Comparison of multimetric D index with keratometric, pachymetric, and posterior elevation parameters in diagnosing subclinical keratoconus in fellow eyes of asymmetric keratoconus patients

Orkun Muftuoglu, MD, Orhan Ayar, MD, Volkan Hurmeric, MD, Faik Orucoglu, MD, Ilkay Kılıc, MD

PURPOSE: To compare the multimetric D index and other keratoconus-screening parameters in patients with clinical keratoconus in 1 eye and subclinical keratoconus in the fellow eye.

SETTING: Medipol University Hospital and Birinci Eye Hospital, Istanbul, Turkey.

DESIGN: Retrospective case-control study.

METHODS: Patients with clinical keratoconus in 1 eye and subclinical keratoconus in the fellow eye and eyes of normal subjects were evaluated with a rotating Scheimpflug imaging system (Pentacam). Parameters included anterior curve analysis, keratometry (K) values, minimum corneal thickness, pachymetric progression index, Ambrósio relational thickness, posterior elevation, back difference elevation, and D-index values. The receiver operating characteristic (ROC) curves were analyzed to evaluate the area under curve (AUC), sensitivity, and specificity of each parameter.

RESULTS: Forty-five patients and 67 normal subjects were evaluated. The pachymetric progression indices, posterior elevation, and the D-index measurements were statistically significantly higher whereas corneal thickness and Ambrósio relational thickness measurements were significantly lower in eyes with keratoconus or subclinical keratoconus than in eyes of normal subjects ($P < .05$). Using the ROC analysis, the AUC values of the mean steep K, minimum corneal thickness, pachymetric progression index minimum, Ambrósio relational thickness maximum, posterior elevation, back difference elevation, and D index to distinguish between subclinical keratoconus from control subjects were 0.52, 0.64, 0.71, 0.72, 0.71, 0.76, and 0.83, respectively.

CONCLUSION: The new multimetric D index seems to be better than other single-metric parameters in diagnosing keratoconus and subclinical keratoconus with good specificity. However, the sensitivity levels of all parameters were relatively limited in the diagnosis of subclinical keratoconus.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2015; 41:557–565 © 2015 ASCRS and ESCRS

Since the 1990s, millions of excimer laser refractive surgeries have been performed to correct refractive errors with good long-term results.[1,2] However, iatrogenic corneal ectasia, in particular with laser in situ keratomileusis (LASIK) treatments, remains one of the most feared postoperative complications of laser refractive surgery.[3] Different factors might contribute to the development of iatrogenic corneal ectasia after laser refractive surgery, and undiagnosed subclinical keratoconus is reported to be a main reason.[4] Although screening for subclinical keratoconus before laser refractive surgery is important to prevent postoperative ectasia, it may be difficult to rule out the disease because of subtle signs

http://dx.doi.org/10.1016/j.jcrs.2014.05.052
0886-3350

and borderline features that are difficult to establish with certainity.[5]

Keratoconus is usually a bilateral corneal ectatic disorder with a strong genetic component.[6] Therefore, when the fellow eye of a patient with significantly asymmetric keratoconus (so-called unilateral keratoconus) has subclinical keratoconus, it is possibly the earliest and mildest form for the disease and would have the greatest potential for progressing to clinical keratoconus, in particular after laser refractive surgery.[7,8] Therefore, recognizing early signs of the disease in these eyes would help us estimate, with high specificity, the risk for ectasia after laser refractive surgery.

Several keratometric,[6] pachymetric,[9] wavefront,[10] and posterior elevation[11] parameters with different sensitivity and specificity have been used to rule out the possibility of subclinical keratoconus. A new parameter derived from keratometric, pachymetric, and posterior elevation data, called the D index of the Pentacam imaging system (Oculus Optikgeräte GmbH), was recently introduced; the manufacturer states that the index can be used as the sole parameter to identify patients who might have early keratoconus that might progress to ectasia after laser refractive surgery.[A,B]

The purpose of this study was to evaluate and compare keratometry, pachymetry, posterior elevation (including back difference elevation), and the new D parameter in patients with clinical keratoconus in 1 eye and subclinical keratoconus in the fellow eye. To our knowledge, this is the first study to evaluate the ability of the D index to diagnose keratoconus or subclinical keratoconus.

PATIENTS AND METHODS

This retrospective case series and study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committees of the Medipol University and Birinci Eye Hospital. Between July 2012 and March 2013, patients examined at the Medipol University and Birinci Eye Hospital, Istanbul, Turkey, were retrospectively enrolled. All patients included in the study provided informed consent.

Along with a comprehensive ocular examination, clinical keratoconus was defined as evident findings characteristic of keratoconus (eg, corneal topography with an asymmetric bowtie pattern with or without skewed axes) and at least 1 keratoconus sign (eg, stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae, or anterior stromal scar) on slitlamp examination. Patients who were diagnosed as having clinical keratoconus in 1 eye (Group A) and no slitlamp finding and no topography finding significant enough to be diagnosed as clinical keratoconus in the fellow eye (Group B) were included in the study.

Control cases (Group C) were selected from a database of consecutive candidates for refractive surgery with normal corneas and myopia or myopic astigmatism (sphere <6.00 diopters [D]; cylinder <3.00 D). Eyes were considered normal if they had no ocular pathology, no previous ocular surgery, and no irregular corneal pattern. Of the consecutively numbered control cases, only 1 eye of each patient (right eye for single numbers and left eye for even numbers) was evaluated.

Exclusion criteria were a history of corneal surgery or contact lens wear, significant corneal scarring, and significant ophthalmic disease that might affect the outcomes.

