Evolution Profiles of Different Corneal Parameters in Progressive Keratoconus

Joy Tellouck, MD, David Touboul, MD, PhD,* Marcony R. Santhiago, MD, PhD,‡ Laury Tellouck, MD,* Clement Paya, MD,* and David Smadja, MD*†*

Purpose: To analyze the evolution profiles of several corneal topographic and tomographic parameters in progressive keratoconus and compare them with the kinetics of evolution of anterior keratometry.

Methods: One hundred nine eyes of 55 patients were prospectively enrolled and followed up every 3 months for at least 1 year. Forty-five corneal parameters were measured at each visit using a combined Placido-based and dual Scheimpflug imaging system. Percentage of progression between each visit was calculated for each parameter and comparisons were tested between the different variables.

Results: At 1 year, 11% (12/109) of eyes progressed with an increase in maximum anterior keratometry of 1 D or more. Among these eyes, the posterior maximum keratometry and vertical corneal coma had a significantly higher percentage of progression ($P < 0.05$) than the maximum anterior keratometry, 5.9%, 27%, and 3.2%, respectively, and occurred significantly earlier than the modifications of the anterior keratometry, at the third-, sixth-, and 12th-month visits, for vertical corneal coma, posterior keratometry, and anterior keratometry respectively.

Conclusions: Modifications of the posterior surface and corneal vertical coma occurred earlier and were detectable before changes in the anterior keratometry readings in eyes with progressive keratoconus. These parameters may be relevant warning signs when monitoring progressive keratoconus.

Key Words: progressive keratoconus, monitoring, posterior cornea, dual Scheimpflug, topography, corneal coma

(*Cornea* 2016;35:807–813)

The monitoring of ectatic diseases over time [keratoconus (KC) and post-laser in situ keratomileusis (LASIK) ectasia] is a crucial issue because its progression naturally leads to loss of vision that could be halted otherwise by available treatments if appropriately recognized at early stages of progression.[1,2]

Although some variables have been suggested for monitoring KC progression,[3–5] there is still no consensus on the most appropriate clinical, morphological, or biomechanical parameter to track, to closely monitor the disease and detect the earliest manifestation of progression. Interestingly, most of the parameters used for the definition of progressive KC are based on modifications of the anterior surface (anterior keratometry and corneal astigmatism) and corneal thinning,[4–8] whereas it has been demonstrated over the past few years that changes of the posterior surface and corneal aberrations may be the first detectable manifestations of the ectatic diseases.[9–11] It seems therefore reasonable to question the use of anterior corneal parameters alone as the gold standard, to monitor the ectatic process and track the earliest sign of progression, although posterior surface modifications have been considered as a key parameter.

The objective of our study was to compare the evolution profiles of various corneal parameters using a combined Placido-dual Scheimpflug imaging system and to determine whether parameters other than the current gold standard [anterior maximum keratometry (AntKmax)] may be more appropriate to monitor the progression of KC.

METHODS

This prospective study was conducted at the University Hospital of Bordeaux, France, in the National Reference Center for Keratoconus and approved by the Institutional Review Board. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Subjects

A total of 109 eyes of 55 patients were prospectively enrolled in the study and imaged with the Galilei Dual Scheimpflug Analyzer system (Ziemer Ophthalmic Systems AG, Port, Switzerland) as part of their KC follow-up visits.

Eyes of patients who were referred to the National Reference Center for Keratoconus for mild to moderate KC were enrolled. KC was defined using previously described criteria[12,13]: eyes with slit lamp findings such as Vogt striae, Fleisher ring, scissoring on retinoscopy and/or topographic signs such as inferior–superior dioptric asymmetry greater than 1.4, inferior localized steepening, and skewing of the steepest radial axes above and below the horizontal meridian

Received for publication October 27, 2015; revision received January 20, 2016; accepted January 29, 2016. Published online ahead of print April 14, 2016.

From the *Anterior Segment and Refractive Surgery Unit, National Reference Center for Keratoconus, University Center Hospital of Bordeaux, Bordeaux, France; †Ophthalmology Department, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; and ‡Department of Ophthalmology, Federal University of Rio De Janeiro, Rio, Brazil.

