevation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>3 mm 6 mm 3 to 6 mm</td>
<td>Anterior Posterior Pachymetry</td>
<td>Elevation</td>
</tr>
<tr>
<td>Normal vs. suspect</td>
<td>0.989 1.000 1.000</td>
<td>0.971 0.949 0.985 1.000</td>
<td>0.811</td>
</tr>
<tr>
<td>Normal vs. keratoconus</td>
<td>0.988 0.986 1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Suspect vs. keratoconus</td>
<td>0.714 0.751 0.479</td>
<td>1.000</td>
<td>0.986 0.995 0.954 0.995</td>
</tr>
</tbody>
</table>

**Table 4. Sensitivity and Specificity of the AUROC with Mahalanobis Distance for Each Combined Index**

<table>
<thead>
<tr>
<th>Parameter Sets</th>
<th>Retardation</th>
<th>Anterior Fourier Indexes</th>
<th>Pachymetry Elevation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3 mm 6 mm 3 to 6 mm</td>
<td>Anterior Posterior Pachymetry</td>
<td>Elevation</td>
</tr>
<tr>
<td>Normal vs. suspect</td>
<td>0.857 1.000 1.000</td>
<td>0.857 0.571 0.857 1.000</td>
<td>0.714</td>
</tr>
<tr>
<td>Normal vs. keratoconus</td>
<td>0.903 0.935 1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Suspect vs. keratoconus</td>
<td>1.000 1.000 1.000</td>
<td>0.960</td>
<td>0.960 0.920 1.000</td>
</tr>
</tbody>
</table>
ROC analysis using Mahalanobis distance revealed that phase retardation parameters are more sensitive for discriminating between normal and suspect than between suspect and keratoconus corneas. In keratoconus suspect, surprisingly, more than 40% of the corneas showed apparent birefringence alterations without morphologic alterations in the anterior surface; however, these birefringence alterations were not observed in normal controls. Despite widespread efforts to better understand keratoconus, the underlying cause of corneal ectasia is still unclear. Although it remains unknown when changes in collagen fibers occur, macroscopic morphologic alterations have been extensively investigated. These results indicate the possibility that collagen fiber changes precede morphologic alterations. Conceivably, collagen fiber changes might occur long before any morphologic alteration. While birefringence increased with keratoconus severity, there was no consistent pattern in moderate or advanced keratoconus. Keratoconus diagnosis based on corneal phase retardation may offer additional information on tissue properties that are not available with topography. Since PS-OCT is able to detect corneal shape as with conventional OCT, PS-OCT can acquire information on internal tissue properties and corneal outer shape simultaneously. Recently, many indices or parameters have been investigated for diagnosing keratoconus; however, these parameters describe the same tendency, that is, for the corneal outer shape to become ectatic and asymmetric. Thus, even if a new outer shape profile index was added to the conventional items (such as corneal curvature, irregularity, and elevation), the improvement in diagnostic capability would be limited. Birefringence is strongly linked to internal tissue properties; thus it is completely different from the corneal outer shape profile indices and provides new information for diagnosis.

By ROC analysis, minimum corneal thickness showed good ability to discriminate between the normal cornea and keratoconus, because corneal thinning is one of the key pathologic features of keratoconus. However, AUROC values for normal versus suspect (0.926) and suspect versus keratoconus (0.926) were lower than for normal versus keratoconus corneas (0.997). To complement minimum corneal thickness information, Li et al. reported the new parameters Min-Med to detect focal thinning and IS and ITSN to detect focal and asymmetric thinning. As in their report, in the current study, the AUROC of Min-Med showed a high value (1.000 for normal versus keratoconus). Li et al. also reported that the vertical location of the thinnest corneal point had better discriminative power. In our study, vertical location of the thinnest corneal point showed a low AUROC value. This disparity might be related to different ranges of keratoconus severity in the two studies. After combining pachymetry map parameters with the use of Mahalanobis distance, pachymetry maps showed excellent AUROC values for discriminating between normal and suspect and between normal and keratoconus (1.000 in both cases). The AUROC value of the pachymetry map was high in normal versus suspect and in normal versus keratoconus discrimination, and moderate in suspect versus keratoconus discrimination. This tendency was similar with AUROCs of phase retardation parameters. This result might indicate that, as with the phase retardation parameters, the pachymetry map also comprises information about the tissue properties of collagen fibers.

Anterior and posterior indices (KS, Kf, AveK, DSI, OSI, and CSI) also showed excellent AUROC values for keratoconus versus normal discriminations (0.979–1.000). Previous studies have also reported the importance of the change of posterior surface in early keratoconus screening. According to Mihaltz et al. reported that posterior elevation showed best predictive accuracy by AUROC analysis (0.97 and 0.96) for mild keratoconus. De Sanctis reported that AUROC showed high overall predictive accuracy of posterior elevation for both keratoconus and subclinical keratoconus (0.99 and 0.93) as measured by Pentacam. It has been suggested that an increase in posterior elevation may be one of the earliest signs of subclinical keratoconus. However, the results presented in the current study indicate the possibility that the alteration of phase retardation caused by collagen fiber changes might develop prior to posterior elevation. This hypothesis could be reinforced by the fact that some cases of keratoconus suspect showed increased birefringence but no alterations in posterior elevation.

Previous studies have reported that anterior and posterior regular and irregular astigmatism is greater in keratoconus eyes than in normal controls. Tanabe et al. reported that all of the Fourier indices—spherical, regular, asymmetry, and higher-order aberration—in the keratoconus group were significantly greater than those in the normal group. Similarly, but to a lesser extent, eyes with suspect keratoconus showed significantly larger Fourier indices than normal controls. In the current study, 6 mm and 3 to 6 mm retardation, as well as pachymetry, showed the highest AUROC value (1.000) with use of Mahalanobis distance. The value was followed by 3 mm retardation (0.989) and posterior (0.989) and anterior (0.983) Fourier indices.

All parameter sets provided very high AUROC values (near 1.000) for normal versus keratoconus discrimination when combined with Mahalanobis distance analysis. Parameters such as corneal curvature, irregularity, and elevation, which reflect the outer profile of the cornea, are more sensitive with regard to normal versus keratoconus discrimination than phase retardation parameters. On the other hand, indices that represent internal tissue properties, such as phase retardation parameters and pachymetry parameters, are more sensitive with regard to discriminating between normal and suspect corneas.

Our study has some limitations. The sample size was relatively small, and only normal and keratoconus subjects were evaluated. Measurements of eyes with ocular diseases characterized by corneal thinning and ectasia will be the target for future discrimination analysis. In the current study, the same data retrieved from the normal controls was used not only as a standard to represent the general population, but also as an input for the Mahalanobis distance analysis. Thus, there is a risk that the AUROC values could have been artificially boosted if the normal control group was not well sampled. To avoid this risk, a larger number of normal controls will be needed. In addition, we plan to conduct a large-scale study for diagnosis of early keratoconus with use of PS-OCT.

In this study, we found that increased corneal birefringence was sensitive to alterations or variations of internal properties of corneal tissue. In some cases within the keratoconus suspect group, en face phase retardation maps were highly inhomogeneous with only few posterior surface alterations. Phase retardation parameters appeared to be more sensitive to very early or even subclinical keratoconus by AUROC with Mahalanobis distance analysis. In the future, discussion concerning the diagnosis of early keratoconus may be objectively based on findings related to the internal properties of corneal tissues.

References

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