Quantitative Evaluation of the Natural Progression of Keratoconus Using Three-Dimensional Optical Coherence Tomography

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PURPOSE. We quantified the chronologic progression of keratoconus using anterior segment optical coherence tomography (AS-OCT).

METHODS. A total of 217 eyes from 113 patients with keratoconus, keratoconus suspect, or forme fruste keratoconus were evaluated by corneal tomography using swept-source OCT. Age-dependent changes in the radius of the posterior best-fit sphere (\(R_{post}\)), minimum corneal thickness (\(T_{min}\)), and distance from the thinnest point to the corneal vertex (\(D_{min}\)) were examined over follow-up periods of up to 5.79 years and were analyzed using generalized estimating equation (GEE) nonlinear regression model.

RESULTS. Annual changes in \(R_{post}\) (mean, \(-0.017\) mm) and \(T_{min}\) (\(-2.69\) mm) were significantly higher in younger patients (\(P < 0.01\), GEE nonlinear regression) and in patients with higher maximal K value (\(K_{max}\); \(P < 0.01\), GEE nonlinear regression), whereas no changes were observed in \(D_{min}\). Even in patients 30 years or older, 14% of eyes revealed remarkable progression in \(R_{post}\). In eyes with acute hydrops, annual changes in \(R_{post}\) (\(-0.22\) mm) and \(T_{min}\) (\(-33.8\) mm) before acute corneal hydrops were more than 10 times faster than those in other eyes (\(P < 0.001\), GEE nonlinear regression).

CONCLUSIONS. Chronologic measurements of corneal tomography in keratoconus demonstrated that the progression of steepening at posterior corneal surface was found not only in patients under 30 years but also in older patients, particularly in advanced keratoconus. The rate of progression can be measured by mapping of corneal curvature and thickness using OCT, and the risk of progression was greater in younger patients with steeper \(K_{max}\).

Keywords: keratoconus, anterior segment optical coherence tomography, corneal topography

Keratoconus is a chronic disease, leading to the development of corneal steepening, thinning, and asymmetric distortion in the apical zone of the translucent cornea. It causes visual impairment because of irregular corneal astigmatism.

It is important to understand the natural course of keratoconus for determining disease etiology and appropriate surgical interventions over the lifetime of these patients. Kennedy, et al.3 reported the results of longitudinal evaluations using retinoscopy with follow-up periods of up to 48 years. The Collaborative Longitudinal Evaluation of Keratoconus Study performed a chronological follow-up of keratoconic patients.4 However, studies that have longitudinally examined the pachymetric and tomographic progression of keratoconus are limited.

Evaluation of disease progression is clinically important especially for surgical treatments in keratoconus, such as corneal cross-linking,5,6 intrastromal ring segments,7 and deep anterior lamellar keratoplasty (DALK).8–10 Quantitative and longitudinal evaluations of keratoconus were previously performed using serial keratometry and corneal topography.11,12 The annual change in topographic parameters have been reported in studies, including large numbers of keratoconic or keratoconus suspect (KCS) eyes.13,14 However, previous studies reported changes to the anterior surface in mild-to-moderate cases. When using a Placido topographer or Scheimpflug camera, identification of mire images or segmentation of the anterior and posterior corneal surfaces is technically challenging in severe cases of keratoconus because of the presence of highly irregular surfaces or opacities.15

With the rapid advances in optical coherence tomography (OCT), it is considered as a novel modality for corneal tomographic analysis.16 As anterior segment (AS) OCT can scan the entire cornea at a high-speed using an infrared light source that has better tissue penetration than visible light source; OCT identifies the anterior and posterior surfaces with high reliability and good repeatability.15,17 Therefore, OCT can be used for severely irregular and/or opacified corneas, which cannot be measured by Placido topographer or Scheimpflug tomography.15

In the present study, we investigated the natural progression of keratoconus by evaluating tomographic changes over time in a large number of eyes using AS-OCT. To minimize the influence of a rigid gas-permeable contact lens, analyses of the posterior surface were subjected. We further conducted an epidemiologic analysis with a generalized estimating equation regression...
model for predicting the progression that was considered to be pathognomonic in keratoconus. Finally, for cases of acute corneal hydrops during the follow-up period, precursory findings from corneal tomography before acute hydrops were quantitatively evaluated.

