Vector Analysis of Evolutive Corneal Astigmatic Changes in Keratoconus

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PURPOSE. To evaluate by vector analysis the corneal astigmatic changes occurring in keratoconic corneas during a 3-year follow-up and to determine the relationship between these changes and other clinical changes.

METHODS. Keratoconic eyes ($n = 114$) of 75 patients ranging in age from 14 to 70 years were retrospectively reviewed in four different centers. In all cases, a 3-year follow-up was completed after the diagnosis of keratoconus. Visual, refractive, keratometric, aberrometric, internal astigmatism (IA), and pachymetric changes were evaluated during the follow-up. In addition, corneal astigmatic changes were evaluated by examining the following parameters, using a modification of the Alpins vectorial method: evolutive astigmatism (EA) and angle of error (AE).

RESULTS. An increase in the magnitude of refractive ($P = 0.02$) and corneal astigmatism ($P = 0.05$) was found. The mean magnitude of EA was 1.21 ± 0.97 D at 3 years, with no significant changes at each annual visit ($P \geq 0.52$). Mean absolute AE increased significantly by the end of the follow-up ($P < 0.01$). Absolute AE and the increase in corneal astigmatism were found to correlate at 2 years ($r = 0.675$, $P < 0.01$). This correlation became poorer at 3 years ($r = 0.352$, $P = 0.02$). The magnitude of the EA was also found to be significantly correlated with central corneal thinning ($r = -0.441$, $P = 0.02$). Multiple regression analysis revealed that the magnitude of EA at 3 years correlated significantly with the baseline sphere and IA ($R^2 = 0.86$, $P < 0.01$).

CONCLUSIONS. Corneal vector astigmatic changes are related to some signs of keratoconus progression and are therefore predictive. (*Invest Ophthalmol Vis Sci.* 2011;52:4054–4062) DOI:10.1167/iovs.10-6856

Keratoconus is an ectatic corneal disorder characterized by progressive corneal thinning that results in corneal protrusion, irregular astigmatism, and decreased vision.[1] Several factors have been found to be associated with the progression of this corneal condition, such as changes in irregular astigmatism (Fourier series harmonic analysis),[2,3] the magnitude of the corneal cylinder at baseline,[2,4] severe and constant eye rubbing,[5–7] changes in inferior corneal steepening,[5] changes in apex location,[6] the age at presentation,[4–6,8–10] the presence of corneal scarring at diagnosis,[6] Snellen acuity at baseline,[4,9] manifest astigmatism[10] at baseline, and racial group.[4] Predictive models for the probability of keratoconus progression or the need for keratoplasty according to the clinical conditions at diagnosis have been defined in several studies.[4,10,11] All have demonstrated that the progression of keratoconus is a multifactorial process that depends on several entities or factors.

From a clinical point of view, several signs are indicators of the progression of this disease, such as the presence of corneal steepening with time, corneal thinning, or an increase in corneal aberrations.[2,3,7,9,12–15] In addition, an increase in corneal astigmatism has been found to be a clinical sign of the progression of this ectatic disease.[2,9,13,14] However, all studies about changes in corneal astigmatism in keratoconus due to the progression of the disease have been focused on the analysis of changes in the magnitude of astigmatism, but not in its axis. It should be remembered that astigmatism is a vectorial variable and that it has an associated magnitude and an axis. The vectorial character of astigmatism should be considered if a precise and complete analysis of corneal astigmatic changes due to keratoconus progression is undertaken. The Alpins method is a vectorial analysis that allows assessment of the effectiveness of a specific astigmatic treatment.[16,17] It considers the magnitude and orientation of astigmatism. Three fundamental vectors are used in this analysis: target-induced astigmatism (TIA), surgically induced astigmatism (SIA), and difference vector (DV).[16,17] The various relationships among these three vectors provide a complete description of the astigmatic correction achieved with a specific modality of treatment. This methodology has never been used for the evaluation of corneal astigmatic changes in keratoconus. For this purpose, the TIA could be assumed to be 0, and the SIA would then be the real astigmatic change induced by the evolution of the corneal disease. The information obtained with this vectorial analysis would be of great value in defining predictive factors for those cases experiencing a significant vector astigmatic change with time and for assessing the complex change that happens in the evolution of keratoconus.

The purpose of the present study was to analyze, by means of the Alpins vectorial method, the corneal astigmatic changes that occurred in keratoconic corneas during a 3-year follow-up and to determine the relationship between these changes and all other changes normally associated with the progression of the disease, such as age, curvature, and pachymetric or corneal aberrometric variations.

METHODS

Patients

This study comprised 114 consecutive keratoconic eyes of 75 patients ranging in age from 14 to 70 years. All these cases were included after a retrospective review of all cases with the diagnosis of keratoconus during the period 2001 to 2009 in four different Spanish ophthalmology centers: Vissum Alicante, Vissum Madrid, University Clinic of the University of Navarra, and the Barraquer Ophthalmology Center in Barcelona. Forty-eight (64.0%) patients were male and 27 (36.0%) were female. The diagnosis of keratoconus was based on corneal topography and slit lamp observation. In all cases, clinical findings characteristic of keratoconus were evident: corneal topography revealing an asymmetric bowtie pattern, with or without skewed axes, and at least one keratoconus sign on slit lamp examination, such as stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae, or anterior stromal scar.[1] The Amsler-Krumeich classification system was used to grade keratoconus.[18,19] The inclusion criteria were keratoconus with no previous ocular surgery and a completed 36-month follow-up, with visual, refractive, topographic, and pachymetric data at baseline and all subsequent yearly visits. The exclusion criteria were the indication and performance of corneal surgery during the follow-up, the presence of any other active ocular disease, and withdrawal from the study during the 3-year follow-up (no attendance at one of the yearly visits). A total of 39 bilateral cases were included in the analysis after it was confirmed that poor correlations of visual, refractive, topographic, aberrometric, and biomechanical data were present between the right and left eyes (asymmetric cases). Consent to include clinical information in scientific studies was taken from all the participating patients during the follow-up, in accordance with the Declaration of Helsinki. In addition, ethics committee approval was obtained from our institution for this investigation.

Study Design

The study was a retrospective, consecutive, multicenter, observational, noncomparative examination of a series of cases.