Dr D. Smadja and M. R. Santhiago receive consulting fees from Ziemer, Inc. The other authors have no funding or conflicts of interest to disclose.

Reprints: David Smadja, MD, Ophthalmology Department, Tel Aviv Sourasky Medical Center, Tel Aviv 61000, Israel (e-mail: davidsmadj@hotmail.fr).

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 1. Demographic and Baseline Data in the Progressive and Nonprogressive KC Groups

	Nonprogressive KC (n = 97)			Progressive KC (n = 12)		
	Mean	SD	Range (Min; Max)	Mean	SD	Range (Min; Max)
Anterior Kmax, D	49.2	4.7	43.6; 53.5	50.1	4.8	44.4; 53.5
Posterior Kmax, D	−7.4	0.88	−6; −8.9	−7.5	0.9	−6.8; −8.8
Corneal vertical coma, μm	0.8	0.66	0.3; 2.2	0.8	0.7	0.4; 1.4

K, keratometry.

greater than 20°. Patients were asked to discontinue soft and rigid gas-permeable contact lenses, respectively, 1 and 2 weeks before the scheduled examination. Eyes that had already undergone a specific treatment for KC, such as intracorneal ring implantation or keratoplasty, as well as eyes with marginal pellucid degeneration and post-LASIK ectasia, measurements that did not satisfy the minimum quality required by the imaging system, or eyes with advanced KC with low potential of progression and/or poorly reliable topography were excluded from the study. For patients who became candidates for corneal collagen cross-linking over the course of the study because of documented progression, data were included until the last preoperative visit and then removed from the data analysis.

Study Protocol

All patients received detailed preoperative ophthalmic evaluation at their initial visit and at their sixth- and 12th-month visits, including uncorrected visual acuity, best spectacle-corrected visual acuity, manifest refraction, slit lamp examination, applanation tonometry, fundus examination, and a topo-tomographic evaluation using a combined Placido-dual Scheimpflug imaging system. Topo-tomographic evaluation was, however, performed every 3 months at each follow-up visit as part of a scheduled protocol for monitoring disease progression.

Dual Scheimpflug Analyzer System and Procedure

Measurements were performed with the Galilei Dual Scheimpflug Analyzer system (software version 5.2.1) according to the manufacturer's guidelines. The Galilei is a rotating Scheimpflug tomography–based device combining dual-channel Scheimpflug cameras and a Placido disk. Placido and Scheimpflug data are acquired simultaneously. Height data from the Scheimpflug images and slope data, converted into height data from the Placido, are merged to provide a surface fitted to the anterior corneal data, whereas posterior corneal surface data are measured using edge detection in images provided by the dual Scheimpflug system.

Simultaneously, the system allows for corneal aberration analysis separately from the aberrations of the lens and displays the total higher order corneal wave front aberrations calculated from the front and back surfaces.

Analyzed Parameters and Description

Forty-three parameters were extracted from the system and can be briefly described as followed:

1. Anterior and posterior curvature–based parameters: Kmax, directly recorded from the curvature map; simulated and mean keratometry readings over the center (0–4 mm), paracenter (4–7 mm), and periphery (7–10 mm); as well as the anterior inferior-superior (I-S) value.[12]
2. Anterior and posterior elevation–based parameters: Highest elevation value, elevation at the thinnest point, and elevation at the Kmax location, within the 8-mm-diameter zone, were measured with 2 different reference bodies: The best-fit sphere in float mode and the best-fit toric and aspheric body were also measured.[14]
3. Corneal wave front–based parameters: Root mean square (RMS) total corneal higher order aberrations from the third to the sixth order as well as the RMS spherical aberration Z (4,0), RMS vertical Z (3,−1) and horizontal Z (3,1) coma, and RMS total coma through a 6-mm pupil size were recorded from the wave front maps displayed in micronmeters.
4. Pachymetric (central and thinnest point) and biometric–based parameters (corneal and anterior chamber volume).

