Special Issue

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 μm) 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 μm) 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.[1] 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.[2] 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

TABLE 1. Clinical Characteristics of Patients with Keratoconus, KCS, and FFK, and Normal Controls of Healthy Subjects

	No. Patients	Eyes (Rigid Gas-Permeable Lens Wearers)	Men/ Women	Age, y
Keratoconus	109	189 (189)	67/42	18–75
KCS	12	14 (14)	5/7	16–62
FFK	14	14 (9)	10/4	18–60
Normal control	16	23 (0)	6/10	26–76

model for predicting the progression that was considered to be pathognomonic in keratoconus.[1,11,18] 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 ± 0.83). 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 (37.7 ± 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.[19] 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.[20] 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.[21] All the diagnoses 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 1310 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.[17] 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 (T_{min}) was defined as the pachymetric value at the thinnest location. The distance from the thinnest point to the corneal vertex (D_{min}) was calculated. Calculations of BFS, T_{min}, and D_{min} 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 (K_{max}). 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 (R_{post}), radius of anterior BFS (R_{ant}), T_{min}, D_{min}, and K_{max} were calculated for each eye using linear regression analysis. The repeatability of T_{min}, R_{ant}, R_{post}, D_{min}, and K_{max} 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[21] 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, K_{max}. Maximum K values and age were fitted with nonlinear restricted cubic splines. The annual change for R_{post}, R_{ant}, T_{min}, K_{max}, and D_{min} 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 K_{max} values in a GEE regression, where age and the initial value of K_{max} were modeled with nonlinear restricted cubic splines.

Similar GEE nonlinear regression curves for annual changes in R_{post}, T_{min}, and D_{min} values were fitted as a function of age, K_{max}, and sex, and for age and K_{max} as cross-product terms.

The progression of keratoconus was defined as a decrease in R_{post} 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 K_{max} by 18.5 diopters (D) and a remarkable thinning in T_{min} by 129 μm.