Examination Protocol

The follow-up consisted of a baseline visit and yearly visits for 3 years. Therefore, four reviews were performed in all cases: at baseline and at 1, 2, and 3 years. All visits included a comprehensive examination with the following tests: logMAR uncorrected distance visual acuity (UDVA), logMAR corrected distance visual acuity (CDVA), manifest refraction (sphere and cylinder), slit lamp biomicroscopy, Goldmann tonometry, fundus evaluation, ultrasonic pachymetry (DHG500 US pachymeter; DHG Technology Inc, Exton, PA), and corneal topographic analysis. As topographic data were collected from four different centers, two different corneal topography systems were used for corneal examination: the CSO (CSO, Firenze, Italy) and the Orbscan IIz (Bausch & Lomb, Rochester, NY). The first device is a Placido-based system, and the second is a combined scanning-slit and Placido-disc topography system. Although the agreement between these specific devices has not been reported, Orbscan and Placido-based devices have been shown to provide similar accuracy and precision on calibrated spherical test surfaces.[20] To avoid the introduction of additional variability and potential bias, only keratoconus cases evaluated with the same topographic device during all follow-up visits were included in the current retrospective analysis. This was considered to be an additional exclusion criterion for the study. The following corneal topographic parameters were recorded and analyzed in all cases: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2), mean corneal power for the 3-mm central zone (KM), corneal astigmatism for the 3-mm central zone (AST; calculated as the difference between K2 and K1), mean asphericity for a corneal area 4.5 mm in diameter (Q45), and mean asphericity for a corneal area 8 mm in diameter (Q8).

The patients who were wearing contact lenses for the correction of the refractive error were instructed to discontinue their use for at least 2 weeks before each examination for soft contact lenses and at least 4 weeks before each examination for rigid gas-permeable contact lenses.

Corneal Aberrometry. Corneal aberrometry was recorded and analyzed only in those patients examined with the CSO topography system (36 eyes), because this device was the only one with the capability of calculating this specific information directly. It analyzes a total of 6144 corneal points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33 and an outer radius of 10 mm, with respect to the corneal vertex. The software of the CSO (EyeTop2005; CSO) automatically performs the conversion of corneal elevation profile into corneal wavefront data using the Zernike polynomials with an expansion up to the seventh order. In this study, the aberration coefficients and root mean square (RMS) values were calculated for a 6-mm pupil in all cases. The corresponding RMS values were calculated for the following types of aberrations: higher order, primary coma (computed for the Zernike terms $Z_3{}^{\pm1}$), comalike (computed for third, fifth, and seventh order Zernike terms), spherical-like (computed for fourth and sixth order Zernike terms), and higher order residual (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration). The corresponding Zernike coefficient for primary spherical aberration ($Z_4{}^0$) was also reported with its sign.

Internal Astigmatism Calculation. Changes in internal astigmatism (IA) were also investigated during the follow-up. This parameter was calculated on computer as the vectorial difference between refractive (calculated to the corneal plane) and corneal astigmatism[16,21] (ASSORT refractive surgery planning and outcomes analysis; Assort Pty. Ltd., Cheltenham, VIC, Australia) and the Alpins guidelines for the calculation.[16,21–23] The IA was equivalent to the combination of the toric components of the crystalline lens and the posterior corneal surface.[22,23]

Vector Analysis of Corneal Astigmatic Changes. As mentioned, the Alpins method of vector analysis was used to evaluate the corneal astigmatic changes[16,17] occurring during a 3-year follow-up period. All calculations were performed with software that is especially designed for Alpins vectorial analysis (Assort Pty. Ltd.). For the purpose of the present study, the TIA was considered to have a magnitude of 0, and then the SIA was calculated. This vector was renamed EA instead of SIA, because the effect of a specific surgical procedure was not being evaluated. This vector represents the real astigmatic change induced by the evolution of the corneal disease in the period analyzed. As the TIA vector was 0, the DV, defined as the additional astigmatic change that would enable achieving the intended target (TIA = 0, no change), was equivalent in magnitude to the EA vector in all cases, but with an axis 90° away from the EA axis, and therefore it was not included in the analysis. The angle of error (AE), defined as the angle described by the axes of the TIA and EA vectors, was also calculated in all cases. It represents a misalignment in relation to the baseline conditions of the induced corneal astigmatism with time.

Statistical Analysis

The normality of all data samples was first checked by means of the Kolmogorov-Smirnov test. When the use of parametric statistics was possible, the Student's *t*-test for paired data was performed for all parameter comparisons between consecutive visits of the follow-up, whereas the Student's *t*-test for unpaired data was performed to compare data from specific groups (contact lens wear or not, more or less advanced eye). When the use of parametric statistics was not possible, the Wilcoxon rank sum test was applied to assess the significance of differences between consecutive visits, and the Mann-Whitney test was performed for the comparison between independent groups, using the same level of significance in all cases ($P < 0.05$; all calculations performed with SPSS, ver. 15.0 for Windows; SPSS, Chicago, IL).

Correlation coefficients (Pearson or Spearman depending on whether the normality condition could be assumed) were used to

assess the correlation between different variables. In addition, a multiple regression analysis was performed using the backward elimination method with the purpose of obtaining a mathematical expression relating the magnitude of EA at 3 years of follow-up and different clinical parameters (visual acuity, refraction, keratometry, corneal astigmatism, and pachymetry) at the baseline conditions. The assumptions of all linear models were evaluated by analyzing residuals, normality of unstandardized residuals (homoscedasticity), and Cook's distance to detect influential points or outliers. In addition, the lack of correlation between errors and multicollinearity was assessed by means of the Durbin-Watson test and calculation of the collinearity tolerance and the variance inflation factor (VIF), respectively.

Furthermore, a ROC (receiver operating characteristic) curve analysis for the EA and AE during the first year of the follow-up was performed to obtain their critical values (cutoff values), allowing the detection of a visual loss during the complete 3-year follow-up (loss of CDVA). These cutoff values corresponded with the points of the curve with the highest accuracy associated (minimal false-negative and -positive results). In addition, the area under the ROC curve, a measure of test accuracy, was calculated. An area of 1 represents a perfect test, while an area of 0.5 represents an unusable test. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test. Specifically, this means that the test is able to identify more true positives while minimizing the number of false positives.