TABLE 2. Statistical Significance of the Change Between Baseline and Follow-up Visit in the Different Parameters Within the 2 Groups

	M3 (n = 109)		M6 (n = 103)		M9 (n = 97)		M12 (n = 95)	
Follow-up Visit	*P* in PG	*P* in NPG	*P* in PG	*P* in NPG	*P* in PG	*P* in NPG	*P* in PG	*P* in NPG
Anterior Kmax	0.24	0.4	0.25	0.4	0.2	0.5	**<0.01**	0.4
Posterior Kmax	0.78	0.6	**0.05**	0.4	**0.01**	0.4	**<0.01**	0.5
Vertical coma	**0.06**	0.3	**0.03**	0.2	**0.02**	0.3	**<0.01**	0.4

K, keratometry; M, month; n, number of eyes; NPG, nonprogressive group; PG, progressive group.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

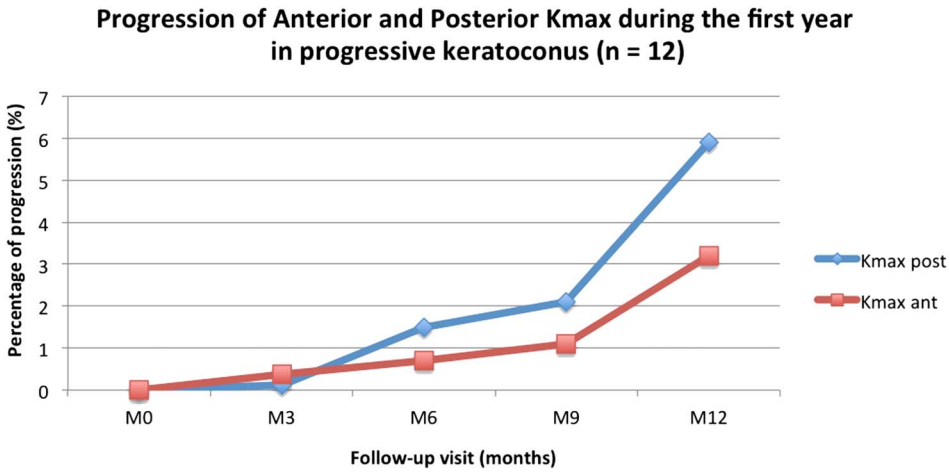

FIGURE 1. Evolution profile of anterior maximal keratometry and posterior maximal keratometry in progressive KC over the first year follow-up period.

Data Analyses and Statistics

Outcomes Measured

After 1-year follow-up, patients were divided into 2 groups: progressive KC, when an increase in Ant Kmax of at least 1 D was noted, or stable KC when no change or less than 1 D increase was noted. At each visit, the value of the change (Δ) and the percentage of progression (PP) were calculated for all the parameters analyzed. The PP between the inclusion visit and the follow-up visit was calculated as followed:

[(Value at follow-up visit X—Value at inclusion visit)/ Value at inclusion visit] × 100.

Step-by-Step Analysis

The first step involved comparing within each respective group (progressive and nonprogressive KC), changes and PPs at each visit, between the gold standard, the Ant Kmax, and the others variables. After this first step, we were able to identify in the progressive group if there were variables that underwent changes that were significantly greater and/or occurred significantly earlier than the changes noted in Ant Kmax. We then used this limited group of relevant variables in the second step and compared their changes throughout the year between the progressive and nonprogressive groups. Our intention was to ensure that these changes were not random and were statistically significantly different from the kinetics observed in the nonprogressive group. Finally, we performed in parallel, an additional analysis on 30 eyes to analyze the SDs of the measurements for this group of variables. Although already demonstrated in normal eyes,[15] eyes after refractive surgery,[16] and keratoconic eyes,[17] we considered this step necessary for verifying if the value of the changes experienced was greater than the SD of the measured variable. Therefore, measurements were taken 3 times at each visit, by the same operator, and the averaged value and SDs were recorded. The value of a change was considered reliable only if it was at least greater than twice the value of the SD of the parameter measured.

Statistics

All statistical analyses were performed with STATA (version stata9 software; StataCorp 2005). Normality in the data samples analyzed was confirmed by using the Kolmogorov–Smirnov test. Therefore, the Student *t* test was used for comparing the variables at different time points, with *P* value <0.05 chosen as the threshold of significance.