All eyes were examined by rotating Scheimpflug corneal tomography (Pentacam HR, software version 1.18r08). Four patients with clinical keratoconus stopped using rigid gas-permeable contact lenses 3 days before the measurements. No patient was using any type of contact lens in the fellow eye. During the Scheimpflug corneal tomography examination, the patient was comfortably positioned at the instrument with proper placement on the chinrest and forehead strap. The patient was asked to blink a few times and to open both eyes and stare at the fixation target. After proper alignment was obtained, the automatic release mode started the scan using 25 single Scheimpflug images captured within 2 seconds for each eye. Three consecutive scans were taken of each eye by the same examiner. Only cases with acceptable-quality images were included in the study. Each eye was required to have a corneal map with at least 9.0 mm of corneal coverage and no extrapolated data.

The sagittal curvature and tangential curvature maps were evaluated, and the map patterns were noted. The following anterior and posterior corneal surface parameters were evaluated with the Scheimpflug system: corneal dioptric power in the flattest meridian in the 3.0 mm central zone (flat keratometry [K]), corneal dioptric power in the steepest meridian in the 3.0 mm central zone (steep K), and mean corneal power in the 3.0 mm zone (mean K). The inferior–superior (I–S) dioptric asymmetry value on the sagittal curvature maps was calculated by subtracting the superior average value of 3 data points 3.0 mm from the center of the cornea at 30-degree intervals (60 degrees, 90 degrees, 120 degrees) from the average value of the 3 corresponding data points along the inferior cornea (240 degrees, 270 degrees, 300 degrees); the value of the steepest point (steepest K) on sagittal steepest and tangential steepest curvature maps was determined manually by moving the cursor on the map.

Central corneal thickness (CCT) at the apex (geometric center of the examination); corneal thickness at the thinnest point (CTmin); and the distance between the CCT and

Submitted: December 24, 2013.
Final revision submitted: May 6, 2014.
Accepted: May 8, 2014.

From the Department of Ophthalmology (Muftuoglu), Medipol University, Birinci Eye Hospital (Orucoglu), and Istanbul Egitim Arastirma Hastanesi (Kılıc), Istanbul, the Department of Ophthalmology (Ayar), Zonguldak Bülent Ecevit University, Zonguldak, and Dunya Eye Hospital (Hurmeric), Ankara, Turkey.

Corresponding author: Orkun Muftuoglu, MD, Medipol University, Department of Ophthalmology, Medipol Mega Universite Hastanesi, Goz Hastaliklari, TEM otoyolu No: 1, Bagcilar 34214, Istanbul, Turkey. E-mail: orkunm@yahoo.com.

CTmin (Dist CCT_CTmin), both in the horizontal plane (Dist CCT_CTminH) and the vertical plane (Dist CCT_CTminV), were recorded. The average progression index (PPIavg) is calculated as the progression value at the different rings, referenced to the mean curve. The minimum (PPImin) and maximum PPI (PPImax) values and axes were recorded along with the PPI average (PPIavg). Ambrósio relational thickness (ART) was calculated by the following formulas: ARTavg = CTmin/PPIavg; ARTmin = CTmin/PPImin; ARTmax = CTmin/PPImax.[12]

The posterior elevation maps were evaluated, and the posterior corneal elevation values from the corneal apex were analyzed. Elevation was measured in a standardized fashion relative to a reference best-fit sphere calculated at a fixed optical zone of 8.0 mm, as previously described.[13] The back difference posterior elevation and the D-index values were extrapolated from the difference maps of the Belin/Ambrósio Enhanced Ectasia Display of the Pentacam system.

Because the data were not normally distributed, the nonparametric Mann-Whitney *U* test was performed to compare each parameter between the 2 groups. Receiver operating characteristic (ROC) curves were used to determine the overall predictive accuracy of the test parameters as described by the area under the curve (AUC) and to calculate the sensitivity and specificity of the parameters. A *P* value less than 0.05 was considered statistically significant. The Bonferroni correction was used for multiple comparisons, and a *P* value less than 0.0166 was considered significant.

RESULTS

Forty-five patients were diagnosed as having clinical keratoconus in 1 eye (Group A) and no slitlamp finding or no topography finding significant enough to be diagnosed as clinical keratoconus in the fellow eye (Group B). The mean age was 29.0 years ± 8.8 (SD) (range 13 to 63 years) in keratoconus patients and 29.0 ± 5.9 years (range 18.0 to 41.0 years) in controls. There was no significant difference in age between the 2 groups ($P = .712$). Two patients were older than 45 years (50 years and 63 years).

Table 1 shows the mean K, pachymetric, and posterior elevation parameters in all groups. The corneal power (steep K, flat K, mean K), keratometric parameters (I–S, sagittal steepest, tangential steepest), Dist CCT_CTminV (more in the negative way, inferiorly), PPI (avg, min, max), posterior corneal elevation (posterior elevation, back difference elevation), and D-index measurements were statistically significantly higher whereas corneal thickness (CTmin, CCT, Dist CCT_CTmin, Dist CCT_CTminH) and Ambrósio relational thickness (avg, min, max) measurements were statistically significantly lower in eyes with keratoconus than in eyes of normal control subjects ($P < .05$).

There was no significant difference in steep K, flat K, mean K, I–S, tangential steepest, sagittal steepest, Dist CCT_CTmin, Dist CCT_CTminH, or PPIavg between eyes with subclinical keratoconus and control eyes. The Dist CCT_CTminV (more in the negative way, inferiorly), PPImin, PPImax, posterior corneal elevation (posterior elevation, back difference elevation), and D-index measurements were statistically significantly higher whereas corneal thickness (CTmin, CCT) and Ambrósio relational thickness (avg, min, max) measurements were statistically significantly lower in eyes with subclinical keratoconus than in eyes of normal control subjects ($P < .016$).