RESULTS

The contribution of the four participating centers to the present study was as follows: 37 eyes from Vissum Alicante, 12 eyes from Vissum Madrid, 37 eyes from the University of Navarra, and 28 eyes from the Barraquer Ophthalmology Center. The study included 53 (46.5%) right eyes and 61 (53.5%) left eyes. Cone opacity was observed in six (5.3%) eyes. According to the Amsler-Krumeich grading system, 86 (75.4%) eyes had a grade 1; 19 (16.7%), grade 2; 4 (3.5%), grade 3; and 5 (4.4%), grade 4. Statistically significant differences in cylinder ($P = 0.03$; mean $\pm$ SD, less advanced -1.81 ± 1.49, more advanced -3.11 ± 2.80) and CDVA ($P = 0.02$; mean $\pm$ SD; less advanced, 0.11 ± 0.24; more advanced, 0.23 ± 0.29) were found between the more and the less advanced keratoconic eyes in each bilateral case included in the present study. In addition, significant differences in KM ($P = 0.01$; mean $\pm$ SD; less advanced, 45.59 ± 2.24; more advanced, 47.53 ± 3.60), IA ($P = 0.01$; mean $\pm$ SD; less advanced, 1.43 ± 1.23; more advanced, 2.62 ± 2.12) and corneal comalike aberrations ($P = 0.04$; mean $\pm$ SD; less advanced, 1.28 ± 0.85; more advanced, 2.01 ± 1.17) were detected between the more and less advanced keratoconic eyes in bilateral cases. The mean age of the sample was 37.30 years (SD 13.26; Fig. 1).

Table 1 shows a summary of the visual, refractive, corneal topographic, pachymetric, IA, and tonometry data of the sample of keratoconic eyes analyzed in the present study.

Visual and Refractive Changes

No statistically significant changes in the magnitude of the manifest sphere were detected during the follow-up ($P \geq 0.35$, Wilcoxon test). However, a significant increase in the magnitude of the refractive cylinder in absolute terms was found when the baseline and 3-year conditions were compared ($P = 0.02$, Wilcoxon test). Figure 2 summarizes the evolution of changes in sphere and cylinder during the follow-up. No significant changes in CDVA were observed during the follow-up ($P \geq 0.44$, Wilcoxon test).

Corneal Topographic and Aberrometric Changes

A statistically significant increase in K2 ($P = 0.02$, Wilcoxon test) and KM ($P = 0.02$, Wilcoxon test) was detected at the end
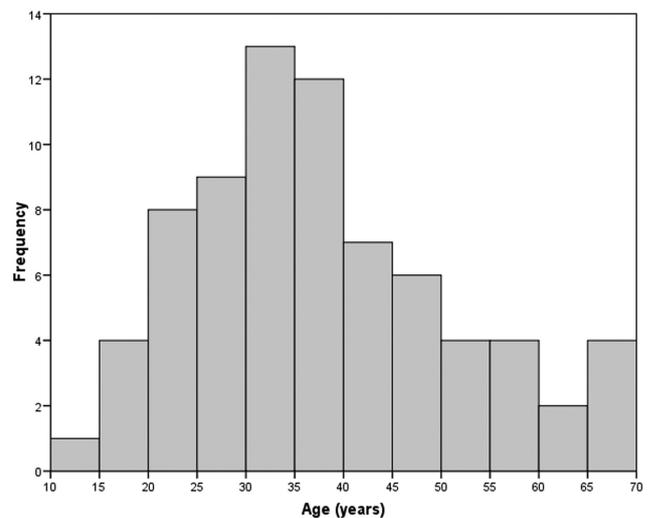

FIGURE 1.   Distribution of age of the eyes.

of the follow-up. Specifically, an increase of 0.62 D on average in the K2 reading was observed during the last year of the follow-up (2–3 years; $P = 0.03$, Wilcoxon test). Figure 3 shows the evolution of changes in keratometric readings during the follow-up. As shown, the central cornea became steeper with time, with the largest change occurring in K2 between the second and third year of follow-up ($P = 0.03$, Wilcoxon test). Regarding central corneal astigmatism, an increase in the limit of statistical significance was observed between the second and third year of follow-up ($P = 0.05$, Wilcoxon test). At 3 years, the mean change in central corneal astigmatism was 0.31 D (SD 1.03). Furthermore, no statistically significant changes in corneal asphericity (Q45 and Q8) were detected in any interval of the 3-year follow-up ($P \geq 0.26$). In addition, 42.1% (48) of eyes experienced an increase in KM or AST larger than 0.5 D during the follow-up. AST increased >0.5 D in 28 (24.6%) eyes.

Table 2 summarizes the evolution of all the aberrometric coefficients evaluated. As shown, a significant change in the primary spherical aberration toward to a more negative value was observed (preop–3 years; $P = 0.01$, Wilcoxon test), especially during the second year of the follow-up (1–2 years; $P = 0.03$, Wilcoxon test). Increases in residual (2–3 years; $P = 0.23$, Wilcoxon test), spherical-like (2–3 years; $P = 0.14$, Wilcoxon test), and comalike (2–3 years; $P = 0.22$, Wilcoxon test) RMS values were observed at the end of the follow-up, but these changes did not reach statistical significance.

Pachymetry and IA Changes

A slight central thinning of the cornea was observed at the end of the follow-up, but the change did not reach statistical significance (2–3 years; $P = 0.33$, paired Student's t-test). Regarding the IA, no significant changes were detected ($P \geq 0.26$, Wilcoxon test), although a nonsignificant trend toward an increase was found at the end of the follow-up ($P = 0.26$, Wilcoxon test).

Vector Analysis of Corneal Astigmatic Changes

The mean magnitude of EA was 1.55 (SD 3.92), 1.42 (SD 1.74), and 1.21 (SD 0.97) at 1, 2 and 3 years of the follow-up, respectively. Changes between annual visits in this parameter were not statistically significant (1–2 years, $P = 0.52$; 2–3 years, $P = 0.90$, Wilcoxon test). Figure 4 shows the distribution of the EA vector in the analyzed sample of keratoconic eyes. Great variability in the orientation and magnitude of this vector was observed. Large changes in the magnitude of the

TABLE 1. Summary of Visual, Refractive, Corneal Topographic, Pachymetric, and Tonometric Data