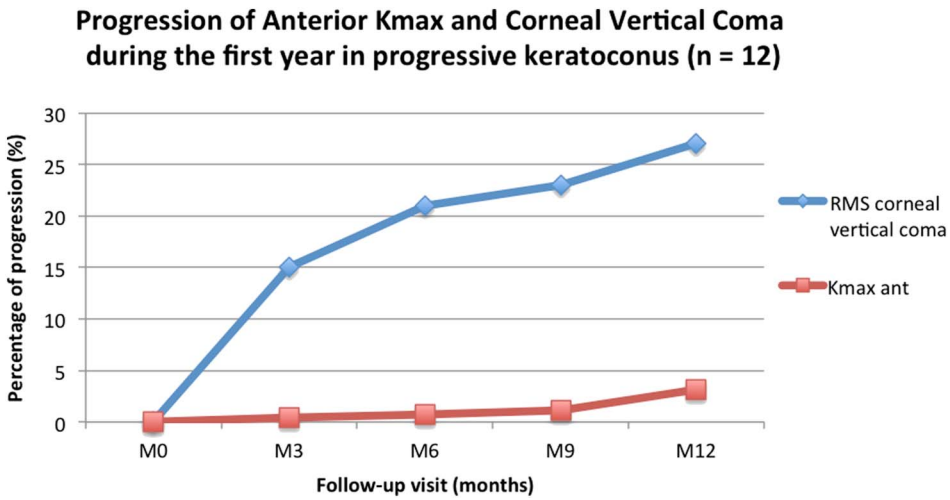

FIGURE 2. Evolution profile of anterior maximal keratometry and corneal vertical coma in progressive KC over the first year follow-up period.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

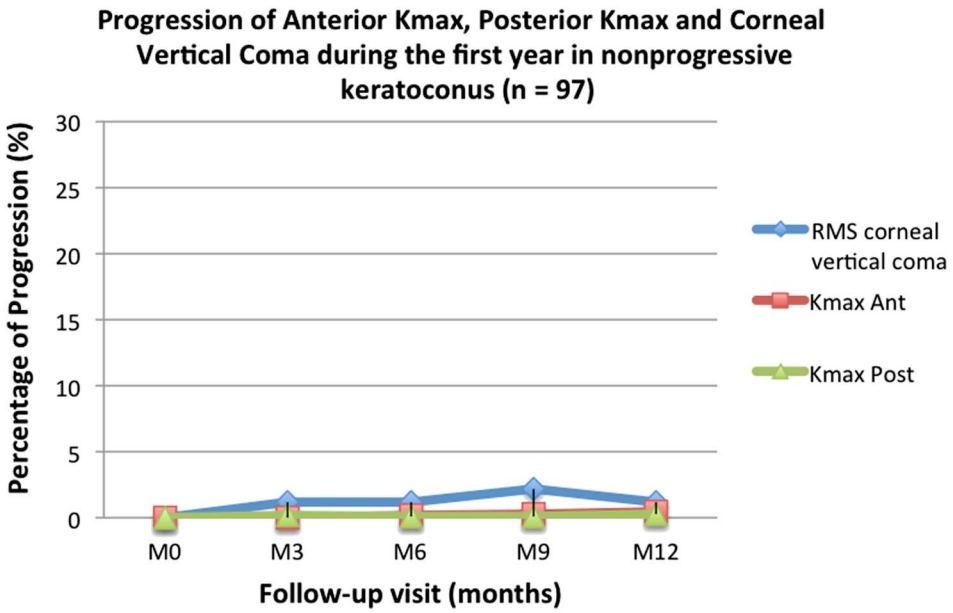

FIGURE 3. Evolution profile of anterior maximal keratometry, posterior maximal keratometry, and corneal vertical coma in nonprogressive KC over the first year follow-up period.