**Subjects and Methods**

**Subjects**

Patients with keratoconus, KCS, or forme fruste keratoconus (FFK) and normal controls of healthy subjects were recruited at the Osaka University Hospital, Osaka, Japan from January 2008 to July 2014. Subjects who had been evaluated more than twice by corneal tomography using AS-OCT with follow-up periods longer than 1 year were included in the study (Table 1). The follow-up period ranged from 1.31 to 5.79 years (mean ± SD, 3.07 ± 0.85). The numbers of tomographic examinations ranged from 2 to 7 (3.9 ± 0.9). The age of the patients at initial examination ranged from 16 to 75 years (57.7 ± 11.5). We examined 217 corneas in 113 patients, comprising 189 corneas from 109 patients with keratoconus, 14 corneas of 12 patients with KCS, and 14 corneas of 14 patients with FFK. In addition, 23 corneas of 16 normal controls of healthy subjects were included. Eyes with any previous ocular surgeries, including penetrating keratoplasty (PKP), DALK, and cataract surgery, were excluded. The majority of the patients wore rigid gas-permeable contact lenses, except for five eyes that had FFK. In six eyes, an acute hydrops event occurred during the follow-up period.

Keratoconus was defined as eyes with the presence of central corneal thinning, Fleischer rings, and/or Vogt’s striae with slit-lamp examination. Keratoconus suspect was defined as the eye with keratoconus pattern in Placido corneal topography, namely abnormal localized steepening or lazy 8 figure, without abnormal findings on slit-lamp examination. Best-corrected visual acuity was 20/20 or better in eyes with KCS. Forme fruste keratoconus was defined as the fellow eye of a keratoconic eye with no abnormal findings on Placido corneal topography or slit-lamp examination. All the diagnostics were made by an experienced ophthalmologist (NM).

The institutional review board of Osaka University Hospital approved the study, which adhered to the tenets of the Declaration of Helsinki.

**Measurements**

The corneal tomographic analysis was performed using AS-OCT (CASIA SS-1000; Tomey Corporation, Inc., Nagoya, Japan) with an infrared wavelength of 1510 nm and a scanning speed of 30,000 axial scans per second. An alignment function, which automatically moves the head unit to the measurement position based on corneal reflex, and an automatic focusing function were installed into the system. Therefore, the measurement was performed along the vertex normal, and the images were centered on the corneal vertex. The analysis program identified and digitized the anterior and posterior corneal surfaces, and the reference axis of the measurement was aligned with the vertex normal. Tomographic and pachymetric maps were calculated from 16 radial cross-sectional images through the central 10-mm diameter of the corneas obtained over 0.34 seconds. Each cross-sectional image consisted of 512 telecentric A-scans. Swept-source OCT measurements have been shown to have adequate repeatability in normal and keratoconic eyes. The best-fit spheres (BFS) were computed for the anterior and posterior corneal surfaces, and differences between fitted surfaces and real data were plotted as elevation maps. Tomographic maps of corneal thickness also were displayed. Minimum corneal thickness (Tmin) was defined as the pachymetric value at the thinnest location. The distance from the thinnest point to the corneal vertex (Dmin) was calculated. Calculations of BFS, Tmin, and Dmin were performed inside the central 9-mm diameter of the cornea. In the axial power maps, corneal power was calculated by a circular approximation that fixed the center of curvature at the corneal vertex based on the data of each localized corneal shape, and the maximal power in the central 8-mm diameter of corneas was defined as the maximal K value (Kmax). All calculations used the same calibration files, ensuring all the measurements were performed using identical software and hardware.

**Statistical Analysis**

All statistical analyzes were performed using R version 3.2.0 (available in the public domain at www.r-project.org). Annual changes in the radius of posterior BFS (Rpost), radius of anterior BFS (Rant), Tmin, Dmin, and Kmax were calculated for each eye using linear regression analysis. The repeatability of Tmin, Rant, Rpost, Dmin, and Kmax was confirmed using intraclass correlation coefficients (ICC) for two measurements within 15 minutes on the same day (Supplementary Table S1).