Parameter	Initial Examination	12-Month Examination	24-Month Examination	36-Month Examination	*P*
Manifest refraction					
Sphere, D	−2.25 (4.65)	−2.40 (5.07)	−2.38 (4.51)	−2.43 (5.11)	0.41
	−0.75 (−23.00 to + 6.00)	−1.00 (−24.00 + 7.00)	−1.50 (−24.00 to + 6.00)	−0.88 (−24.00 to + 3.50)	
Cylinder, D	−2.83 (2.37)	−2.82 (2.24)	−2.88 (2.19)	−3.71 (2.54)	0.02
	−2.00 (−12.00 to 0.00)	−2.25 (−11.00 to 0.00)	−2.25 (−12.00 to 0.00)	−3.00 (−9.00 to 0.00)	
CDVA, log MAR	0.18 (0.24)	0.16 (0.26)	0.17 (0.28)	0.16 (0.22)	0.11
	0.10 (−0.10 to 1.30)	0.06 (−0.08 to 1.40)	0.08 (−0.10 to 1.78)	0.10 (−0.08 to 1.78)	
Central keratometry					
K, D	45.39 (3.09)	45.29 (3.15)	45.74 (3.15)	45.20 (3.23)	0.18
	45.00 (40.70 to 55.75)	44.88 (40.10 to 57.61)	45.25 (40.05 to 56.00)	44.48 (40.35 to 56.00)	
K2, D	48.75 (4.53)	48.54 (4.66)	49.16 (4.90)	48.94 (4.15)	0.02
	47.89 (41.88 to 71.15)	47.85 (41.32 to 74.26)	47.85 (42.90 to 72.08)	47.90 (41.36 to 72.08)	
KM, D	47.07 (3.66)	46.92 (3.72)	47.45 (3.87)	47.07 (3.55)	0.02
	46.00 (41.30 to 62.30)	46.30 (41.16 to 65.94)	46.53 (42.20 to 63.25)	46.40 (41.30 to 63.25)	
AST, D	3.36 (2.55)	3.25 (2.81)	3.42 (2.79)	3.74 (2.21)	0.12
	2.68 (0.00 to 17.71)	2.54 (0.00 to 16.65)	2.65 (0.22 to 17.67)	3.09 (0.12 to 17.67)	
Corneal asphericity					
Q45	−0.54 (1.33)	−0.42 (1.29)	−0.47 (1.14)	−0.34 (1.10)	0.40
	−0.23 (−8.55 to 0.89)	−0.15 (−8.77 to 1.01)	−0.20 (−6.53 to 0.92)	−0.11 (−5.47 to 0.72)	
Q8	−0.39 (0.55)	−0.42 (0.66)	−0.35 (0.54)	−0.33 (0.54)	0.55
	−0.21 (−2.77 to 0.39)	−0.21 (−3.23 to 0.39)	−0.21 (−2.54 to 0.51)	−0.26 (−2.10 to 0.80)	
IA, D	2.39 (2.65)	2.18 (2.58)	2.44 (2.31)	2.57 (1.81)	0.50
	1.52 (0.12 to 16.14)	1.50 (0.10 to 15.33)	1.89 (0.02 to 15.17)	2.32 (0.12 to 15.17)	
Central pachymetry, μm	475.7 (66.2)	464.3 (73.9)	472.8 (73.0)	462.2 (72.7)	0.93
	490.0 (317 to 606)	486.0 (300 to 620)	490.5 (321 to 599)	459.0 (304 to 599)	(Paired Student's *t*-test)
IOP, mm Hg	12.9 (3.0)	13.8 (3.1)	12.8 (3.2)	12.3 (3.0)	0.36
	12.0 (8 to 21)	13.0 (7 to 21)	12.0 (8 to 21)	12.0 (7 to 19)	

n = 114. Data are expressed as the mean (SD) with the median (range). Most of the samples did not follow a normal distribution (nonparametric statistics; before surgery vs. after surgery; Wilcoxon test, unless otherwise noted.).

K1, corneal dioptric power in the flattest meridian for the 3 mm central zone; K2, corneal dioptric power in the steepest meridian for the 3 mm central zone; KM, mean corneal dioptric power for the 3 mm central zone; AST, corneal astigmatism for the 3 mm central zone; Q45, mean asphericity for a corneal area of 4.5 mm of diameter; Q8, mean asphericity for a corneal area of 8 mm of diameter.

vector were found, even between consecutive visits in the same individual. The mean of the EA vector changed from $1.4 \times 9°$ at 1 year to $1.3 \times 3°$ at 3 years.

The AE and its changes during the 3-year follow-up were also evaluated. The mean magnitude of this angle was positive (change is clockwise to the initial astigmatic axis) at 1 year (mean, 0.15° [SD 61.76°]; Fig. 5). However, AE became progressively more negative (counterclockwise change) with time (2 years; mean −5.02° [SD 68.39°]; 3 years, mean −4.72° [SD 88.14°]), but these changes did not reach statistical significance ($P \geq 0.49$, Wilcoxon test). In any case, as shown in Figure 5, a great variability in the AE was observed, even between annual visits in the same subject. In addition, the

mean AE in absolute terms was calculated, and the values were 48.20° (SD 38.21°), 52.89° (SD 43.30°), and 75.06° (SD 45.10°) at 1, 2, and 3 years, respectively. The absolute AE did not changed significantly between the first and the second years of the follow-up ($P = 0.37$, Wilcoxon test), but it increased significantly at 3 years ($P < 0.01$, Wilcoxon test).

The influence of age and contact lens wear on the vectorial astigmatic change during the 3-year follow-up was also investigated. In the analyzed sample, 36 eyes were those of patients aged 30 years or younger, whereas 78 eyes were of patients
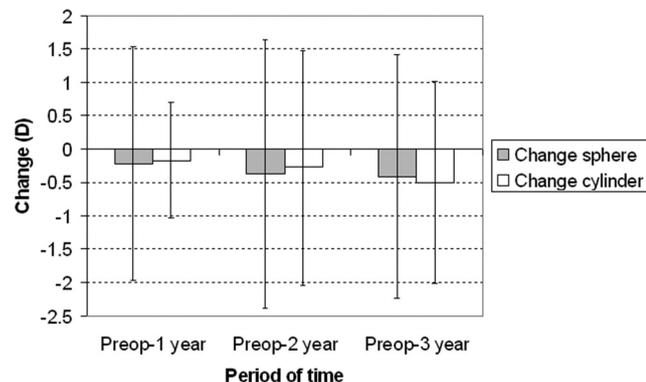

FIGURE 2. Annual changes in sphere and cylinder (☐) observed during the 3-year follow-up.
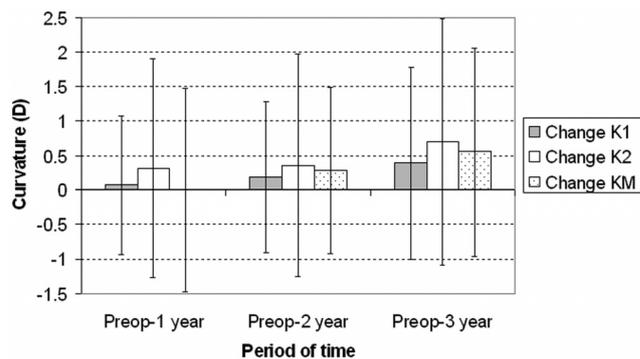

FIGURE 3. Annual changes in keratometric readings during the 3-year follow-up that were observed in the sample of keratoconic eyes analyzed. K1, corneal dioptric power in the flattest meridian for the 3-mm central zone; K2, corneal dioptric power in the steepest meridian for the 3-mm central zone; KM, mean corneal dioptric power for the 3-mm central zone.

