Modeling the Intracorneal Ring Segment Effect in Keratoconus Using Refractive, Keratometric, and Corneal Aberrometric Data

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Purpose. To characterize the refractive, keratometric, and corneal aberrometric effect of a specific type of intracorneal ring segment (ICRS) as a function of its thickness and the preoperative conditions of the cornea.

Methods. A total of 72 consecutive keratoconic eyes of 57 patients ranging in age from 15 to 68 years were retrospectively analyzed and included in the study. All cases had a diagnosis of keratoconus and had undergone implantation of a 160° arc-length KeraRing segment (Mediphacos, Belo Horizonte, Brazil), by femtosecond laser technology. Correlations between ring segment thickness and several clinical parameters were investigated. In addition, a multiple regression analysis was performed to characterize all factors that influence the ring segment effect.

Results. Significant reductions in central curvature, corneal astigmatism, and comalike aberrations were found after surgery ($P \leq 0.03$). Moderate and limited correlations were found between ring segment thicknesses and changes in mean keratometry and higher order aberrations ($r \leq 0.50$, $P < 0.01$). A consistent linear relationship of the superior ring segment thickness to the induced corneal changes, the preoperative cylinder, and the difference in thickness between inferior and superior segments was found ($P < 0.01$, $R^2 = 0.91$). An almost identical model was obtained for the inferior ring segment thickness with the only distinction in the factor being the thickness difference between segments ($P < 0.01$, $R^2 = 0.64$).

Conclusions. The selection of the ring segment to implant in keratoconus should be based, not only on refraction and subjective appearance of the corneal topographic pattern but also on corneal aberrometry. This highly customized selection would allow a more predictable outcome. (*Invest Ophthalmol Vis Sci.* 2010;51:5583–5591) DOI:10.1167/iovs.09-5017

Intracorneal ring segments (ICRSs) have been demonstrated to be effective in improving visual acuity and reducing the refractive error and mean keratometry in keratoconic eyes.[1–22] These segments act as spacer elements between the bundles of corneal lamellae, producing a shortening of the central arc length (arc-shortening effect) that is proportional to the thickness of the implant (Silvestrini T, et al. *IOVS* 1994;35:ARVO Abstract 2023). As a consequence of this effect, the central portion of the anterior corneal surface tends to flatten, and the peripheral area adjacent to the ring insertion is displaced forward.[23,24] In nonpathologic corneas, there is a nearly linear relationship between the degree of central corneal flattening and the thickness of the implanted ring segments.[25,26] However, this mechanism of action is not reproduced exactly in the keratoconic cornea. It should be considered that the well-organized lamellar structure of the cornea is lost when the corneal tissue degenerates, as happens in keratoconus.[27] The regular orthogonal arrangement of the collagen fibrils is destroyed within the apical scar of the keratoconus.[27] Therefore, the effect induced by the ICRS in keratoconus may be different from the effect induced in normal corneas, because the structural properties of the corneal collagen framework are also different.

Several nomograms for ICRS implantation in keratoconus have been developed, all of them intuitive or based on poor and subjective empiric data.[3,5,7–22,28] A nomogram based on objective data or on an accurate mathematical model characterizing the ICRS effect has not yet been developed or reported. Different limited approaches have been proposed as nomograms for ICRS implantation in keratoconus, some of them based on spherical equivalent refraction or on the subjective appearance of the corneal topographic profile (decentered or not decentered cones). Good visual and refractive outcomes have been reported with all of them.[3,5,7–22,28] However, there are still anecdotal cases of ICRS implantation with minimal keratometric reductions or with no keratometric effect, despite the indications provided by these nomograms. It has been demonstrated that the preoperative manifest refraction or best corrected visual acuity are factors with a limited ability to predict the postoperative visual outcome.[29] In contrast, corneal aberrometry has been found to have a great potential for predicting postoperative visual outcome.[2] Therefore, there is a need for readjusting the nomograms by using objective clinical data or more complex mathematical corneal models to obtain more predictable results.

The final purpose of the present study was to characterize the refractive, keratometric, and aberrometric effect of one specific type of intracorneal implants as a function of the thicknesses used and the preoperative conditions of the cornea. To the best of our knowledge, this study is the first attempt to develop a model of the effect of the ICRS, on the

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basis of objective data and considering also corneal aberrometry as an additional influencing factor.