Figure 1 shows the frequency distribution of the posterior elevation, back difference elevation, PPIavg, ARTmax, and D index in eyes with keratoconus, eyes with subclinical keratoconus, and control eyes. Figure 2 shows samples from the keratoconus eyes (Group A) and the fellow eyes with subclinical keratoconus (Group B).

Receiver Operating Characteristic Curve Analysis

The results of the ROC analysis AUC, standard error, 95% confidence intervals, significance level, best cutoff point, and sensitivity and specificity of best cutoff points for each parameter to differentiate between keratoconus eyes and normal control eyes are given in Table 2 and to differentiate subclinical keratoconus eyes and normal control eyes are given in Table 3 and Figure 3. In discriminating between keratoconus eyes (Group A) and control eyes (Group C), almost all parameters had a high AUC; however, the D index and posterior elevation parameters had the highest AUC. In discriminating between fellow eyes with subclinical keratoconus (Group B) and control eyes (Group C), the D index had the highest AUC followed by the back difference elevation and ARTmin.

DISCUSSION

The new D index is a multimetric combination parameter composed of keratometric, pachymetric, pachymetric progression, and back elevation parameters. This study showed that among the keratometric, pachymetric (including progression indices), and posterior elevation indices we evaluated with ROC analysis, the D index had the best AUCs to differentiate between keratoconus and subclinical keratoconus eyes and control eyes. We found that the best cutoff for the D index to differentiate keratoconus from controls was 2.1, with 100% sensitivity and 100% specificity. This result suggests that the new D index can be valuable in diagnosing keratoconus as a sole parameter. On the other hand, the best cutoff for the D index in differentiating eyes with subclinical keratoconus from normal eyes was 1.3, but with a sensitivity of

Table 1. Comparison of Scheimpflug parameters between keratoconus, forme fruste keratoconus, and control groups.

Parameter	KCN	FFKC	Controls	*P* Value*		
				KCN–Cont	FFKC–Cont	KCN–FFKC
Ks (D)	47.6 ± 3.5	43.8 ± 1.7	44.1 ± 1.4	<.001	.215	<.001
Kf (D)	44.0 ± 3.0	42.7 ± 1.7	42.7 ± 1.2	<.001	.993	.011
Km (D)	45.8 ± 2.8	43.2 ± 1.7	43.4 ± 1.2	<.001	.495	.323
Inf–sup (D)	1.19 ± 0.10	1.01 ± 0.02	1.00 ± 0.01	<.001	.182	<.001
Ssteep (D)	50.5 ± 4.3	44.9 ± 1.7	44.3 ± 1.5	<.001	.196	<.001
Tsteep (D)	51.7 ± 5.0	45.6 ± 1.9	44.5 ± 1.5	<.001	.047	<.001
CTmin (μm)	473 ± 34	511 ± 36	540 ± 30	<.001	<.001	<.001
CCT (μm)	485 ± 34	517 ± 35	543 ± 30	<.001	<.001	<.001
Dist CCT_CTmin (μm)	0.89 ± 0.33	0.83 ± 0.25	0.74 ± 0.20	.005	.052	.334
Dist CCT_Ctmin_H (μm)	0.60 ± 0.29	0.63 ± 0.23	0.67 ± 0.20	.168	.551	.557
Dist CCT_Ctmin_V (μm)	−0.58 ± 0.38	−0.48 ± 0.26	−0.20 ± 0.23	<.001	<.001	.634
PPIavg	1.78 ± 0.60	1.05 ± 0.20	0.98 ± 0.12	<.001	.017	<.001
PPImin	1.32 ± 0.53	0.74 ± 0.13	0.62 ± 0.11	<.001	<.001	<.001
PPImax	2.49 ± 0.81	1.39 ± 0.26	1.24 ± 0.15	<.001	<.001	<.001
ARTavg	299 ± 125	511 ± 149	572 ± 90	<.001	<.05	<.001
ARTmin	415 ± 171	719 ± 160	912 ± 194	<.001	<.001	<.001
ARTmax	209 ± 70	381 ± 81	452 ± 73	<.001	<.001	<.001
PE (μm)	47.3 ± 22.8	11.5 ± 5.4	7.7 ± 2.6	<.001	<.001	<.001
BDE (μm)	28.6 ± 17.9	7.9 ± 4.8	4.0 ± 2.6	<.001	<.001	<.001
D index	6.49 ± 3.22	1.49 ± 0.82	0.57 ± 0.59	<.001	<.001	<.001

ART = Ambrosió relational thickness; avg = average; BDE = back difference elevation on Belin-Ambrosió display of Scheimpflug device; CCT = central corneal thickness; Cont = controls; Ctmin = minimum corneal thickness; Dist CCT_Ctmin = distance between central corneal thickness and minimum corneal thickness; Dist CCT_Ctmin_H = distance between central corneal thickness and minimum corneal thickness on the horizontal plane; Dist CCT_Ctmin_V = distance between central corneal thickness and minimum corneal thickness on the vertical plane; FFKC = forme fruste keratoconus; Inf–sup = inferior/superior sagittal; KCN = keratoconus; Kf = flat keratometry; Km = mean keratometry; Ks = steep keratometry; max = maximum; min = minimum; PE = posterior corneal elevation; PPI = pachymetric progression index; Ssteepest = steepest keratometry on sagittal curvature map; Tsteepest = steepest keratometry on tangential curvature map

*Mann-Whitney *U* test

60% and specificity of 90%, suggesting a good specificity to diagnose subclinical keratoconus but a limited sensitivity. In other words, although false positives are rare with the D index in the diagnosis of subclinical keratoconus, false negatives are possible. Clinically, this might imply that it is still possible to miss subclinical keratoconus eyes when screening with the D index. However, if the result becomes positive, it may be advisable to refrain from performing corneal refractive surgery, such as LASIK, in that eye. To our knowledge, we are unaware of a published study of the D index to screen for keratoconus or subclinical keratoconus; thus, we cannot compare our results with those in other studies.