Annual changes then were analyzed using the generalized estimating equation (GEE) regression model to account for a possible correlation between fellow eyes of the same patient and the repeated measurement in the same eye. Annual changes were regressed as a function of sex and age as well as a disease severity index, Kmax. Maximum K values and age were fitted with nonlinear restricted cubic splines. The annual change for Rpost, Rant, Tmin, Kmax, and Dmin were tested using the Wilcoxon rank sum test to evaluate the tendency of the progression in each index. Along with these annual changes, we also evaluated parameters at the initial examination as a function of acute hydrops, age, and initial Kmax values in a GEE regression, where age and the initial value of Kmax were modeled with nonlinear restricted cubic splines.

Similar GEE nonlinear regression curves for annual changes in Rpost, Tmax, and Dmin values were fitted as a function of age, Kmax, and sex, and for age and Kmax as cross-product terms. The progression of keratoconus was defined as a decrease in Rpost of greater than three within-subject SDs of the regression line.

**Results**

**Chronologic Changes in Tomographic Indices**

A representative example of chronologic keratoconic changes in axial power maps, and pachymetric maps is presented in Figure 1. Over a 2-year follow-up period, there was an apparent steepening in Kmax by 18.5 diopters (D) and a remarkable thinning in Tmin by 129 μm.
To reduce the influences of the pathologic irregularities of the anterior surface or rigid gas-permeable contact lens over the measurement for natural progression, changes in \( R_{\text{post}} \) which represent the corneal steepening were quantified (Fig. 2). There was a trend toward a greater decrease in \( R_{\text{post}} \) in eyes with steeper initial \( R_{\text{post}} \) for young and elderly patients; \( R_{\text{post}} \) at initial examinations ranged between 4.52 and 7.09 \( \text{mm} \) (mean \( \pm \) SD, 5.97 \( \pm \) 0.59 mm). The annual change for \( R_{\text{post}} \) was \(-0.017 \pm 0.052 \text{ mm/y} \) (mean \( \pm \) SD; 95% confidence interval [CI], \(-0.024 \text{ to } -0.010\)). Furthermore, in GEE nonlinear regression, the annual changes in \( R_{\text{post}} \) was significantly higher with a younger age (\( P = 0.0033 \)) or greater \( K_{\text{max}} \) (\( P = 0.0064 \)). This showed that significantly greater \( R_{\text{post}} \) change was observed in younger patients and those with greater disease severity; \( R_{\text{ant}} \) depicted the same tendency (Fig. 3).

To indicate the longitudinal changes in corneal thinning, \( T_{\text{min}} \) for all eyes are shown in Figure 4. The mean \( T_{\text{min}} \) at initial examinations ranged from 134 to 547 \( \text{um} \) (mean \( \pm \) SD, 406 \( \pm \) 86 \( \text{um} \)). The annual change in \( T_{\text{min}} \) was \(-2.69 \pm 8.59 \text{ um/y} \) (mean \( \pm \) SD, 95% CI, \(-3.83 \text{ to } -1.53\)). In GEE nonlinear regression, the annual change in \( T_{\text{min}} \) was significantly higher with a younger age (\( P = 0.0024 \)) or greater \( K_{\text{max}} \) (\( P = 0.0006 \); i.e., there was a significantly higher reduction in \( T_{\text{min}} \) in younger patients and those with greater disease severity).

The natural progression in \( D_{\text{min}} \), representing corneal asymmetry, is shown in Supplementary Figure S1. The annual change for \( D_{\text{min}} \) was \(-0.006 \pm 0.067 \text{ mm/y} \) (mean \( \pm \) SD, 95% CI, \(-0.015 \text{ to } +0.003\)). Unlike \( R_{\text{post}} \) and \( T_{\text{min}} \), no significant difference in \( D_{\text{min}} \) was observed associated with age or disease severity. Generalized estimating equation nonlinear regression revealed no significant difference in the annual change in \( D_{\text{min}} \) based on age (\( P = 0.54 \)) or \( K_{\text{max}} \) (\( P = 0.11 \)).