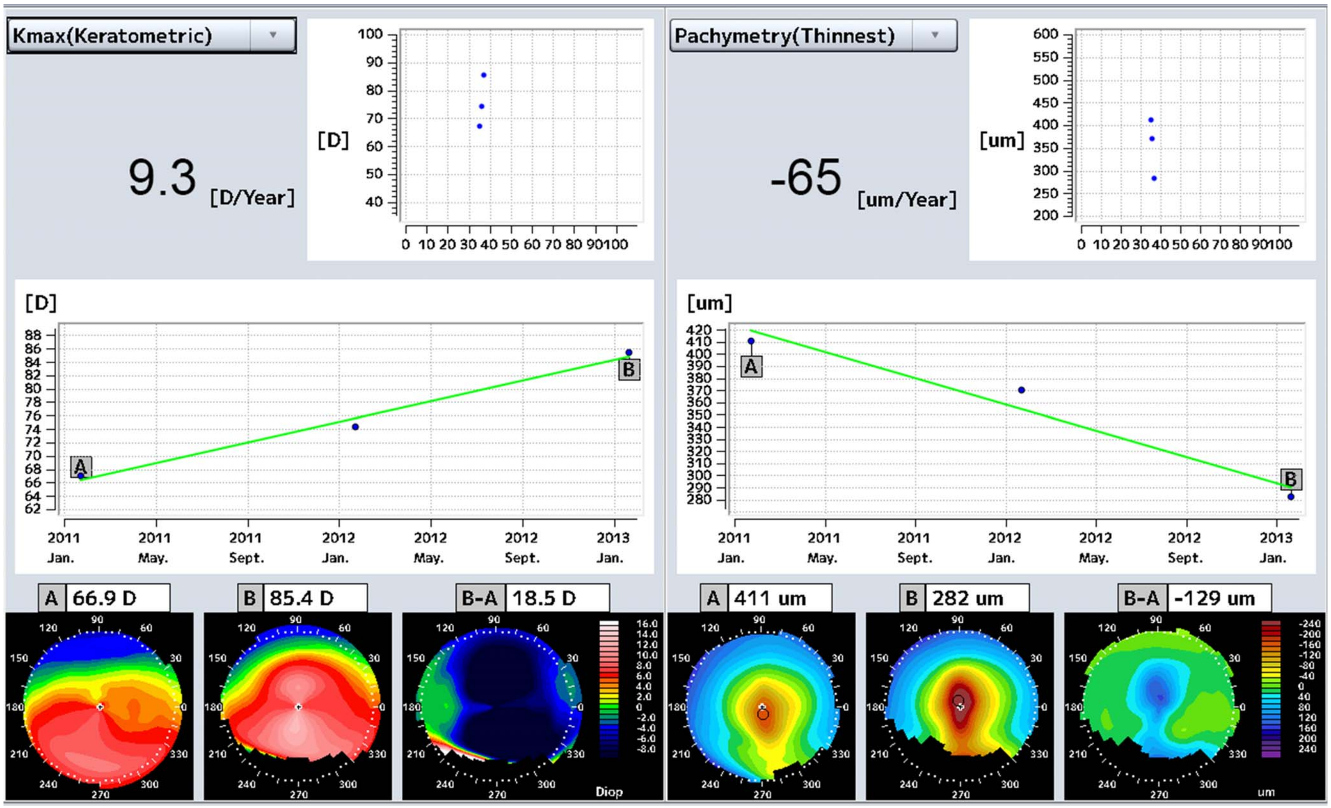

Figure 1. Representative chronologic changes of corneal tomography in the left eye of a 35-year-old man. Changes over the 2-year period in axial power maps (K_{max}, *left*), and pachymetric maps (T_{min}, *right*) are presented. Chronologic changes (*middle*) and the original and differential maps (*bottom*) are shown. Chronologic changes with age are presented at the *top*. The overlays at the *top* for all eyes are presented in Figures 4 (T_{min}) and Supplementary Figure S2 (K_{max}).

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_{post} which represent the corneal steepening were quantified (Fig. 2). There was a trend toward a greater decrease in R_{post} in eyes with steeper initial R_{post} for young and elderly patients; R_{post} at initial examinations ranged between 4.52 and 7.09 µm (mean ± SD, 5.97 ± 0.59 mm). The annual change for R_{post} was –0.017 ± 0.052 mm/y (mean ± SD; 95% confidence interval [CI], –0.024 to –0.010). Furthermore, in GEE nonlinear regression, the annual changes in R_{post} was significantly higher with a younger age ($P = 0.0033$) or greater K_{max} ($P = 0.0064$). This showed that significantly greater R_{post} change was observed in younger patients and those with greater disease severity; R_{ant} depicted the same tendency (Fig. 3).

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

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

The natural progression of K_{max} is shown in Supplementary Figure S2. There was a greater increase in K_{max} in younger patients and those with greater disease severity; however, the tendency is not as obvious as R_{post} or T_{min}, possibly because of dependency on ocular fixation and relatively low reliability of K_{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_{post} greater than 3 SD (Supplementary Fig. S3, Supplementary Table S1). Therefore, progression was defined as the steepening of R_{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_{post}.

Of the eyes with a K_{max} of ≥53 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_{post} fitted as a function of age, K_{max}, and sex, and as a cross-product of age and K_{max} are presented in Figure 5. For R_{post}, the annual change was greater in younger patients and patients with greater K_{max}. These results indicated that the average progression rates in R_{post} can be predicted with patient age and K_{max} using GEE nonlinear regression.