In this study, we also found that after the D index, the second best index was the back difference elevation, followed by ARTmin, ARTmax, PPImin, and posterior elevation. These results are in accordance with findings in our previous study[14] in which the back difference elevation and PPImin had the highest AUCs to diagnose subclinical keratoconus. Our results also confirmed our previous finding that the back difference elevation seems to be better than posterior elevation in diagnosing early subclinical keratoconus.[5] However, in this study the best cutoff levels for posterior elevation and back difference elevation to differentiate subclinical keratoconus eyes from normal controls were 11.0 and 8.0, respectively, which were lower than in our previous report.[14] This may be explained by the use of newer software that allowed automated posterior elevation and back difference elevation measurements and the inclusion of more subjects consisting of a different group of 45 patients (previous study had 29 patients) with asymmetric (so-called unilateral) keratoconus in this study. However, it should be kept in mind that significant overlaps in posterior elevation and back difference elevation levels between subclinical keratoconus eyes and control eyes were still noted (Figure 1). This suggests that both back difference elevation and posterior elevation as sole parameters have limited sensitivity and specificity to diagnose very early keratoconus.

In accordance with findings in previous studies,[9,12,14] the corneal pachymetric progression indices had a relatively good AUC to differentiate

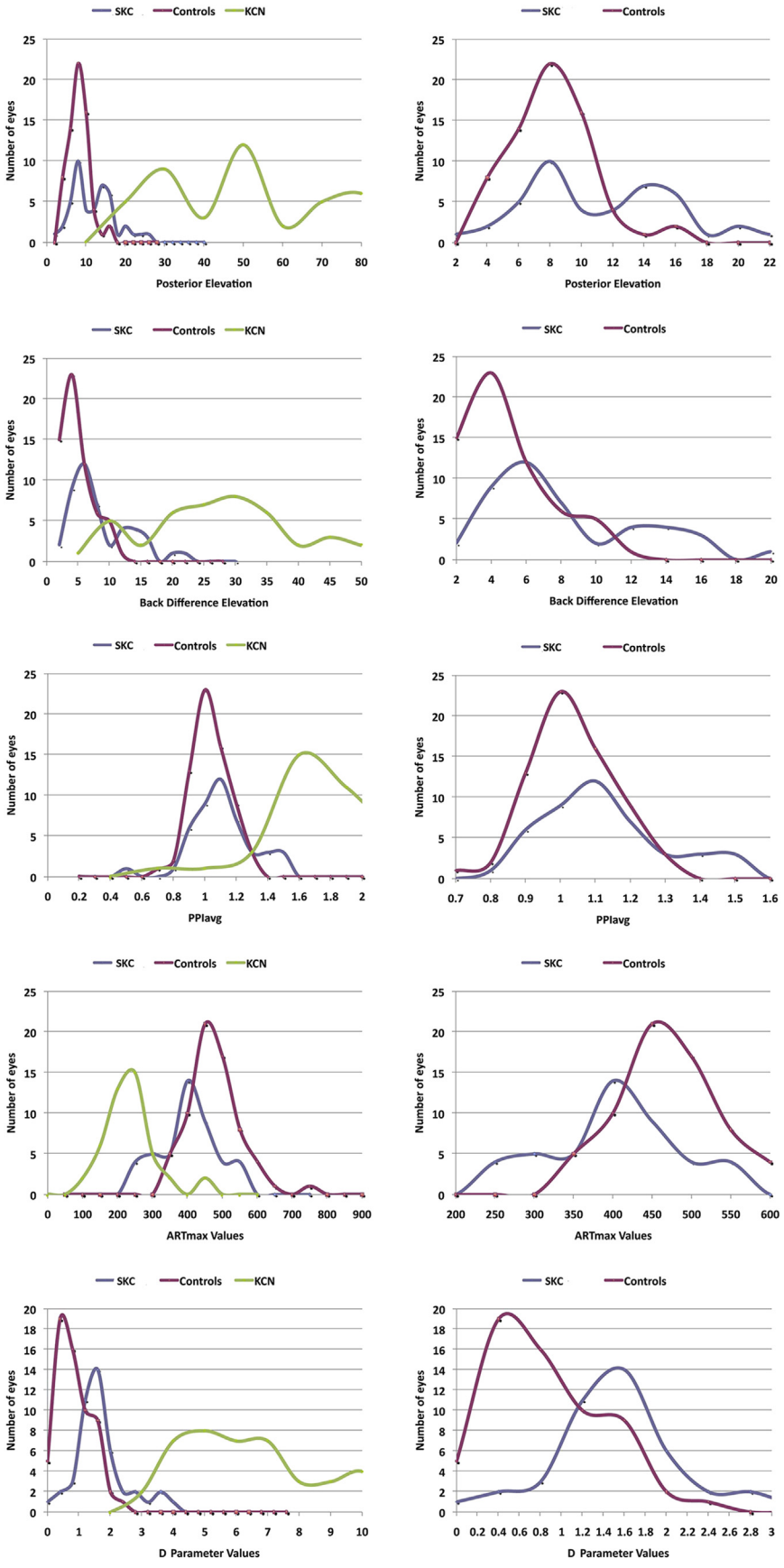

Figure 1. Distribution frequency of different parameters: posterior elevation, back difference elevation, pachymetric progression index–average (PPIavg), Ambrósio relational thickness–maximum (ARTmax), and D parameter in eyes with subclinical keratoconus (SKC) (fellow eyes), eyes with keratoconus (KCN), and control eyes.