The natural progression of \( K_{\text{max}} \) is shown in Supplementary Figure S2. There was a greater increase in \( K_{\text{max}} \) in younger patients and those with greater disease severity; however, the tendency is not as obvious as \( R_{\text{post}} \) or \( T_{\text{min}} \), possibly because of dependency on ocular fixation and relatively low reliability of \( K_{\text{max}} \) in the advanced cornea (Table 2).

Keratoconus Progression

In the Bland–Altman plot of 107 keratoconic eyes, only three eyes were above the within-subject error in \( R_{\text{post}} \) greater than 3 SD (Supplementary Fig. S3, Supplementary Table S1). Therefore, progression was defined as the steepening of \( R_{\text{post}} \) greater than 3 within-subject SDs (0.101 mm) with a mean false-positive rate for the progression of approximately 3%.

With this definition, 18% of all 217 included eyes were categorized as progression (Table 3). Even in patients 30 years or older, 14% of eyes revealed progression in \( R_{\text{post}} \).

Of the eyes with a \( K_{\text{max}} \) of \( \geq 53 \text{ D} \), 28% of eyes in patients aged 30 to 45 years exhibited progression, while up to 42% of eyes in patients younger than 30 years demonstrated the progression of keratoconus.

The GEE nonlinear regression curves of annual change for \( R_{\text{post}} \) fitted as a function of age, \( K_{\text{max}} \), and sex, and as a cross-product of age and \( K_{\text{max}} \) are presented in Figure 5. For \( R_{\text{post}} \), the annual change was greater in younger patients and patients with greater \( K_{\text{max}} \). These results indicated that the average progression rates in \( R_{\text{post}} \) can be predicted with patient age and \( K_{\text{max}} \) using GEE nonlinear regression.
Tomographic Change Before Acute Corneal Hydrops

Acute corneal hydrops occurred in six eyes during the follow-up period. In all cases, \( R_{\text{post}} \) remarkably decreased before the event of acute hydrops as shown in Figure 2. The average annual change in \( R_{\text{post}} \) for eyes before acute hydrops was \(-0.22 \pm 0.12 \text{ mm/y}\). This was more than 10 times faster than those in the other 211 eyes \((P < 0.001, \text{ GEE nonlinear regression})\). The initial \( R_{\text{post}} \) also did not differ significantly \((P > 0.05, \text{ GEE nonlinear regression})\) between the eyes that developed acute hydrops and the other eyes \((5.57 \pm 0.46 \text{ mm})\).

Minimum corneal thickness also continuously decreased in all eyes before acute hydrops. The average annual change in \( T_{\text{min}} \) for eyes before acute hydrops was \(-33.8 \pm 17.2 \mu \text{m/y}\) and faster than that in the other eyes \((P < 10^{-4}, \text{ GEE nonlinear regression})\). Initial \( T_{\text{min}} \) values did not differ significantly between the eyes with acute hydrops \((\text{mean } \pm \text{ SD}, 368 \pm 65 \mu \text{m})\) and the other eyes \((P > 0.05, \text{ GEE nonlinear regression})\).

Unlike \( R_{\text{post}} \), or \( T_{\text{min}} \), no significant difference in the annual change in \( D_{\text{min}} \) values was observed between eyes that developed acute hydrops \((\text{mean } \pm \text{ SD}, -0.08 \pm 0.21 \text{ mm})\) and the other eyes \((P > 0.05, \text{ GEE nonlinear regression})\).
Asymmetry subjects (normal control). Eyes were subdivided into keratoconus, KCS, and FFK groups. The radius of the Rpost and the Tmin consistently tended to change, whereas the Dmin did not.

FIGURE 5. Generalized estimating equation nonlinear regression analysis. Generalized estimating equation nonlinear regression curves of annual change for Rpost fitted as a function of age, Kmax, as well as sex, age, and Kmax as cross-product terms. Black dashed lines, normal controls of healthy subjects (control); black, Kmax < 48 D; cyan, 48 D ≤ Kmax < 53 D; and magenta, 53 D ≤ Kmax. Annual change in Rpost was greater in younger eyes and eyes with larger Kmax values. The shadowed area represents the 95% CI of the regression curve slope.