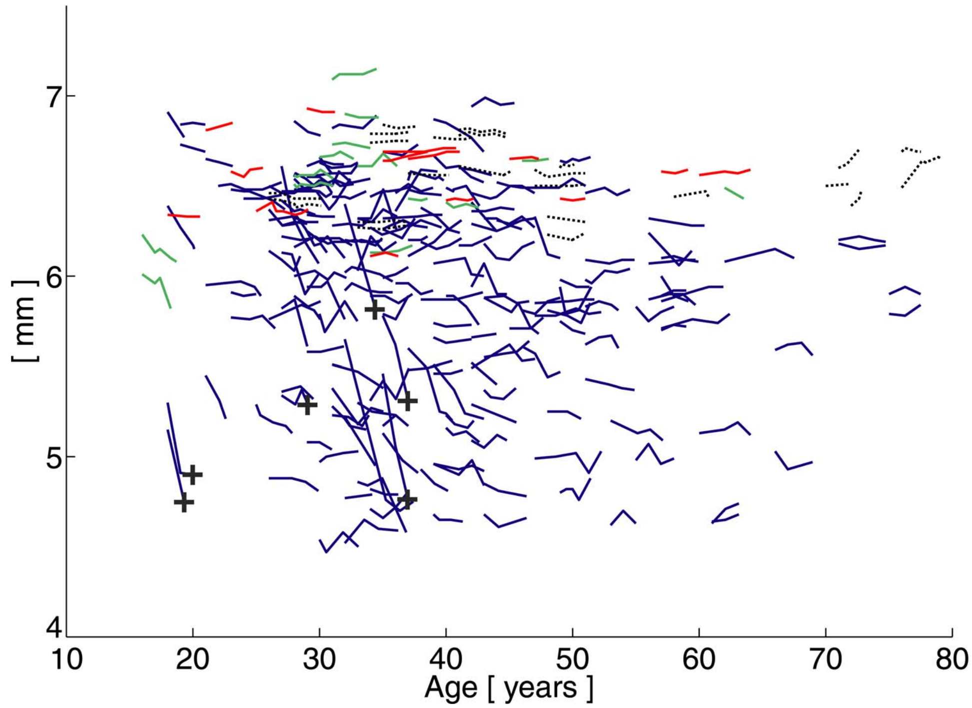

Figure 2. Chronologic changes in the best-fit sphere of the posterior surface (R_{post}). The *left* and *right* ends of each line represent values of initial and final examination of one eye, respectively. Eyes were subdivided into keratoconus (*blue lines*), KCS (*green lines*), FFK (*red lines*), and normal controls of healthy subjects (*black dashed lines*). +, indicate the last examination before the development of acute hydrops.

Tomographic Change Before Acute Corneal Hydrops

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

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

Unlike R_{post}, or T_{min}, no significant difference in the annual change in D_{min} values was observed between eyes that developed acute hydrops (mean ± SD, –0.08 ± 0.21 mm) and the other eyes ($P > 0.05$, GEE nonlinear regression).

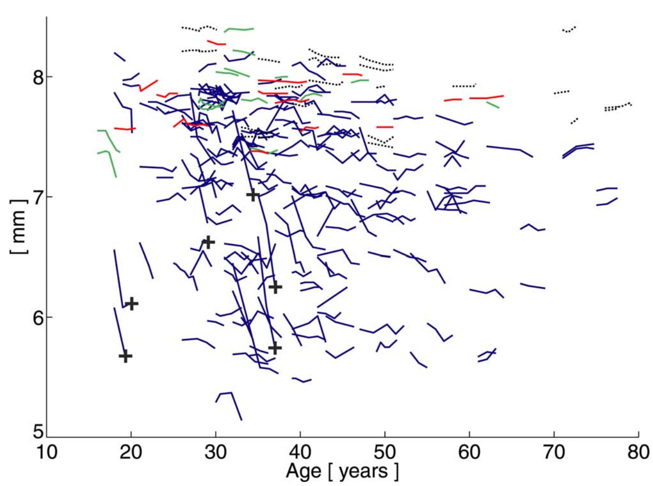

Figure 3. Chronologic changes in the best-fit sphere of the anterior surface (R_{ant}). *Blue*, *green*, *red*, and *black dashed lines* represent eyes with keratoconus, KCS, FFK, and normal controls, respectively. +, indicates the last examination before the development of acute hydrops.

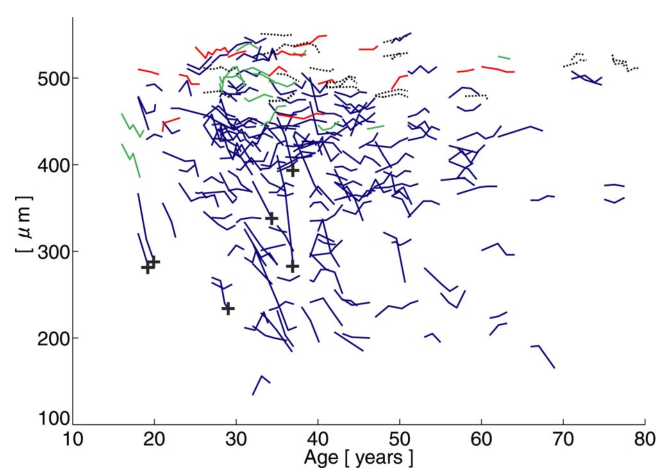

Figure 4. Chronologic changes in T_{min}. *Blue*, *green*, *red*, and *black dashed lines* represent eyes with keratoconus, KCS, FFK, and normal controls, respectively. +, indicates the last examination before the development of acute hydrops.