Methods

Patients

Eyes with the diagnosis of keratoconus and implanted with 160° arc length KeraRing (Mediphacos, Belo Horizonte, Brazil) segments (Fig. 1) were retrospectively analyzed in four Spanish ophthalmology centers: three centers from Vissum Corporation (Alicante, Seville and Madrid) and the Barraquer Ophthalmologic Centre in Barcelona. A total of 72 consecutive keratoconic eyes of 57 patients ranging in age from 15 to 68 years were included (mean age, 32.93 ± 11.20 years). Of the patients included in this study, 59.6% were male and 40.4% were female. Fifteen of the keratoconus cases were bilateral and 57 were unilateral.

Only keratoconus cases with KeraRing implantation (Fig. 1) by femtosecond laser technology and with no other ocular surgery and active ocular disease were included in the study. Keratoconus diagnosis was based on corneal topography and slit lamp observation. In all cases, preoperative 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.[30] The Alió-Shabayek[31] classification was used for grading keratoconus in those cases in which corneal aberrations were evaluated. In all cases ICRS implantation was indicated because of the existence of reduced BSCVA and/or contact lens intolerance.

Ethics committee approval at the institutions participating in this study was obtained for the investigation. In addition, during the process of consent for surgery, consent was obtained for inclusion of clinical information in later scientific studies, according to the tenets of the Declaration of Helsinki.

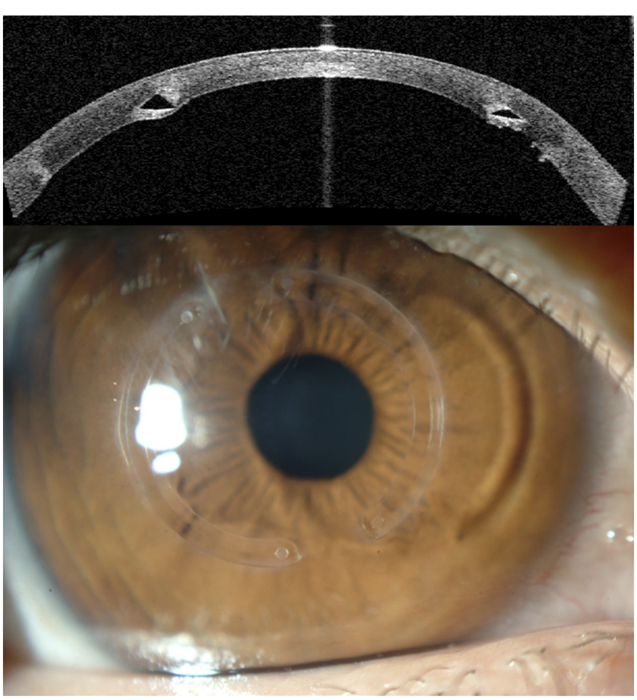

Figure 1. Keratoconic cornea implanted with KeraRing (Mediphacos, Belo Horizonte, Brazil) segments with an arc length of 160°. *Top*: high-resolution corneal image (Visante OCT system; Carl Zeiss Meditec, Inc.). *Bottom*: frontal image obtained with a slit lamp biomicroscope.

Examination Protocol

A comprehensive examination was performed before surgery in all cases that included Snellen uncorrected visual acuity (UCVA; logMAR scale), Snellen best spectacle-corrected visual acuity (BSCVA; logMAR scale), manifest refraction, slit lamp biomicroscopy, Goldmann tonometry, fundus evaluation, ultrasonic pachymetry, 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 CSO device is a Placido-based system, and the Orbscan II 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.[32] In this study, the following topographic data were evaluated and recorded with all corneal topographic devices: 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), and mean corneal power in the 3-mm zone (KM).

Corneal aberrometry was also recorded and analyzed only in those patients examined with a topography system (59 eyes; CSO; Vissum, Alicante, Spain, and Vissum Madrid, Spain), because this device was the only one with the capability of calculating this specific information directly. This topographic system analyzes 6144 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 by using 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 following parameters were analyzed and recorded: higher order root mean square (RMS), primary coma RMS (computed for the Zernike terms $Z_3^{\pm 1}$), coma-like RMS (computed for third-, fifth-, and seventh-order Zernike terms), spherical-like RMS (computed for fourth- and sixth-order Zernike terms), and higher order residual RMS (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.

Surgery

Surgical procedures were performed by four experienced surgeons (JLA from Vissum Alicante, AUM from Vissum Sevilla, MAT from Vissum Madrid, and RIB from Centro de Oftalmología Barraquer), who used the same femtosecond technology for corneal tunneling (30-kHz IntraLase femtosecond system; IntraLase Corp, Irvine, CA) and the same surgical protocol, which is the standard procedure described in detail in many published works.[2,4,6–8,13]

In all cases, an antibiotic prophylaxis consisting of topical ciprofloxacin (Oftacilox; Alcon Cusí, Barcelona, Spain) every 8 hours for 2 days was prescribed to be applied before surgery.