TABLE 2. Annual Rates of Change for Tomographic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>95% CI</th>
<th>P Value, Wilcoxon Rank-Sum Test</th>
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</thead>
<tbody>
<tr>
<td>Steepening</td>
<td></td>
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<tr>
<td>Rpost, mm</td>
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<tr>
<td>KC Total</td>
<td>–0.017 ± 0.052</td>
<td>–0.024 to –0.010</td>
<td>4.1 × 10⁻⁵</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>–0.019 ± 0.055</td>
<td>–0.027 to –0.011</td>
<td>1.4 × 10⁻⁵</td>
</tr>
<tr>
<td>KCS</td>
<td>–0.011 ± 0.026</td>
<td>–0.027 to +0.004</td>
<td>0.27</td>
</tr>
<tr>
<td>FFK</td>
<td>+0.004 ± 0.008</td>
<td>–0.006 to +0.008</td>
<td>0.08</td>
</tr>
<tr>
<td>Normal Control</td>
<td>+0.008 ± 0.026</td>
<td>–0.004 to +0.019</td>
<td>0.95</td>
</tr>
<tr>
<td>Rmin, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KC Total</td>
<td>–0.020 ± 0.064</td>
<td>–0.029 to –0.012</td>
<td>2.3 × 10⁻⁷</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>–0.023 ± 0.068</td>
<td>–0.032 to –0.013</td>
<td>5.0 × 10⁻⁷</td>
</tr>
<tr>
<td>KCS</td>
<td>–0.016 ± 0.030</td>
<td>–0.033 to +0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>FFK</td>
<td>+0.002 ± 0.011</td>
<td>–0.004 to +0.008</td>
<td>0.67</td>
</tr>
<tr>
<td>Normal control</td>
<td>–0.001 ± 0.017</td>
<td>–0.002 to +0.007</td>
<td>0.38</td>
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<tr>
<td>Thinning</td>
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<tr>
<td>Tmin, μm</td>
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<td></td>
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</tr>
<tr>
<td>KC Total</td>
<td>–2.70 ± 8.59</td>
<td>–3.83 to –1.53</td>
<td>1.7 × 10⁻³</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>–3.09 ± 8.96</td>
<td>–4.38 to –1.80</td>
<td>5.2 × 10⁻⁴</td>
</tr>
<tr>
<td>KCS</td>
<td>–1.02 ± 5.63</td>
<td>–4.27 to +2.23</td>
<td>0.81</td>
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<tr>
<td>FFK</td>
<td>–1.21 ± 3.28</td>
<td>–0.68 to +3.09</td>
<td>0.19</td>
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<tr>
<td>Normal control</td>
<td>+0.41 ± 2.52</td>
<td>–0.67 to +1.51</td>
<td>0.39</td>
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<tr>
<td>Asymmetry</td>
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<tr>
<td>Dmin, mm</td>
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<tr>
<td>KC Total</td>
<td>–0.006 ± 0.067</td>
<td>–0.015 to +0.003</td>
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</tr>
<tr>
<td>Keratoconus</td>
<td>–0.009 ± 0.067</td>
<td>–0.018 to +0.001</td>
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<tr>
<td>KCS</td>
<td>+0.017 ± 0.065</td>
<td>–0.020 to +0.055</td>
<td>0.27</td>
</tr>
<tr>
<td>FFK</td>
<td>+0.006 ± 0.072</td>
<td>–0.035 to +0.048</td>
<td>0.58</td>
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<tr>
<td>Normal control</td>
<td>+0.010 ± 0.071</td>
<td>–0.020 to +0.041</td>
<td>0.23</td>
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<tr>
<td>Power</td>
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<tr>
<td>Kmax, D</td>
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</tr>
<tr>
<td>KC Total</td>
<td>–0.017 ± 0.052</td>
<td>–0.024 to –0.010</td>
<td>4.1 × 10⁻⁵</td>
</tr>
<tr>
<td>Keratoconus</td>
<td>+0.51 ± 1.43</td>
<td>+0.11 to +0.52</td>
<td>9.6 × 10⁻¹</td>
</tr>
<tr>
<td>KCS</td>
<td>+0.26 ± 0.86</td>
<td>–0.24 to +0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>FFK</td>
<td>–0.13 ± 0.31</td>
<td>–0.31 to +0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>Normal control</td>
<td>+0.04 ± 0.20</td>
<td>–0.05 to +0.12</td>
<td>0.38</td>
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</table>