Table 2. Summary of the Corneal Aberrometric Changes Occurring in the Anterior Corneal Surface of the Keratocomic Eyes

Parameter	Initial Examination	12-Month Examination	24-Month Examination	36-Month Examination	P
Higher order RMS	2.12 (1.50)	1.90 (1.41)	1.91 (1.41)	2.42 (1.36)	0.65
	2.03 (0.24 to 6.74)	1.50 (0.26 to 7.04)	1.50 (0.52 to 6.05)	1.95 (0.68 to 5.32)	
Primary coma RMS	1.80 (1.42)	1.63 (1.31)	1.61 (1.33)	1.83 (1.47)	0.99
	1.57 (0.07 to 5.72)	1.21 (0.10 to 6.24)	1.24 (0.12 to 5.13)	1.39 (0.14 to 5.11)	
Zernike coefficient for primary spherical aberration	−0.15 (0.40)	−0.13 (0.43)	−0.19 (0.30)	−0.44 (0.23)	0.01
	−0.14 (−1.09 to 0.51)	−0.21 (−0.99 to 0.54)	−0.30 (−0.73 to 0.45)	−0.44 (−0.83 to 0.04)	
Residual higher order RMS	0.92 (0.73)	0.82 (0.60)	0.92 (0.65)	1.28 (0.62)	0.67
	0.72 (0.13 to 3.51)	0.58 (0.17 to 3.12)	0.70 (0.28 to 3.14)	1.41 (0.46 to 2.43)	
Spherical-like RMS	0.72 (0.47)	0.63 (0.41)	0.63 (0.37)	0.86 (0.28)	0.54
	0.61 (0.16 to 2.33)	0.61 (0.11 to 2.20)	0.56 (0.15 to 2.08)	0.88 (0.32 to 1.34)	
Comalike RMS	1.97 (1.45)	1.77 (1.38)	1.77 (1.40)	2.23 (1.39)	0.65
	1.93 (0.16 to 6.32)	1.34 (0.24 to 6.69)	1.34 (0.24 to 5.68)	1.80 (0.31 to 5.20)	

$n = 36$. Data are expressed as mean micrometers (SD) with the median (range). Most of the sample did not follow a normal distribution (nonparametric statistics; before surgery vs. 24 months after surgery; Wilcoxon test).

older than 30. No significant differences in visual, refractive, keratometric, aberrometric, or pachymetric data were present between these two groups of eyes at the baseline ($P \geq 0.10$, Mann-Whitney and unpaired Student's t-tests). The only significant difference found between groups was in the baseline IA, with the largest value for the youngest group (30 years or younger: mean, 3.40 [SD 3.56]; older than 30 years: mean, 1.84 [SD 1.79]). Table 3 shows a comparative analysis of the vectorial parameters, analyzing the corneal astigmatic change at 3 years of follow-up in the eyes of subjects of 30 years old or younger and those of subjects older than 30. As shown, the magnitude of EA was significantly higher in the youngest group. In contrast, no significant differences between groups were found in the AE due to the large variability that was present in this parameter in both groups.

Regarding the influence of the contact lens wear, no significant differences were found in the magnitude of the EA, the AE, and the AE in absolute terms between contact lens (CL) and non-CL wearers ($P \geq 0.14$, Mann-Whitney test). First, no statistically significant differences in most of the preoperative conditions were found between the CL and non-CL wearers ($P \geq 0.17$, Mann-Whitney test). Significant differences were found before surgery only in CDVA (CL wearers: mean, 0.23 [SD 0.28]; non-CL wearers: mean, 0.15 [SD 0.23]; $P = 0.04$, Mann-Whitney test) and central corneal thickness (CL wearers: mean, 452.2 [SD 79.2]; non-CL wearers: mean, 489.0 [SD 53.9]; $P = 0.01$, unpaired Student's t-test).

Correlation of Vectorial Astigmatic Changes with other Clinical Changes

A good, statistically significant correlation of the absolute AE with the change in AST was found at 1 ($r = 0.62$, $P < 0.01$) and 2 ($r = 0.675$, $P < 0.01$) years (Fig. 6). However, this correlation was poor although statistically significant at 3 years of the follow-up ($r = 0.352$, $P = 0.02$). In addition, moderate but statistically significant correlations were found at 2 and 3 years between the magnitude of the EA and some baseline clinical parameters: K2 (2 years: $r = 0.420$, $P < 0.01$; 3 years: $r = 0.314$, $P = 0.03$), IA (2 years: $r = 0.392$, $P < 0.01$; 3 years: $r = 0.477$, $P < 0.01$), and corneal higher order RMS (2 years: $r = 0.430$, $P = 0.02$; 3 years: $r = 0.565$, $P = 0.05$). At the end of the follow-up, the magnitude of the EA ($r = -0.441$, $P = 0.02$) was found to be significantly correlated with the change in
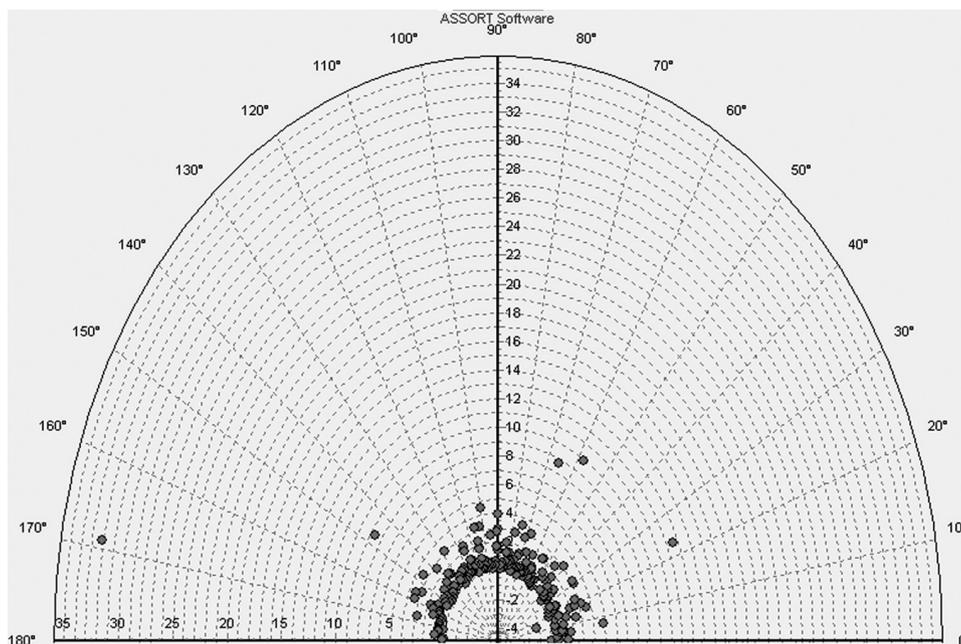