RESULTS

This study included 109 eyes with KC from 55 subjects, including 19 females and 36 males, which were retrospectively divided into 2 groups according to their evolution: progressive KC (n = 12; 11%) and stable KC (n = 97; 89%). The average age of all patients was 26.4 ± 4.8 years (range 18–33). Baseline data of the subjects by groups are summarized in Table 1. The 12 eyes that were documented with progression received a corneal cross-linking procedure over the period of the study (4, 3, and 5 eyes, respectively after the sixth-, ninth-, and 12th-month visit) and were excluded from the analysis afterward accordingly. Additionally, respectively, 6, 8, and 7 eyes were lost to follow-up and/or missed the sixth, ninth, and 12th visits (Table 2).

Identification of Potentially Relevant Variables in the Progressive Group

After comparing the changes in AntKmax with the changes experienced in the remaining 42 variables analyzed in the progressive group, only 2 variables, the posterior maximum keratometry (PostKmax) and the corneal vertical coma, were identified as potentially relevant because of the consistently different progression profiles. Their changes and PPs in the progressive group were both greater in magnitude than the changes noted in the AntKmax throughout the first year (Figs. 1, 2), whereas in the nonprogressive group, the kinetics of evolution had a similar profile between the 3 variables, with no significant difference observed at any time point (Fig. 3). Additionally, significant changes in the parameter were noted earlier in both vertical coma (at the third-month visit) and posterior K (at the sixth-month visit), than in anterior K (only at the 12th-month visit) as shown in Table 2.

Comparisons of the changes in AntKmax with those in PostKmax and vertical coma in the progressive group are summarized in Table 3.

Differences Between the Progressive and Nonprogressive Groups

Changes and PPs were statistically significantly different for the 3 variables between the progressive and nonprogressive groups; however, this difference between the 2 groups occurred significantly earlier in both vertical coma (third-month visit) and PostKmax (sixth-month visit), than in AntKmax (12th-month visit), as illustrated in Table 4.

TABLE 3. Comparison of the Percentage of Progression of the Anterior Kmax in Progressive and Nonprogressive KC with that in the Posterior Kmax and Corneal Vertical Coma: Statistical Significance at Different Time Points

	M3, % (*P*)		M6, % (*P*)		M9, % (*P*)		M12, % (*P*)	
Follow-up Visit	**PG (n = 12)**	**NPG (n = 97)**	**PG (n = 12)**	**NPG (n = 97)**	**PG (n = 12)**	**NPG (n = 97)**	**PG (n = 12)**	**NPG (n = 97)**
Anterior Kmax	0.4 (NA)	0.02 (NA)	0.7 (NA)	0.16 (NA)	1.1 (NA)	0.26 (NA)	3.2 (NA)	0.5 (NA)
Posterior Kmax	0.1 (0.2)	0.2 (0.4)	1.5 (0.17)	0.12 (0.6)	2.1 (0.18)	0.12 (0.6)	5.9 (**0.03**)	0.28 (0.5)
Vertical corneal coma	15 (<**0.01**)	1.2 (0.47)	21 (<**0.01**)	1.2 (0.2)	23 (<**0.01**)	2.2 (0.4)	27 (<**0.01**)	1.2 (0.5)

%, percentage of progression between baseline and the follow-up visit; K, keratometry; NA, not applicable; NPG, nonprogressive group; *P*, statistical significance of the difference between the percentage of progression of the anterior Kmax and the other variables posterior Kmax and vertical corneal coma; PG, progressive group.

Bold values indicate statistical significance.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 4. Comparison of the Changes and Percentage of Progression in 3 Relevant Corneal Parameters Between Progressive (n = 12) and Nonprogressive KC (n = 97)

	Anterior Kmax, D			Posterior Kmax, D			Vertical Corneal Coma, μm		
	ΔP ± SD (%)	ΔNP ± SD (%)	*P*	ΔP ± SD (%)	ΔNP ± SD (%)	*P*	ΔP ± SD (%)	ΔNP ± SD (%)	*P*
M3	0.23 ± 0.6 (0.4)	0.01 ± 0.5 (0.02)	0.22	0.01 ± 0.1 (0.1)	−0.02 ± 0.1 (0.2)	0.8	0.10 ± 0.18 (15)	0.01 ± 0.14 (1.2)	**0.03**
M6	0.3 ± 1.3 (0.7)	0.08 ± 0.6 (0.16)	0.09	−0.12 ± 0.1 (1.5)	−0.01 ± 0.1 (0.1)	**0.04**	0.14 ± 0.2 (21)	0.01 ± 0.1 (1.2)	**<0.01**
M9	0.5 ± 0.3 (1.1)	0.13 ± 0.6 (0.26)	0.08	−0.16 ± 0.1 (2.1)	−0.01 ± 0.1 (0.1)	**0.01**	0.16 ± 0.1 (23)	0.018 ± 0.13 (2)	**<0.01**
M12	1.6 ± 0.6 (3.2)	0.26 ± 0.5 (0.5)	**<0.01**	−0.48 ± 0.2 (5.9)	−0.02 ± 0.2 (0.3)	**<0.01**	0.22 ± 0.25 (27)	0.01 ± 0.2 (1.2)	**<0.01**