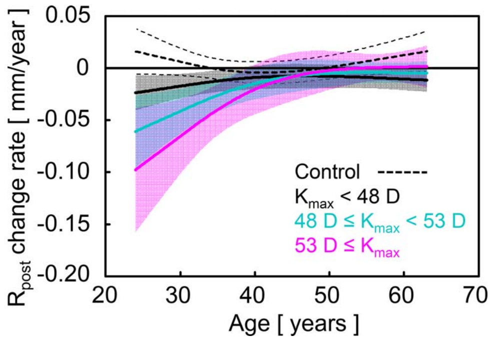

Figure 5. Generalized estimating equation nonlinear regression analysis. Generalized estimating equation nonlinear regression curves of annual change for R_{post} fitted as a function of age, K_{max}, as well as sex, age, and K_{max} as cross-product terms. *Black dashed lines*, normal controls of healthy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

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 $\leq K_{max} < 53$ D in

Table 2. Annual Rates of Change for Tomographic Parameters

Parameter	Annual Change Rate: Mean ± SD	Annual Change Rate: 95% CI	P Value, Wilcoxon Rank-Sum Test
Steepening			
R_{post}, mm			
KC Total	−0.017 ± 0.052	−0.024 to −0.010	4.1×10^{-5}
Keratoconus	−0.019 ± 0.055	−0.027 to −0.011	1.4×10^{-5}
KCS	−0.011 ± 0.026	−0.027 to +0.004	0.27
FFK	+0.004 ± 0.008	−0.006 to +0.008	0.08
Normal Control	+0.008 ± 0.026	−0.004 to +0.019	0.93
R_{ant}, mm			
KC Total	−0.020 ± 0.064	−0.029 to −0.012	2.3×10^{-7}
Keratoconus	−0.023 ± 0.068	−0.032 to −0.013	5.0×10^{-7}
KCS	−0.016 ± 0.030	−0.033 to +0.001	0.08
FFK	+0.002 ± 0.011	−0.004 to +0.008	0.67
Normal control	−0.001 ± 0.017	−0.002 to +0.007	0.38
Thinning			
T_{min}, μm			
KC Total	−2.70 ± 8.59	−3.83 to −1.53	1.7×10^{-3}
Keratoconus	−3.09 ± 8.96	−4.38 to −1.80	5.2×10^{-4}
KCS	−1.02 ± 5.63	−4.27 to +2.23	0.81
FFK	−1.21 ± 3.28	−0.68 to +3.09	0.19
Normal control	+0.41 ± 2.52	−0.67 to +1.51	0.39
Asymmetry			
D_{min}, mm			
KC Total	−0.006 ± 0.067	−0.015 to +0.003	0.17
Keratoconus	−0.009 ± 0.067	−0.018 to +0.001	0.07
KCS	+0.017 ± 0.065	−0.020 to +0.055	0.27
FFK	+0.006 ± 0.072	−0.035 to +0.048	0.58
Normal control	+0.010 ± 0.071	−0.020 to +0.041	0.23
Power			
K_{max}, D			
KC Total	−0.017 ± 0.052	−0.024 to −0.010	4.1×10^{-5}
Keratoconus	+0.31 ± 1.43	+0.11 to +0.52	9.6×10^{-4}
KCS	+0.26 ± 0.86	−0.24 to +0.76	0.76
FFK	−0.13 ± 0.31	−0.31 to +0.05	0.12
Normal control	+0.04 ± 0.20	−0.05 to +0.12	0.38

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 R_{post} and the T_{min} consistently tended to change, whereas the D_{min} did not.