Figure 4. Vectorial display of the EA vector during the postoperative follow-up. This vector represents the real astigmatic change induced by the evolution of the corneal disease during the period analyzed.
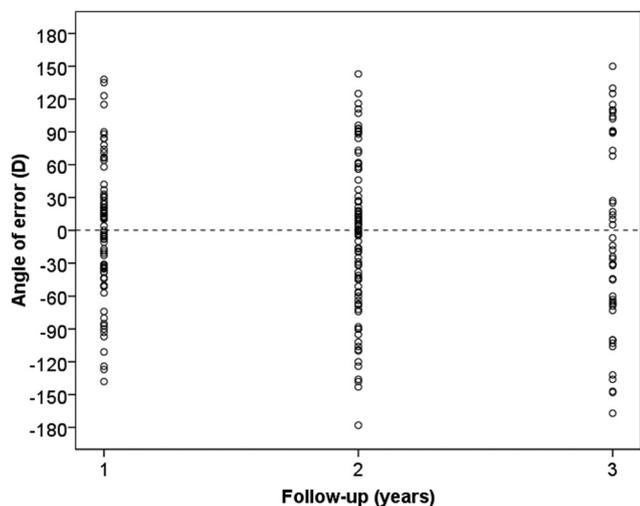
FIGURE 5. Changes in the AE during the follow-up in all cases. Significant variability was observed in this parameter.

central pachymetry. Weak and nonsignificant correlations were found between age and vector analysis parameters ($r \leq 0.20$, $P \geq 0.17$).

Multiple Regression Analysis

Multiple regression analysis revealed that the magnitude of EA at 3 years of the follow-up correlated significantly with the baseline refractive status (sphere) and IA ($P < 0.01$). Specifically, a model with predictability (R^2) of 0.86 and adjusted R^2 of 0.83 was developed:

$$EA = -0.01 - 0.16 \times SPH_0 + 0.33 \times IA_0$$

where EA is the magnitude of the evolutive astigmatism vector, SPH_0 is the manifest sphere at baseline, and IA_0 is the magnitude of the IA at baseline.

The homoscedasticity of the model was confirmed by the normality of the unstandardized residuals distribution ($P = 0.40$) and the absence of influential points or outliers (mean Cook's distance $= 0.17 \pm 0.32$). With this model, 53.49% of unstandardized residuals were lower than or equal to 0.5 D in absolute terms and 81.40% lower than or equal to 1.0 D in absolute terms. The poor correlation between residuals (Durbin-Watson test $= 1.65$) and the lack of multicollinearity (tolerance, 0.89; VIF, 1.12) was also confirmed.

TABLE 3. Comparative Analysis of Vectorial Parametes Analyzing the Corneal Astigmatic Change at 3 Years of Follow-up in Eyes in the Two Age Groups

Parameter	30 Years or Younger	Older Than 30 Years	P
EA, D	1.90 (1.09)	0.99 (0.83)	0.01
	1.65 (0.18 to 3.32)	0.71 (0.22 to 3.90)	
AE, deg	19.09 (108.114)	−12.00 (81.47)	0.29
	68 (−167 to 125)	−25 (−148 to 150)	
Absolute Ae, deg	97.09 (41.47)	68.33 (44.53)	0.07
	108 (14 to 167)	68 (5 to 150)	

Data are expressed as the mean (SD) with the median (range). Most of the sample did not following a normal distribution (nonparametric statistics; Mann-Whitney test).
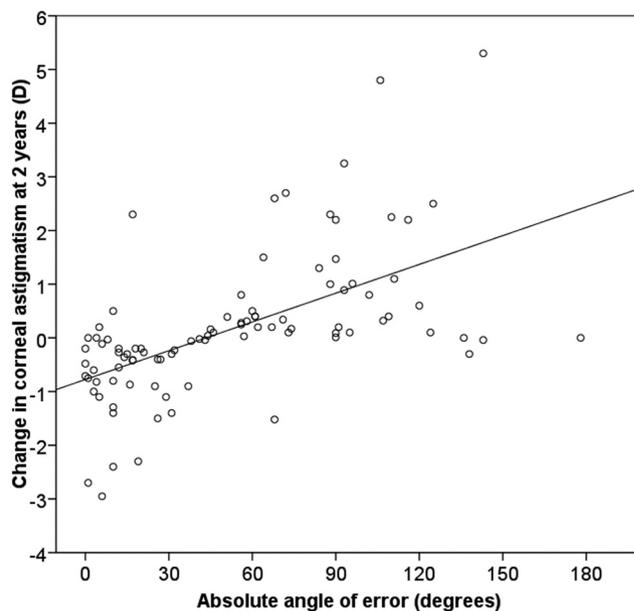

FIGURE 6. Scattergram showing the relationship between the change in central corneal astigmatism at 2 years of follow-up and the angle of error in absolute terms (AbsAE). The adjusting line to the data obtained by means of the least-squares fit is shown in the graph: Change in corneal astigmatism (D) $= 0.02 \times$ AbsAE (degrees) $- 0.77$ ($R^2 = 0.33$).

ROC Analysis

Regarding the ROC analysis for the detection of visual losses during a 3-year follow-up in keratoconic eyes, the area under the ROC curve was statistically significant only for the magnitude of the EA at 1 year ($P = 0.03$). This ROC was 0.675 (SE 0.08; 95% CI, 0.516–0.833). The cutoff point showing the best balance between sensitivity and specificity was 0.565 D, with associated values of sensitivity and specificity of 63.2% and 53.8%, respectively (Fig. 7).
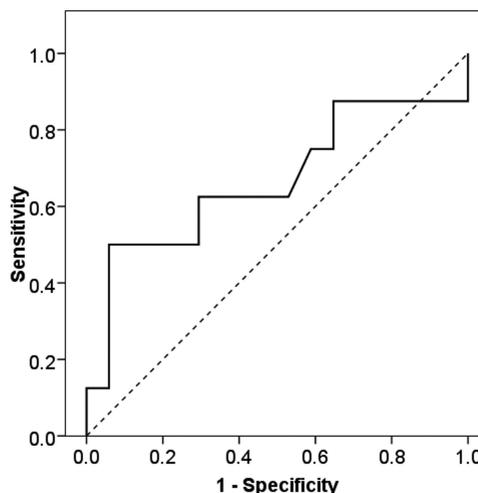

FIGURE 7. ROC curve for the detection of visual losses during a 3-year follow-up in keratoconic eyes from the magnitude of the corneal EA vector during the first year of evolution. Shown is the separation of the curve from the diagonal (*dotted line*). The nearer the curve comes to the *top left corner* of the graph, the larger the area under the ROC curve. A large area under the curve indicates that the false-negative rate is high and the false-positive rate is low, and therefore, the sensitivity and specificity of the EA vector are sufficiently high.