%, percentage of progression; K, keratometry; NP, nonprogressive KC; P, progressive KC; *P*, statistical significance of the comparison between the progressive and nonprogressive group; Δ, Mean change from the inclusion (in diopters or micronmeters).

Additionally, no significant changes between baseline and successive follow-up visits were noted in any of the 3 parameters within the nonprogressive group (Table 2).

SD Analysis for PostKmax and Vertical Coma

The magnitude of changes in PostKmax and vertical coma in the progressive group was found to be more than twice the magnitude of their SDs. Mean values and SDs for AntKmax, PostKmax, and vertical coma are summarized in Table 5.

DISCUSSION

Although early diagnosis of KC has been extensively studied,[9,10,17] because it allows identification of eyes with a potentially progressive corneal disorder, interestingly, the optimal approach for monitoring ectatic disease and detecting the first warning signs of progression has still not been established. Therefore, the aim of this study was to analyze the evolution profiles of different corneal parameters in both progressive and nonprogressive KC, to identify variables that may be subsequently considered as potential warning signs of a progression state.

Although a current leading hypothesis is that KC may be first detectable at the posterior surface,[9,10,14,18,19] in part due to the potential of corneal epithelium to smooth corneal anterior topographic irregularities,[20,21] surprisingly, the gold standard to define a progressive state and to recommend a cross-linking procedure to halt the disease still remains the anterior keratometric changes.[1,7] In the present study, after 1 year of follow-up, 4 major findings were observed: first, 2 variables, the PostKmax and the corneal vertical coma, were considered of particular interest for monitoring compared with all other variables included in the analysis, because their evolution profiles were consistently different in magnitude and kinetics of changes, than what was observed over the year with AntKmax in progressive KC (Figs. 1, 2). Second, the PP noted in both posterior curvature and vertical coma, in progressive KC was greater than that in the anterior keratometry already from the sixth month visit, although at this time point, it was statistically significantly greater only in the vertical coma (Table 3). Third, the onset of these modifications occurred significantly earlier in the posterior surface and vertical coma than in the anterior surface, with significant changes occurring in the progressive group, at the third-, sixth-, and 12th-month visits, respectively, for the vertical coma, posterior curvature, and anterior curvature (Table 2). Finally, and to further support the reliability of these findings in the progressive group, the evolution profiles (magnitudes and PPs) of the above-mentioned variables were statistically significantly different from the values noted in the nonprogressive group, respectively from the third- and sixth-month visit, in the vertical coma and posterior curvature (Table 4). No statistically significant differences were noted between the posterior curvature changes, the vertical coma, and the anterior curvature in the nonprogressive group. Additionally, the magnitude of these changes were also considered reliable and not random, because these values were at least twice greater than the magnitude of their SDs when tested independently (Table 5).

TABLE 5. Repeatability and Reliability of the Measurements of the Variables Selected for KC Monitoring With the Placido-Dual Scheimpflug Analyzer in KC, Normal Eyes, and Post–Refractive Surgery

	Anterior Kmax, D	Posterior Kmax, D	Corneal Vertical Coma, μm
Current study in KC eyes (n = 30)			
Mean	49.35	−7.54	1.38
Mean of SDw	0.31	0.05	0.08
SD of the SDw	0.31	0.06	0.06
Increase factor with the magnitude of the change at 12 mo	5.1	9.6	2.75
Yagci et al[17]			
SDw in KC (n = 88)	0.37	NA	NA
SDw in normal eyes (n = 62)	0.10	NA	NA
Wang et al[15]			
SDw in normal eyes (n = 20)	0.09	0.03	0.08
Savini et al[16]			
SDw in post–refractive surgery (n = 15)	0.12	0.03	NA