Table 3. Number of Eyes With Progression

	No. Progress/No. Eyes (%)			
	Age <30 y	Age 30–45 y	Age ≥45 y	All Ages
K_{max} < 48 D	3/22 (14%)	2/30 (7%)	0/11 (0%)	5/63 (8%)
48 D ≤ K_{max} < 53 D	4/16 (25%)	4/32 (13%)	3/16 (19%)	11/64 (17%)
53 D ≤ K_{max}	8/19 (42%)	13/47 (28%)	1/24 (4%)	22/90 (24%)
All K_{max}	15/57 (26%)	19/109 (17%)	4/51 (8%)	38/217 (18%)

Progression of keratoconus was defined as the steepening of the R_{post} of more than three within-subject SDs (0.101 mm). Eyes were subdivided into nine groups according to age and K_{max} at the initial AS-OCT examination.

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.[23,24] 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 K_{max}.

Measurement of time-dependent changes also is important before any corneal surgeries, including corneal cross-linking,[6] intrastromal ring segments,[7] toric phakic IOLs, and cataract surgery with toric IOLs in keratoconus.

For example, corneal cross-linking has been considered as a preventive treatment for keratoconus progression.[6] The quantification of progression speed in keratoconus is required for determining surgical indications and for assessing the outcomes of corneal cross-linking. Although the preventative effects of corneal cross-linking may depend on the speed of keratoconic progression before surgery, to our knowledge no studies have yet evaluated this relationship precisely.

In cases where keratoconic progression is halted, toric phakic IOLs or toric IOLs may be reasonable as the refractive corrections. The progression of keratoconus after implantation of toric phakic IOLs or toric IOLs made it difficult to wear rigid gas-permeable contact lenses due to the residual cylinder of these toric lenses.

In severe cases of keratoconus, DALK is an alternative therapeutic option to conventional PKP.[8] In general, DALK is not indicated for eyes following acute corneal hydrops because of the rupture of Descemet's membrane.[9,10] Accordingly, the detection of precursory signs or risk factors for acute hydrops will be important for selecting DALK instead of PKP.

The severity of keratoconus has been evaluated with slit-lamp findings or indicators, such as contact lens intolerance, history of acute hydrops, or keratoplasty.[9,11] Moreover, keratoconic progression has been recorded according to visual acuity, regular astigmatism, spherical equivalent in manifest refraction, or keratometric readings.

Placido topography and Scheimpflug tomography are reproducible and provide sensitive measurements in mild cases of keratoconus. However, they occasionally are unreliable in cases with epithelial disorders or stromal scars.[15] Through the use of AS-OCT, we were able to include successfully the cases of severe keratoconus for which reliable corneal topography or tomography could not be obtained using either the Placido topographer or Scheimpflug tomographer. The time course of 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.[22] However, the progression of keratoconus after disease onset remains poorly understood.[12] 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 R_{post} and T_{min} were significantly greater in younger patients and patients with larger K_{max}. On the other hand, no relationships between D_{min} values and age or K_{max} 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 R_{post} and T_{min} in cases with acute hydrops were 10 times greater than average rates in other eyes. Our results suggested that rapid changes in R_{post} and T_{min} were sensitive precursory findings for acute hydrops. Tuft et al.[9] 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 R_{post} 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.[25]

Reinstein et al.[26] reported epithelial thinning at the cone apex using very high-frequency digital ultrasound scanning measurements. These findings were later confirmed by spectral domain OCT.[27] 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 rather than refractive power because refractive power was less reliable in the repeatability in our preliminary study and largely dependent on ocular fixation, particularly in severe keratoconus. The present study included a large number of cases with severe keratoconus, which were not included in previous longitudinal studies. Monitoring severe 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.[13,28] However, this period is not sufficient to predict disease progression over a lifetime.[3] 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[29] mechanisms underlying the development of keratoconus.