DISCUSSION

In the present study, time-dependent changes in tomographic parameters in patients with keratoconus were evaluated using serial corneal tomography measurements over a follow-up period of up to 5.79 years. Moreover, to ensure consistency, the hardware and calibration software used were identical throughout the entire follow-up period.

To the best of our knowledge, this study represents the first to quantitatively and chronologically evaluate corneal steepening, thinning, and asymmetry in keratoconus with a large number of eyes with a disease severity ranging from FFK to an advanced status.²²

Interestingly and unexpectedly, 14% of eyes in patients 30 years or older exhibited progression. In general, the onset of keratoconus often occurs during adolescence and progression tends to end after 30 years.¹ The results of the present study demonstrated that the natural progression of corneal steepening decelerated after 30 years as expected. However, some eyes showed marked progression in patients older than 30 years not only in severe cases, but also in mild keratoconus. Approximately 15% of mild cases with a 48 D ≤ Kmax < 53 D in annual change of each index was evaluated for all 217 keratoconic corneas (KC total) and 23 corneas from the normal controls of healthy subjects (normal control). Eyes were subdivided into keratoconus, KCS, and FFK groups. The radius of the Rpost and the Tmin consistently tended to change, whereas the Dmin did not.
patients older than 30 years had a progression in corneal steepening. These results indicated that careful observation will be needed for the progression even in elderly patients or in mild keratoconus.

Recent advances in clinical epidemiology enabled us to perform more accurate statistical analyses to predict temporal trends with multiple confounding variables. Generalized estimating equations account for a possible correlation between fellow eyes of the same subject. In addition, GEE takes the repeated measurement in the same eye into consideration. By GEE nonlinear regression, we clearly estimated the average progression rates according to age and disease severity. These results demonstrated that progression rates in keratoconus were predictable according to patient age and Kmax.

Measurement of time-dependent changes also is important before any corneal surgeries, including corneal cross-linking, intrastralom ring segments, toric phakic IOLs, and cataract surgery with toric IOLs in keratoconus.

In cases where keratoconic progression is halted, toric phakic IOLs or toric IOLs may be reasonable as the refractive influences of rigid gas-permeable contact lens use on measure-ments. These findings were later confirmed by spectral domain OCT. In the present study, acute corneal hydrops developed in six eyes during the follow-up period. In all cases, corneas demonstrated remarkable steepening and thinning over a 2-year period before the development of acute hydrops. Annual changes in Rpost and Tmin in cases with acute hydrops were 10 times greater than average rates in other eyes. Our results suggested that rapid changes in Rpost and Tmin were sensitive precursory findings for acute hydrops. Tuft et al. reported younger age, steeper ectasia, and a history of allergic conjunctivitis as risk factors for the development of acute hydrops. Our study added rapid corneal steepening and thinning as the precursory findings of acute hydrops quantitatively.

Our study had some limitations. First, the majority of patients wore rigid gas-permeable contact lenses, except for patients with KCS or FFK. Observed progressions may have been influenced by the contact lens-induced corneal warpage. However, the long-term follow-up of patients with keratoconus is almost impossible without contact lenses. To minimize the influence of rigid gas-permeable contact lens use on measurements, we quantified the Rpost to evaluate the keratoconic progression. A study comparing stage and age-matched patients who wear and do not wear rigid gas-permeable contact lenses may be useful in evaluating the effect of contact lens wear on corneal tomography, and also in improving the management of rigid gas-permeable lenses wearers in keratoconus.