Two criteria were used to determine the location of the incision. The former patients included in the study underwent surgery with a temporal incision, which was the initial standard procedure. Twenty-one eyes had this incision modality (in seven cases, the incision was near the flattest meridian, and in the remainder, it was oblique to the flattest and steepest corneal meridian). In contrast, the most recent surgical cases had the incision at the steepest corneal meridian (51 eyes, 70.8%), which is the current most accepted incision criterion for this type of surgical procedure. In any case, the geometric center of the ring segment was always placed on the flattest corneal meridian.

The selection of the number (1 or 2) and thickness of KeraRing (Fig. 1) segments to implant was performed according to the nomogram defined by the manufacturer.[2,8] In 24 (33.3%) eyes, only one ring segment was implanted, whereas in the remaining 48 (66.7%) eyes, two segments were necessary.

Table 1. Summary of the Refractive Outcomes after KeraRing Implantation

Parameter (Range)	Preop	Postop	P*
UCVA, logMAR	0.99 ± 0.67 (0.10 to 2.78)	0.70 ± 0.35 (0.13 to 1.30)	<0.01
Sphere, D	−3.70 ± 4.82 (−21.00 to +4.00)	−2.51 ± 4.46 (−17.50 to +3.25)	<0.01
Cylinder, D	−4.07 ± 2.40 (−9.50 to 0.00)	−2.86 ± 1.91 (−9.00 to 0.00)	<0.01
SE, D	−5.64 ± 5.00 (−22.25 to +1.00)	−3.99 ± 4.50 (−19.00 to +2.00)	<0.01
BSCVA, logMAR	0.36 ± 0.27 (0.00 to 1.30)	0.27 ± 0.23 (0.00 to 1.30)	<0.01

Data are the mean ± SD with ranges in parentheses.
* Wilcoxon signed rank test.

No intraoperative complications occurred. Topical tobramycin and dexamethasone eye drops (TobraDex; Alcon Laboratories, Inc, Fort Worth, TX) were used after surgery every 6 hours for 1 week and then stopped. Topical lubricants were also prescribed to be applied every 6 hours for 1 month (Systane; Alcon Laboratories, Inc.).

Follow-up Evaluation

Visual, refractive, and corneal aberrometric outcomes were evaluated 3 months after surgery. The follow-up was not longer because we wanted to analyze the real effect of the ring segments, not changes with time once they had been implanted. Bear in mind that corneal biomechanical changes and a progression of the ectatic corneal process can still occur despite the implantation of ring segments.[2,33] No explantations or reposition of the ring segments were needed during these first 3 months after surgery.

Statistical Analysis

The normality of all data samples was first checked by means of the Kolmogorov-Smirnov test. When parametric analysis was possible, the Student's *t*-test for paired data was performed for all parameter comparisons between preoperative and postoperative examinations or consecutive postoperative visits. When parametric analysis was not possible, the Wilcoxon rank sum test was applied, to assess the significance of differences between preoperative and postoperative data, with the same level of significance used in all cases ($P < 0.05$; SPSS ver. 15.0 for Windows; SPSS, Chicago, IL).

For simplifying the statistical analysis, the following notations and criteria were used: The superior segment was defined as any segment with a geometric center located on the superior half of the cornea, the inferior segment was any segment with a geometric center located on the inferior half of the cornea, and a nonimplanted segment (superior or inferior) was assigned a thickness of 0. With these criteria, the bivariate correlations of visual, refractive, and corneal aberrometric changes with superior and inferior ring segment thicknesses were evaluated (Pearson or Spearman correlation coefficients, depending on whether normality could be assumed). Furthermore, a multiple regression analysis was performed by using the backward elimination method with the purpose of obtaining a mathematical expression relating the different kind of changes induced by each ring segment, superior and inferior, separately. Model assumptions were evaluated by analyzing residuals, the normality of unstandardized residuals (homoscedasticity), and the 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 the calculation of the collinearity tolerance and the variance inflation factor (VIF).

Results

The contribution of the four participating centers to the present study was as follows: 60 eyes from the Vissum Corporation centers (Alicante, Seville, and Madrid) and 12 eyes from the Barraquer Ophthalmologic Centre. There was a balanced distribution of right and left eyes (35 vs. 37). Cone opacity was observed in only five (6.9%) cases. Considering the corneal aberrations and according to the Alió-Shabayek grading system,[31] 14 (26.9%) eyes had a grade I cone, 16 (30.8%) a grade II cone, 8 (15.4%) a grade III cone, and 14 (26.9%) a grade IV cone.