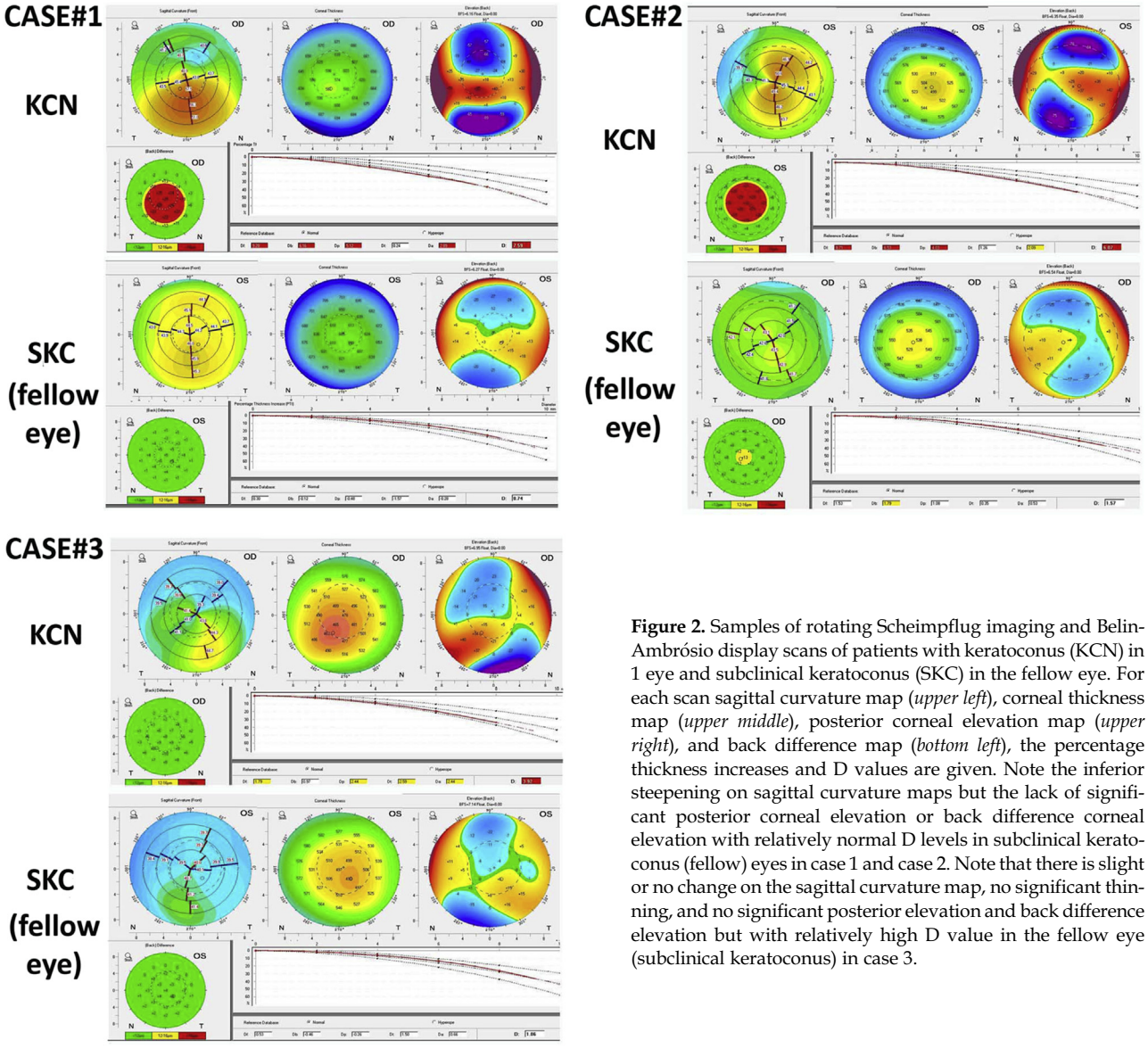

Figure 2. Samples of rotating Scheimpflug imaging and Belin-Ambrósio display scans of patients with keratoconus (KCN) in 1 eye and subclinical keratoconus (SKC) in the fellow eye. For each scan sagittal curvature map (*upper left*), corneal thickness map (*upper middle*), posterior corneal elevation map (*upper right*), and back difference map (*bottom left*), the percentage thickness increases and D values are given. Note the inferior steepening on sagittal curvature maps but the lack of significant posterior corneal elevation or back difference corneal elevation with relatively normal D levels in subclinical keratoconus (fellow) eyes in case 1 and case 2. Note that there is slight or no change on the sagittal curvature map, no significant thinning, and no significant posterior elevation and back difference elevation but with relatively high D value in the fellow eye (subclinical keratoconus) in case 3.