Increase factor, ratio between the magnitude of the change in the parameter at 12 months and the magnitude of its SD when tested.
K, keratometry; SDw, within-subject SD.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

These results, although observed in already labeled KC patients, are consistent with the recent findings that point out the key role of posterior surface and corneal coma modifications in the diagnosis of early KC. Although generally accepted for screening out ectasia-susceptible corneas, surprisingly, none of these indices have ever been used for monitoring the ectatic disorders and tracking down the earliest signs of progression. With this study, we now have demonstrated that significant modifications of the posterior surface and vertical coma in progressive KC were detectable before significant changes in the anterior surface keratometry readings. However, a larger sample size followed up for a longer period would still be needed in order to identify reliable cutoff values of magnitude change for drawing new recommendations when considering a cross-linking procedure in suspicious progression. Nevertheless, although observed over a moderate sample size, interestingly, our rate of progression in this study was slightly lower than what were reported in other studies. One of the reasons for this discrepancy likely resides in the difference between methodologies used in the studies, including criteria used to define progression, stage of KC observed at baseline, follow-up, and sample age. Choi and Kim[22] reported an average progression of 26.5% at 3.5 years, using an increase of 1.5 D in central keratometry as the criterion for progression, but did not report the rate at 1-year follow-up. Similarly, Li et al.[23] reported in a longitudinal study a rate of 29.4% progression from clinically normal fellow eyes to KC within the first 6 years. However, Léoni-Mesplié et al[24] reported within the first year, a progression rate similar to that reported by us using the same criteria (increase in Kmax >1 D), but significantly greater in children than in adults, 21% and 13%, respectively, thus also highlighting the influence of age on the potential of progression.

Although it has curiously not yet influenced the recommendations for closely monitoring KC, progressive changes at the posterior surface are already well identified as a potential warning sign and indirect sign of corneal weakening.[25,26] Similar conclusions could be drawn from the present finding, and the intervention of cross-linking discussed whenever a progressive change at the posterior surface and/or in the vertical coma is consistently observed over 3 successive follow-up visits, even before modifications of the anterior surface are noted. In order to go even further into the nomenclature, a new recognized and well-accepted entity has been named "suspect keratoconus" when the cornea shares similarities with an ectatic cornea, including posterior surface asymmetry and higher coma values than normal.[19,27,28] This label ensures that we should be careful before considering a LASIK procedure in such corneas and that close monitoring with or without subsequent photorefractive keratectomy should probably be the recommended approach in those cases.[29,30]

Therefore, in a similar way, "suspicious progression" should be diagnosed and monitoring frequency readjusted more closely to discuss earlier the need for cross-linking, whenever progressive changes of the posterior surface or vertical coma are observed before reaching the generally accepted threshold of anterior keratometry change that defines the progressive state.