DISCUSSION

The study of changes in refractive cylinder in keratoconus is problematic because of the poor reliability of cylinder determined by subjective refraction of such eyes.[24] Manifest astigmatism (considering all ocular optics) is measured by testing several spherocylindrical lenses and determining which of them provides the best focus according to the subject criteria. However, in keratoconic eyes, the higher-order aberrations become very important as a consequence of corneal shape deformation, and the perceived blur is therefore not due only to the spherocylindrical error. The analysis of astigmatic changes measured by keratometry or corneal topography is a more objective procedure, but it only considers the effect of corneal optics. In any case, it should be remembered that corneal astigmatism of the anterior surface accounts for a large percentage of total ocular astigmatism, especially in cases of moderate and high astigmatism such as happens in keratoconus. On the other hand, the astigmatism is a vectorial variable, and its magnitude and axis should be evaluated for a complete and accurate study of its evolution in keratoconus. The purpose of the present study was to provide a complete analysis of corneal astigmatic changes during a 3-year follow-up in a sample of keratoconic eyes by means of the Alpins vectorial method and to determine the relationship between these changes and all other changes normally associated with the progression of the disease, such as age, curvature, pachymetric, and corneal aberrometric variations.

In the analyzed sample, we found statistically significant changes in the magnitude of the refractive cylinder during the 3-year follow-up. This finding was consistent with the increase in the limit of statistical significance found in corneal astigmatism. Other investigators have found that manifest refractive components could be regarded as risk factors for keratoconus progression,[3,25] but there is a significant variability in the criteria defined, depending on the study. We found a mean increase in refractive cylinder at 3 years in absolute terms of 0.88 D and an increase in corneal astigmatism of 0.31 D, but a large variability was observed between individuals. Therefore, only a part of the change over time in the magnitude of the refractive cylinder was due to the change in the astigmatism occurring in the anterior corneal surface. Changes in the toricity of the posterior corneal surface can also have a relevant influence on the subjective refraction in these highly aberrated eyes.[22,26–28] This is one of the reasons explaining the large magnitude of IA that used to be present in keratoconic eyes, even in the most incipient cases.[22] Besides refractive cylinder, a progressive increase in manifest sphere was observed during the follow-up but this change did not reach statistical significance due to the large variability observed in this parameter. This subjective parameter is normally affected by bias, due to the difficulty in finding an appropriate focus in keratoconus, especially in the more advanced cases.[24]

In agreement with the myopic change and the increased astigmatism, a significant increase in the steepest keratometric reading was found during the 3-year follow-up. Furthermore, a significant but small change was also found in mean keratometry. Several investigators have evaluated the keratometric changes in keratoconus and have reported different trends.[2,7,13,15] The main factors accounting for discrepancies among studies are the differences in the type of keratoconus patients evaluated (different severity level) and in the length of the follow-up. Kim and Joo[7] found a rate of keratometric change of 0.78 ± 0.99 D per half year during a 3-year follow-up by using the Orbscan II topographic system, but in a sample of eyes including a larger percentage of advanced cases than in our series (mean baseline KM, 55.06 ± 4.82 D). In our sample, we found a mean change in K2 of 0.28 at 2 years of follow-up

and 0.62 D at 3 years (mean baseline KM, 47.07 ± 3.66 D). A great part of the keratometric change occurred in our sample during the last year of the follow-up. Possibly, the progression of the disease was delayed because most cases in our series were incipient, and a longer period was required for detecting evolutive changes. This possibility should be addressed in future studies.

Besides corneal topographic changes in the anterior corneal surface, aberrometric variations with time were evaluated in the current series. To the best of our knowledge, this is the first study to evaluate the evolutive changes of anterior corneal aberrations in keratoconus. We found a significant negativization of the primary spherical aberration, which was consistent with the central steepening also observed in our series. It has been shown that larger amounts of negative primary spherical aberration are present in the more advanced keratoconic cases compared with the mild cases.[22,29] Furthermore, an increase in corneal comalike aberrations was also observed, although the change did not reach statistical significance, possibly because of the limitations in the sample size of eyes with corneal aberrometric evaluation available. Our research group demonstrated that the comalike RMS was a valid parameter for grading the severity of keratoconus,[19] and it was related with the underlying biomechanical alteration of the keratoconic cornea.[29] Pachymetric and IA variations during the 3-year follow-up were evaluated as well. A progressive central thinning and increase in IA were observed, but changes did not reach statistical significance, mainly due to the variability observed in the sample. In any case, the trends detected were consistent with those found in previous studies (Piñero DP, et al., manuscript submitted).[13] As the IA is the result of the combination of the toric components of the crystalline lens and the posterior corneal surface, its variability should be largely influenced by changes in the astigmatism of the posterior corneal surface, provided that we assume an approximately constant and limited contribution of the lenticular astigmatism in noncataractous eyes[30] to the internal and refractive astigmatism.

The Alpins vectorial analysis method was used for evaluating the changes occurring with time in corneal astigmatism. To the best of our knowledge, this is the first study to apply the Alpins method to the analysis of evolutive changes in the astigmatism of the anterior corneal surface in keratoconic corneas. Specifically, we used a modification of the Alpins vector method, assuming a TIA of 0. This means that our target was the stability of keratoconus, with no progression of corneal astigmatism. Therefore, the SIA vector was equivalent to the real astigmatic change induced by the evolution of the corneal disease in the period analyzed and it was renamed the EA vector. In the current series, the mean magnitude of this vector was different from 0, and it remained constant during the whole follow-up. However, the AE, defined as the angle described by the axes of the TIA and EA vectors, changed during the follow-up. Its mean value became on average more negative with time, which implied a change in the axis of astigmatism in a counterclockwise direction (after the guidelines of the Alpins method). In addition, the mean absolute AE value increased significantly during the third year of the follow-up. Therefore, changes in the orientation of the corneal astigmatism occurred during the 3-year follow-up that would not have been detected with a simple analysis of the magnitude of the astigmatism. On the other hand, a significant variability was observed in the magnitude of EA and AE at each annual visit, despite the general trends. Some keratoconus cases progressed during the evaluated follow-up, whereas others did not. More research is needed to ascertain which exact causes and factors lead to the progression of keratoconus, because most of studies are focused only on the definition of predictive factors. Dogru et al.[31] concluded that the ocular surface disease in keratoco-

nus is characterized by a disorder of tear quality, squamous metaplasia, and goblet cell loss, all of which seem to relate to the extent of keratoconus progression.