Reinstein et al. reported epithelial thinning at the cone apex using very high-frequency digital ultrasound scanning measurements. These findings were later confirmed by spectral domain OCT. In the present study, the epithelial thickness was not measured because of the limitations in the resolution of SS-OCT and the software. The time course of epithelial compensation for the stromal protrusion may be necessary for the future to quantify the effects of epithelial compensation on the earlier identification of the progression in anterior stromal steepening.

The present study focused on corneal steepening, thinning, and asymmetry in keratoconus was evaluated without excluding severe cases of keratoconus in this study. Recent developments in hardware and algorithmic techniques for corneal topography and tomography have enabled the detection of early-stage keratoconus. However, the progression of keratoconus after disease onset remains poorly understood. Our results provided a comprehensive view of the natural course of keratoconus from the early stages of the disease. We demonstrated that the annual changes in Rpost and Tmin were significantly greater in younger patients and patients with larger Kmax. On the other hand, no relationships between Dmin values and age or Kmax were observed.

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The present study focused on corneal steepening, thinning, and asymmetry in keratoconus was evaluated without excluding severe cases of keratoconus in this study.

Recent developments in hardware and algorithmic techniques for corneal topography and tomography have enabled the detection of early-stage keratoconus. However, the progression of keratoconus after disease onset remains poorly understood. Our results provided a comprehensive view of the natural course of keratoconus from the early stages of the disease. We demonstrated that the annual changes in Rpost and Tmin were significantly greater in younger patients and patients with larger Kmax. On the other hand, no relationships between Dmin values and age or Kmax were observed.

In the present study, acute corneal hydrops developed in six eyes during the follow-up period. In all cases, corneas demonstrated remarkable steepening and thinning over a 2-year period before the development of acute hydrops. Annual changes in Rpost and Tmin in cases with acute hydrops were 10 times greater than average rates in other eyes. Our results suggested that rapid changes in Rpost and Tmin were sensitive precursory findings for acute hydrops. Tuft et al. reported younger age, steeper ectasia, and a history of allergic conjunctivitis as risk factors for the development of acute hydrops. Our study added rapid corneal steepening and thinning as the precursory findings of acute hydrops quantitatively.

Our study had some limitations. First, the majority of patients wore rigid gas-permeable contact lenses, except for patients with KCS or FFK. Observed progressions may have been influenced by the contact lens-induced corneal warpage. However, the long-term follow-up of patients with keratoconus is almost impossible without contact lenses. To minimize the influence of rigid gas-permeable contact lens use on measurements, we quantified the Rpost to evaluate the keratoconic progression. A study comparing stage and age-matched patients who wear and do not wear rigid gas-permeable contact lenses may be useful in evaluating the effect of contact lens wear on corneal tomography, and also in improving the management of rigid gas-permeable lenses wearers in keratoconus.
Natural Progression of Keratoconus

IOVS | Special Issue | Vol. 57 | No. 9 | OCT175

disease is important when evaluating the indication of interventions, such as DALK or when estimating long-term prognosis in the quality of vision. In the future, comprehensive tomographic follow-up studies that include mild-to-severe cases of keratoconus with complete visual function tests are required to elucidate the relationship between tomographic changes and the quality of vision across a wide range of keratoconus severity.

Our patients were followed for up to 5.79 years, no shorter than the study periods of previous topographic reports. However, this period is not sufficient to predict disease progression over a lifetime. Longer terms are required to conduct a more sophisticated prediction.

Although the present study included 240 corneas, larger numbers of subjects are needed to refine the predictive use of the identified parameters. Our study included a relatively small number of young patients with KCs and FFK, partially due to poor compliance in young patients because of the mild severity and the university setting. Additionally, the eyes that had keratoplasty possibly due to rapid progression also were excluded in the study.

Corneal tomography by OCT from FFK to severe keratoconus provided an overview of keratoconus progression and indicated that R_post and T_min are useful parameters for monitoring disease progression. Studies with larger numbers of cases will enable a better prediction of progression, more sophisticated criteria for medical and surgical interventions, quantitative evaluation of newly-developed treatments, and a better understanding of the pathologic and genetic mechanisms underlying the development of keratoconus.

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References