keratoconus and subclinical keratoconus eyes from normal control eyes. Recently, Ambrósio et al.[12] introduced a new parameter (Ambrósio relational thickness) referring to the relational thickness of the CTmin with PPI (ART = CTmin/PPI) and found that the Ambrósio relational thickness had high sensitivity and specificity to detect keratoconus. In this study, we also found high AUC values for the Ambrósio relational thickness to diagnose keratoconus; however, the AUC levels of the Ambrósio relational thickness were lower in distinguishing subclinical keratoconus eyes from normal control eyes. We hypothesize that in clinical keratoconus, the CTmin is usually decreased, which would result in a low and more sensitive Ambrósio relational thickness (= CTmin/PPI). On the other hand despite a high PPI suggesting ectatic disease, the CTmin might not be significantly decreased in early subclinical keratoconus in some cases. This might result in higher levels of Ambrósio relational thickness and lower sensitivity. Although we were not able to find a significant difference in Dist CCT_CTminH between keratoconus eyes, subclinical keratoconus eyes, or normal controls eyes, the Dist CCT_CTminV values were significantly lower in eyes with keratoconus and subclinical keratoconus than in normal controls. This might indicate inferior decentration of the thinnest point of the cornea in eyes with subclinical keratoconus, supporting the findings of Saad and Gatinel.[5] More studies are needed to compare the efficacy of pachymetric data in detecting early ectatic diseases.

Table 2. Receiver operating characteristic curve analysis for ability of different parameters to differentiate keratoconus eyes from control eyes.

Parameter	AUC	SE	95% CI	*P* Value	Cutoff	Sensitivity	Specificity
Ks (D)	0.735	0.043	0.749, 0.915	<.001	45	80	79
Kf (D)	0.669	0.059	0.555, 0.784	.002	44.3	49	71
Km (D)	0.695	0.059	0.583, 0.836	.030	45.7	81	77
Ssteep (D)	0.962	0.056	0.896, 0.988	<.001	46.9	91	97
Tsteep (D)	0.956	0.056	0.919, 0.981	<.001	47.5	96	93
Inf–sup (D)	0.910	0.031	0.842, 0.956	<.001	1.03	91	100
CTmin (μm)	0.873	0.015	0.824, 0.911	<.001	501	92	71
CCT (μm)	0.832	0.017	0.808, 0.889	<.001	511	87	68
Dist CCT_CTmin (μm)	0.809	0.055	0.791, 0.846	.008	1.04	74	84
Dist CCT_Ctmin_H (μm)	0.579	0.055	0.480, 0.673	.16	NA	NA	NA
Dist CC_Ctmin_V (μm)	0.869	0.041	0.718, 0.874	<.001	−0.50	67	85
PPIavg	0.955	0.030	0.896, 1.000	<.001	1.25	93	99
PPImin	0.960	0.023	0.914, 1.000	<.001	0.84	89	96
PPImax	0.966	0.024	0.919, 1.000	<.001	1.56	93	100
ARTavg	0.963	0.017	0.909, 0.989	<.001	392	93	99
ARTmin	0.973	0.015	0.923, 0.994	<.001	604	91	99
ARTmax	0.985	0.011	0.941, 0.998	<.001	313	93	100
PE (μm)	0.999	0.002	0.964, 1.000	<.001	15	98	100
BDE (μm)	0.981	0.015	0.934, 1.000	<.001	11	87	100
D index	1.000	0.000	1.000, 1.000	<.001	2.1	100	100

ART = Ambrosió relational thickness; AUC = area under curve; avg = average; BDE = back difference elevation on Belin-Ambrosió display of Scheimpflug device; CCT = central corneal thickness; Ctmin = minimum corneal thickness; Dist CCT_Ctmin = distance between central corneal thickness and minimum corneal thickness; Dist CCT_Ctmin_H = distance between central corneal thickness and minimum corneal thickness on the horizontal plane; Dist CCT_Ctmin_V = distance between central corneal thickness and minimum corneal thickness on the vertical plane; Inf–sup = inferior/superior sagittal; Kf = flat keratometry; Km = mean keratometry; Ks = steep keratometry; max = maximum; min = minimum; NA = not available; PE = posterior corneal elevation; PPI = pachymetric progression index; SE = spherical equivalent; Ssteepest = steepest keratometry on sagittal curvature map; Tsteepest = steepest keratometry on tangential curvature map

Using a Scheimpflug camera combined with a Placido cornea topographer, Arbelaez et al.[15] evaluated a learning technique that included curvature-, elevation-, and corneal thickness–based indices in eyes with subclinical keratoconus and found that this system had a sensitivity of 93% and specificity of 98% to discriminate subclinical keratoconus eyes from normal control eyes. In another study, Saad and Gatinel[5] evaluated the topography and tomography indices combined in discriminant functions to diagnose forme fruste keratoconus and found that the combined indices generated from curvature, elevation, corneal thickness increase, and corneal irregularity could identify very mild forms of corneal ectasia with a sensitivity of 93% and specificity of 92%. Although it is not easy to compare our results with those in these 2 reports because of different detection methods and algorithms, study populations, and study designs, the results in these studies might support our finding that multimetric parameters might have better sensitivity and specificity than single-metric parameters in diagnosing keratoconus.

It is well established that keratoconus is a bilateral progressive disease with a strong genetic component.[6,16] However, sometimes the disease is significantly asymmetric; that is, the fellow eye might have a very subtle or even no change that can be detected with the current noninvasive diagnostic methods.[7,8] Little is known about the speed of progression of subclinical keratoconus,[6] and true unilateral keratoconus without progression is a possibility that should be kept in mind when evaluating the results in our study.[8] Therefore, further genetic-based follow-up studies are needed to elucidate the risk these eyes have for developing keratoconus. On the other hand, it is clear that all patients in our study had a proven diagnosis of keratoconus in 1 eye and their fellow eye would have a very high risk for developing ectasia if they were to have a procedure that weakens the cornea, such as LASIK.