The level of correlation of the magnitude of EA and AE with a variety of baseline parameters was also investigated. A positive correlation was found between the absolute value of AE and the change in corneal astigmatism at all time points of the follow-up: the larger the AE, the larger the increase in the magnitude of corneal astigmatism. This type of correlation was good at 1 and 2 years, whereas it became poorer by the end of the follow-up, when the evidence of progression was stronger. Therefore, the increase in the magnitude of corneal astigmatism in cases of keratoconus progression seems also to be associated with a change in its orientation. Besides this relevant finding, the magnitude of the EA vector was found correlate significantly with baseline keratometry, IA, and corneal higher order RMS. The magnitude of the EA vector at 2 and 3 years of follow-up was larger in cases with a baseline steep K2, high IA, and large amounts of corneal higher order aberrations. It should be considered that curvature, IA, and corneal higher order aberrations are factors that have been related to the severity of keratoconus.[18,19,22,29] As expected, cases with signs showing a severe ectatic process seem to involve a more significant induction of corneal astigmatism with time. In any case, all these correlations were moderate and therefore highly accurate predictions of EA only, considering each one of these parameters (K2, IA, and corneal higher order RMS), are not possible. The magnitude of EA and the absolute value of AE were found to correlate significantly with central corneal thinning at the end of the follow-up as well. Specifically, corneas experiencing corneal thinning during the 3-year follow-up had an associated larger magnitude of EA and therefore a larger magnitude of induced astigmatism. Therefore, it seems that an association between the changes in pachymetry and the anterior corneal toricity is present in the short term in keratoconic corneas. In addition, age did not correlate with the vector analysis parameters at any annual visit, although significant differences were found in the magnitude of EA between eyes of subjects 30 years of age or younger and those of subjects older than 30, with the largest mean value in the youngest group. It has been demonstrated that the cornea becomes stiffer with age[32,33] and therefore is less susceptible to development of an ectatic process. However, in our series we did not detect a negative correlation between age and the magnitude of EA. This result supports the idea that the relationship between biomechanical changes and the corneal topographic profile is complex and not linear. There may have been young patients with a significant biomechanical change that did not lead to a relevant modification of the anterior corneal shape in the 3-year period.

As several baseline factors correlated with the magnitude of EA, a multiple regression analysis was performed to establish a linear predictive model of the magnitude of the 3-year EA vector and the baseline conditions. This analysis revealed an inverse relationship between EA and the baseline sphere, as well as a positive relationship between EA and baseline IA. A larger magnitude of the 3-year EA was found in highly myopic eyes with larger amounts of IA. High myopia in keratoconus has been related to steep corneas, whereas the presence of higher amounts of IA may relate to changes in the posterior corneal surface or large amounts of anterior corneal aberration, prohibiting a reliable determination of manifest cylindrical refraction. A model describing this relationship with a predictability of 86% was obtained, which allows a prediction of the astigmatic change that can occur in a virgin keratoconic cornea during a 3-year follow-up. This predictive model was obtained from a sample with a predominance of early to moderate

keratoconic eyes, and it may not be applicable to advanced cases, where the progression is more evident.

As an additional feature, we evaluated the diagnostic ability of the magnitude of EA and AE at 1 year of follow-up for the detection of those cases with a visual worsening and then a keratoconus progression during the remaining follow-up. We found an acceptable sensitivity and specificity for the magnitude of EA. Values of EA larger than 0.565 D during a follow-up of 1 year are associated with a visual worsening due to a progression of the keratoconus. This could be a helpful tool, allowing the clinician to decide the suitability of some surgical treatments as corneal collagen cross-linking or implantation of intracorneal ring segments. In any case, it should be noted that we analyzed a sample including a majority of early to moderate keratoconic cases, and therefore we do not know the validity of the proposed predictions in advanced keratoconus. Furthermore, it is highly recommended that these preliminary predictive models be validated by evaluating the corneal vectorial astigmatic changes in larger samples of eyes and examining different grades of severity, determined according to the standard criteria.

The main drawback of the present study is its retrospective character. We performed retrospective clinical data collection from nonsurgical keratoconus cases with a minimum follow-up of 3 years from different ophthalmology centers. As in most retrospective studies, patients were reviewed by different doctors and sometimes measured with different devices (corneal topography). Despite this limitation, we collected a large and consistent sample of keratoconic eyes with the same duration of follow-up, allowing us to evaluate the vectorial corneal astigmatic changes during a 3-year period associated with this type of corneal ectatic condition as well as to characterize their relationship with other clinical changes. Another potential source of bias was the use of contact lenses by the great part of the patients reviewed. However, all patients were asked to discontinue contact lens wear for a specific period before examination. Indeed, no significant differences were found between contact lens wearers and non–contact lens wearers in all the clinical changes evaluated, as well as at baseline. Another potential limitation is the lack of control of environmental factors that may contribute to the progression of keratoconus, such as exposure to ultraviolet radiation or cigarette smoke. In any case, we evaluated the evolution of keratoconus in a short time and therefore the contribution of environmental factors should be minimal, because no exposition to extreme conditions was revealed in any of the cases.

In conclusion, changes occurred in a short time in keratoconic corneas, not only in the magnitude of astigmatism, but also in the axis. These astigmatic changes are in relation to some signs associated with keratoconus progression, such as an increase in the magnitude of corneal astigmatism and the presence of corneal thinning. Furthermore, baseline corneal curvature, IA, and corneal higher order aberrations seem to be predictors of the corneal astigmatic changes that are going to occur during a 3-year follow-up, predicting a higher rate of progression in those cases with more significant signs of severe disease. Finally, we have demonstrated that the Alpins vectorial method, used to calculate the magnitude of the induced astigmatism, could be a tool for predicting the presence of visual worsening associated with the progression of keratoconus. The algorithms of predictions obtained in the present study must be validated in future studies including larger sample sizes. This validation should also be performed for each different degree of severity of the disease and for longer periods of follow-up.

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