REFERENCES

1. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135:620–627.
2. Bedi R, Touboul D, Pinsard L, et al. Refractive and topographic stability of Intacs in eyes with progressive keratoconus: five-year follow-up. *J Refract Surg.* 2012;28:392–396.
3. Kanellopoulos AJ, Asimellis G. Revisiting keratoconus diagnosis and progression classification based on evaluation of corneal asymmetry indices, derived from Scheimpflug imaging in keratoconic and suspect cases. *Clin Ophthalmol.* 2013;7:1539–1548.
4. Brown SE, Simmasalam R, Antonova N, et al. Progression in keratoconus and the effect of corneal cross-linking on progression. *Eye Contact Lens.* 2014;40:331–338.
5. Belin MW. Tomographic parameters for the detection of keratoconus: suggestions for screening and treatment parameters. *Eye Contact Lens.* 2014;40:326–330.
6. Lamy R, Netto CF, Reis RG, et al. Effects of corneal cross-linking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. *Cornea*. 2013;32:591–596.
7. Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with ribovlin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg.* 2008;34:796–801.
8. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg.* 2011;37:149–160.
9. Smadja D, Touboul D, Cohen A, et al. Detection of subclinical keratoconus using an automated decision tree classification. *Am J Ophthalmol.* 2013;156:237–246.
10. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. *Invest Ophthalmol Vis Sci.* 2010;51:5546–5555.
11. Bühren J, Kühne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. *Am J Ophthalmol.* 2007;143:381–389.
12. Rabinowitz Y. Keratoconus. *Surv Ophthalmol.* 1998;42:297–319.
13. Zadnik K, Barr JT, Edrington TB, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Invest Ophthalmol Vis Sci.* 1998;39:2537–2546.
14. Smadja D, Santhiago MR, Mello GR, et al. Influence of the reference surface shape for discriminating between normal corneas, subclinical keratoconus, and keratoconus. *J Refract Surg.* 2013;29:274–281.
15. Wang L, Shirayama M, Koch DD. Repeatability of corneal power and wavefront aberration measurements with a dual-Scheimpflug Placido corneal topographer. *J Cataract Refract Surg.* 2010;36:425–430.
16. Savini G, Carbonelli M, Barboni P, et al. Repeatability of automatic measurements performed by a dual Scheimpflug analyzer in unoperated and post-refractive surgery eyes. *J Cataract Refract Surg.* 2011;37:302–309.
17. Yagci R, Kulak AE, Güler E, et al. Comparison of anterior segment measurements with a dual Scheimpflug Placido corneal topographer and a new partial coherence interferometer in keratoconic eyes. *Cornea.* 2015;34:1012–1018.
18. Bühren J, Kook D, Yoon G, et al. Detection of subclinical keratoconus by using corneal anterior and posterior surface aberrations and thickness spatial profiles. *Invest Ophthalmol Vis Sci.* 2010;51:3424–3432.
19. Arbelaez MC, Versaci F, Vestri G, et al. Use of a support vector machine for keratoconus and subclinical keratoconus detection by topographic and tomographic data. *Ophthalmology.* 2012;119:2231–2238.
20. Touboul D, Trichet E, Binder PS, et al. Comparison of front-surface corneal topography and Bowman membrane specular topography in keratoconus. *J Cataract Refract Surg.* 2012;38:1043–1049.
21. Gatinel D, Racine L, Hoang-Xuan T. Contribution of the corneal epithelium to anterior corneal topography in patients having myopic photorefractive keratectomy. *J Cataract Refract Surg.* 2007;33:1860–1865.
22. Choi JA, Kim MS. Progression of keratoconus by longitudinal assessment with corneal topography. *Invest Ophthalmol Vis Sci.* 2012;53:927–935.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

23. Li X, Rabinowitz YS, Rasheed K, et al. Longitudinal study of the normal eyes in unilateral keratoconus patients. *Ophthalmology*. 2004; 111:440–446.
24. Léoni-Mesplié S, Mortemousque B, Touboul D, et al. Scalability and severity of keratoconus in children. *Am J Ophthalmol.* 2012;154:56–62.
25. Smadja D, Santhiago MR, Mello GR, et al. Response of the posterior corneal surface to myopic laser in situ keratomileusis with different ablation depths. *J Cataract Refract Surg.* 2012;38:1222–1231.
26. Roberts CJ, Dupps WJ. Paired versus unpaired significance testing: how improper statistical analysis altered interpretation of posterior surface changes after LASIK. *J Cataract Refract Surg.* 2014;40:858–861.
27. Klyce SD. Chasing the suspect: keratoconus. *Br J Ophthalmol.* 2009;93: 845–848.
28. Jafri B, Li X, Yang H, et al. Higher order wavefront aberrations and topography in early and suspected keratoconus. *J Refract Surg.* 2007;23: 774–781.
29. Guedj M, Saad A, Audureau E, et al. Photorefractive keratectomy in patients with suspected keratoconus: five-year follow-up. *J Cataract Refract Surg.* 2013;39:66–73.
30. Randleman JB, Trattler WB, Stulting RD. Validation of the Ectasia Risk Score System for preoperative laser in situ keratomileusis screening. *Am J Ophthalmol.* 2008;145:813–818.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.