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References

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42:297–319.
2. Weed KH, MacEwen CJ, Giles T, et al. The Dundee University Scottish Keratoconus study: demographics, corneal signs, associated diseases, and eye rubbing. *Eye*. 2008;22:534–541.
3. Kennedy RH, Bourne WM, Dyer JAA. 48-year clinical and epidemiologic study of keratoconus. *Am J Ophthalmol*. 1986; 101:267–273.
4. McMahon TT, Edrington TB, Szczotka-Flynn L, et al. Longitudinal changes in corneal curvature in keratoconus. *Cornea*. 2006;25:296–305.
5. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
6. Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev.* 2015;3:CD010621.
7. Colin J, Cochener B, Savary G, et al. Correcting keratoconus with intracorneal rings. *J Cataract Refract Surg*. 2000;26: 1117–1122.
8. Melles GR, Lander F, Rietveld FJ, et al. A new surgical technique for deep stromal, anterior lamellar keratoplasty. *Br J Ophthalmol*. 1999;83:327–333.
9. Tuft SJ, Gregory WM, Buckley RJ. Acute corneal hydrops in keratoconus. *Ophthalmology.* 1994;101:1738–1744.
10. Nakagawa T, Maeda N, Okazaki N, et al. Ultrasound biomicroscopic examination of acute hydrops in patients with keratoconus. *Am J Ophthalmol*. 2006;141:1134–1136.
11. Lass JH, Lembach RG, Park SB, et al. Clinical management of keratoconus. A multicenter analysis. *Ophthalmology.* 1990;97: 433–445.
12. Maguire LJ, Lowry JC. Identifying progression of subclinical keratoconus by serial topography analysis. *Am J Ophthalmol*. 1991;112:41–45.
13. Oshika T, Tanabe T, Tomidokoro A, et al. Progression of keratoconus assessed by Fourier analysis of videokeratography data. *Ophthalmology.* 2002;109:339–342.
14. Shirayama-Suzuki M, Amano S, Honda N, et al. Longitudinal analysis of corneal topography in suspected keratoconus. *Br J Ophthalmol*. 2009;93:815–819.
15. Nakagawa T, Maeda N, Higashiura R, et al. Corneal topographic analysis in patients with keratoconus using 3-dimensional anterior segment optical coherence tomography. *J Cataract Refract Surg*. 2011;37:1871–1878.
16. Radhakrishnan S, Rollins AM, Roth JE, et al. Real-time optical coherence tomography of the anterior segment at 1310 nm. *Arch Ophthalmol*. 2001;119:1179–1185.
17. Szalai E, Berta A, Hassan Z, et al. Reliability and repeatability of swept-source Fourier-domain optical coherence tomography and Scheimpflug imaging in keratoconus. *J Cataract Refract Surg*. 2012;38:485–494.
18. Wilson SE, Lin DT, Klyce SD. Corneal topography of keratoconus. *Cornea*. 1991;10:2–8.
19. Nakagawa T, Maeda N, Kosaki R, et al. Higher-order aberrations due to the posterior corneal surface in patients with keratoconus. *Invest Ophthalmol Vis Sci*. 2009;50:2660–2665.
20. Kosaki R, Maeda N, Bessho K, et al. Magnitude and orientation of Zernike terms in patients with keratoconus. *Invest Ophthalmol Vis Sci*. 2007;48:3062–3068.
21. Klyce SD. Chasing the suspect: keratoconus. *Br J Ophthalmol*. 2009;93:845–847.
22. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130.
23. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. *Invest Ophthalmol Vis Sci*. 2010;51:5546–5555.
24. Fan Q, Teo YY, Saw SM. Application of advanced statistics in ophthalmology. *Invest Ophthalmol Vis Sci*. 2011;52:6059–6065.
25. Ridley F. Contact lenses in treatment of keratoconus. *Br J Ophthalmol*. 1956;40:295–304.
26. Reinstein DZ, Gobbe M, Archer TJ, et al. Epithelial, stromal, and total corneal thickness in keratoconus: three-dimensional display with Artemis very-high frequency digital ultrasound. *J Refract Surg*. 2010;26:259–271.
27. Li Y, Tan O, Brass R, et al. Corneal epithelial thickness mapping by Fourier-domain optical coherence tomography in normal and keratoconic eyes. *Ophthalmology.* 2012;119:2425–2433.
28. Li X, Rabinowitz YS, Rasheed K, et al. Longitudinal study of the normal eyes in unilateral keratoconus patients. *Ophthalmology.* 2004;111:440–446.
29. Lu Y, Vitart V, Burdon KP, et al. Genome-wide association analyses identify multiple loci associated with central corneal thickness and keratoconus. *Nature Genet*. 2013;45:155–163.