A limitation of this study is the control group was recruited from normal patients rather than from a relevant clinical population. This may have led to overestimation of the performance of the parameters with the ROC analysis.[17] It is well known that

Table 3. Receiver operating characteristic curve analysis for ability of different parameters to differentiate forme fruste keratoconus eyes from control eyes.

Parameter	AUC	SE	95% CI	*P* Value	Cutoff	Sensitivity	Specificity
Ks	0.522	0.056	0.442, 0.613	.440	NA	NA	NA
Kf	0.455	0.057	0.383, 0.536	.561	NA	NA	NA
Km	0.496	0.057	0.411, 0.578	.506	NA	NA	NA
Ssteep (D)	0.542	0.057	0.457, 0.649	.382	NA	NA	NA
Tsteep (D)	0.586	0.059	0.585, 0.676	.222	NA	NA	NA
Inf–sup (D)	0.605	0.046	0.560, 0.699	.068	NA	NA	NA
CTmin (μm)	0.639	0.044	0.572, 0.688	.013	515	68	54
CCT (μm)	0.617	0.044	0.551, 0.641	.042	527	66	52
Dist CCT_CTmin (μm)	0.594	0.057	0.517, 0.645	.093	0.91	60	50
Dist CCT_Ctmin_H (μm)	0.524	0.061	0.436, 0.630	.546	NA	NA	NA
Dist CC_Ctmin_V (μm)	0.711	0.047	0.618, 0.790	<.001	−0.28	68	69
PPIavg	0.629	0.055	0.521, 0.718	.021	1.15	54	73
PPImin	0.714	0.048	0.650, 0.803	<.001	0.66	69	70
PPImax	0.679	0.053	0.569, 0.776	.002	1.26	64	64
ARTavg	0.693	0.049	0.611, 0.787	<.001	485	61	74
ARTmin	0.739	0.042	0.674, 0.813	<.001	781	68	73
ARTmax	0.722	0.049	0.652, 0.818	<.001	408	67	71
PE	0.709	0.053	0.616, 0.812	<.001	11	53	90
BDE	0.761	0.045	0.672, 0.850	<.001	8	51	85
D index	0.834	0.039	0.757, 0.911	<.001	1.31	60	90

ART = Ambrosió relational thickness; AUC = area under curve; avg = average; BDE = back difference elevation on Belin-Ambrosió display of Scheimpflug device; CCT = central corneal thickness; CI = confidence interval; Ctmin = minimum corneal thickness; Dist CCT_Ctmin = distance between central corneal thickness and minimum corneal thickness; Dist CCT_Ctmin_H = distance between central corneal thickness and minimum corneal thickness on the horizontal plane; Dist CCT_Ctmin_V = distance between central corneal thickness and minimum corneal thickness on the vertical plane; Inf–sup = inferior/superior sagittal; Kf = flat keratometry; Km = mean keratometry; Ks = steep keratometry; max = maximum; min = minimum; NA = not available; PE = posterior corneal elevation; PPI = pachymetric progression index; SE = spherical equivalent; Ssteepest = steepest keratometry on sagittal curvature map; Tsteepest = steepest keratometry on tangential curvature map

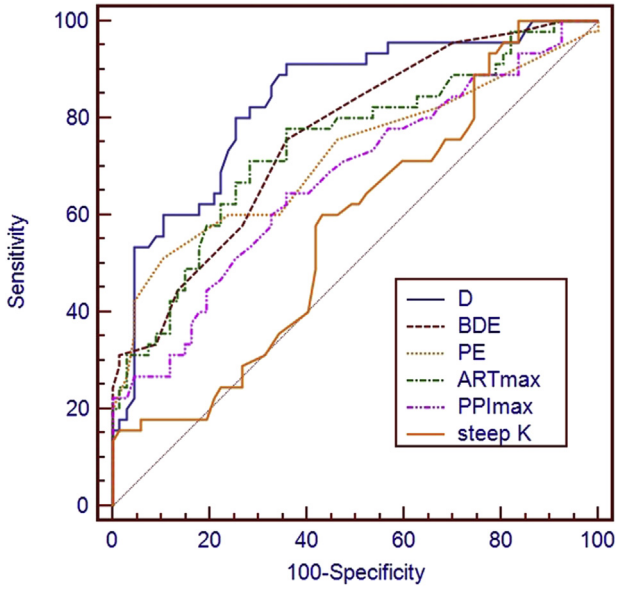

Figure 3. Combined ROCs for steep keratometry (steep K), posterior elevation (PE), back difference elevation (BDE), pachymetric progression index–average (PPImax), Ambrósio relational thickness–maximum (ARTmax), and D parameter to differentiate subclinical keratoconus from normal controls. Note that the D index has the largest AUC.

keratoconus progression slows with age, and there were 2 patients older 45 years in our group. Also, previous studies[18,19] report that corneal biomechanics and total or corneal wavefront aberrations might be useful in the diagnosis of ectatic diseases; we did not evaluate this in our study. Further studies with a large number of patients and with controls composed of a relevant clinical population would be needed to better compare the effectiveness of different parameters in diagnosing early subclinical keratoconus.

In conclusion, in our study the recently developed multimetric D index, as a sole parameter, increased our detection rate of clinical keratoconus and subclinical keratoconus. However, the sensitivities of these parameters in diagnosing subclinical keratoconus, including the new D, are limited. These results suggest that new parameters with higher sensitivities must be developed to more effectively screen eyes in terms of their susceptibility to ectasia. Our results also suggest the importance of a comprehensive approach that includes the evaluation of topographic patterns to screen for early keratoconus.

WHAT WAS KNOWN

- Keratometric, pachymetric, and posterior elevation single-metric parameters can be used to diagnose forme fruste keratoconus.

WHAT THIS PAPER ADDS

- A recently introduced multimetric D index performed better than single-metric parameters in diagnosing early forme fruste keratoconus.
- Although the D index had a good specificity with the best cutoff level of 1.3, its sensitivity was limited.

REFERENCES

1. Alió JL, Muftuoglu O, Ortiz D, Pérez-Santonja JJ, Artola A, Ayala MJ, Garcia MJ, Castro de Luna G. Ten-year follow-up of laser in situ keratomileusis for myopia of up to −10 diopters. Am J Ophthalmol 2008; 145:46–54
2. Solomon KD, Fernández de Castro LE, Sandoval HP, Biber JM, Groat B, Neff KD, Ying MS, French JW, Donnenfeld ED, Lindstrom RL; for the Joint LASIK Study Task Force. LASIK world literature review: quality of life and patient satisfaction. Ophthalmology 2009; 116:691–701
3. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal refractive surgery. Ophthalmology 2008; 115:37–50
4. Wilson SE, Klyce SD. Screening for corneal topographic abnormalities before refractive surgery. Ophthalmology 1994; 101:147–152
5. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. Invest Ophthalmol Vis Sci 2010; 51:5546–5555. Available at: http://www.iovs.org/content/51/11/5546.full.pdf. Accessed October 19, 2014
6. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998; 42: 297–319. Available at: http://www.keratoconus.com/resources/Major+Review-Keratoconus.pdf. Accessed October 19, 2014
7. Rabinowitz YS, Nesburn AB, McDonnell PJ. Videokeratography of the fellow eye in unilateral keratoconus. Ophthalmology 1993; 100:181–186
8. Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes in unilateral keratoconus patients. Ophthalmology 2004; 111:440–446
9. Ambrósio R Jr, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. J Cataract Refract Surg 2006; 32:1851–1859. Available at: http://www.ic.unicamp.br/~wainer/cursos/2s2008/ia/ambrosio_ct_profile.pdf. Accessed October 19, 2014
10. Nilforoushan M-R, Speaker M, Marmor M, Abramson J, Tullo W, Morschauser D, Latkany R. Comparative evaluation of refractive surgery candidates with Placido topography, Orbscan II, Pentacam, and wavefront analysis. J Cataract Refract Surg 2008; 34:623–631
11. de Sanctis U, Loiacono C, Richiardi L, Turco D, Mutani B, Grignolo FM. Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus. Ophthalmology 2008; 115: 1534–1539
12. Ambrósio R Jr, Caiado ALC, Guerra FP, Louzada R, Sinha Roy A, Luz A, Dupps WJ, Belin MW. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. J Refract Surg 2011; 27:753–758. Available at: http://ascrs12.expoplanner.com/handouts_ascrs/000072_12386701_ART_Paper_JRS_2011.pdf. Accessed October 19, 2014
13. Belin MW, Khachikian SS. An introduction to understanding elevation-based topography: how elevation data are displayed – a review. Clin Exp Ophthalmol 2009; 37:14–29. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1442-9071.2008.01821.x/pdf. Accessed October 19, 2014
14. Muftuoglu O, Ayar O, Ozulken K, Ozyol E, Akıncı A. Posterior corneal elevation and back difference corneal elevation in diagnosing forme fruste keratoconus in the fellow eyes of unilateral keratoconus patients. J Cataract Refract Surg 2013; 39:1348–1357
15. Arbelaez MC, Versaci F, Vestri G, Barboni P, Savini G. Use of a support vector machine for keratoconus and subclinical keratoconus detection by topographic and tomographic data. Ophthalmology 2012; 119:2231–2238
16. Edwards M, McGhee CNJ, Dean S. The genetics of keratoconus. Clin Exp Ophthalmol 2001; 29:345–351
17. McClish DK. Analyzing a portion of the ROC curve. Med Decis Making 1989; 9:190–195
18. Schweitzer C, Roberts CJ, Mahmoud AM, Colin J, Maurice-Tison S, Kerautret J. Screening of forme fruste keratoconus with the Ocular Response Analyzer. Invest Ophthalmol Vis Sci 2010; 51:2403–2410. Available at: http://www.iovs.org/content/51/5/2403.full.pdf. Accessed October 19, 2014
19. Saad A, Gatinel D. Evaluation of total and corneal wavefront high order aberrations for the detection of forme fruste keratoconus. Invest Ophthalmol Vis Sci 2012; 53:2978–2992. Available at: http://www.iovs.org/content/53/6/2978.full.pdf. Accessed October 19, 2014

OTHER CITED MATERIAL

A. Belin MW, Khachikian SS. Keratoconus/ectasia detection with the Oculus Pentacam: Belin/Ambrósio enhanced ectasia display. In: New Advances and Technology With Pentacam. Wetzlar, Germany, Oculus Optikgeräte GmbH, 2008; 3–7. Available at: http://www.oculus.de/ru/downloads/dyn/oculus/presse/158/oculus_low_res.pdf. Accessed October 19, 2014

B. Ambrósio R Jr, "Defining the Risky Cornea With Enhanced Corneal Analysis Technology," presented at the XXXI Congress of the European Society of Cataract and Refractive Surgeons and the 4th Eurocornea Congress, Amsterdam, the Netherlands, October 2013. European Ophthalmology News October 2013, page 9. Available at: http://www.oculus.de/fileadmin/images/news_termine/European_Ophthalmology_Times_ESCRS2014.pdf. Accessed October 19, 2014

First author:
Orkun Muftuoglu, MD

Department of Ophthalmology, Medipol University, Istanbul, Turkey