Visual, Refractive, and Corneal Changes

Table 1 summarizes the visual and refractive data before and 3 months after KeraRing implantation. As shown in the table, manifest sphere, and cylinder were reduced significantly by the implants ($P < 0.01$, Wilcoxon test). A statistically significant mean improvement in UCVA of 3 lines was noted ($P < 0.01$, Wilcoxon test). BSCVA showed a statistically significant improvement of ~1 line ($P < 0.01$, Wilcoxon test).

All keratometric readings were reduced significantly 3 months after surgery ($P < 0.01$, Wilcoxon tests; Fig. 2). Specifically, a mean central flattening effect of 2.45 ± 2.45 D was obtained. Regarding corneal aberrations, a significant decrease was observed in the RMS values for coma-like aberrations ($P = 0.03$, Wilcoxon test) and corneal astigmatism ($P = 0.01$, Wilcoxon test) at 3 months after surgery (Table 2). The primary spherical aberration term became, on average, more positive after surgery, although the change did not reach statistical significance (Table 2).

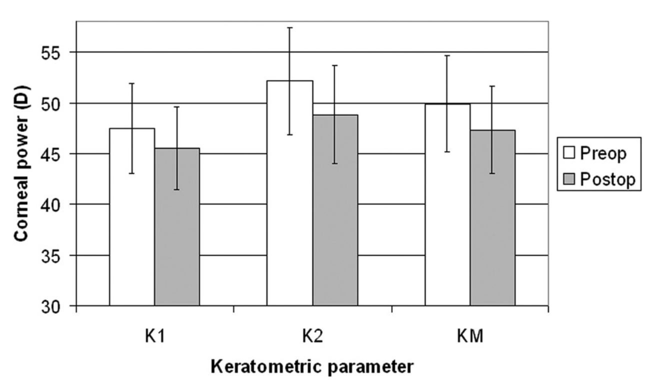

Figure 2. Changes in keratometric parameters during the follow-up: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2), and mean corneal power in the 3-mm zone (KM). A statistically significant reduction was observed in all keratometric parameters.

TABLE 2. Summary of the Corneal Aberrometric Changes after KeraRing Implantation

Parameter	Preop	Postop	*P*
Higher order RMS, μm	3.73 ± 1.97 (0.78 to 10.21)	3.24 ± 1.44 (1.08 to 8.21)	0.09*
RMS for corneal astigmatism, μm	3.21 ± 2.16 (0.33 to 10.86)	2.50 ± 1.73 (0.20 to 8.69)	0.01*
Primary coma RMS, μm	3.11 ± 1.75 (0.33 to 8.38)	2.66 ± 1.46 (0.65 to 7.65)	0.13†
Z40, μm	−0.24 ± 0.94 (−2.06 to 2.69)	−0.01 ± 0.73 (−1.58 to 1.67)	0.09†
Residual RMS, μm	1.56 ± 1.28 (0.47 to 8.10)	1.53 ± 0.68 (0.46 to 3.18)	0.85†
Spherical-like RMS, μm	1.25 ± 0.89 (0.24 to 6.38)	1.21 ± 0.58 (0.33 to 2.73)	0.78*
Comalike RMS, μm	3.46 ± 1.86 (0.40 to 9.96)	2.94 ± 1.45 (0.84 to 7.94)	0.03*

Data are the mean ± SD with ranges in parentheses. Definitions of each kind of corneal aberration: primary coma, Zernike terms $Z_3^{\pm 1}$; primary spherical aberration, Zernike term Z_4^0; residual aberrations, all Zernike terms, except $Z_3^{\pm 1}$ and Z_4^0; spherical-like aberrations, fourth- and sixth-order Zernike terms; comalike aberrations, third- and fifth-order Zernike terms.

* By Wilcoxon test.

† By Student's *t*-test.

Correlation between Ring Segment Thickness and Visual, Keratometric, and Refractive Changes

Table 3 summarizes the statistically significant correlations of the postoperative outcome with different preoperative and ring segment parameters. As shown in this table, the thicknesses of the superior and inferior ring segments correlated inversely with the change achieved in mean keratometry (Fig. 3) and correlated positively with the change induced in corneal residual higher order aberrations (Fig. 4). The change in mean keratometry was found to be significantly correlated with other preoperative clinical parameters, as the UCVA, BSCVA, mean keratometry, and manifest sphere. Furthermore, the change achieved with the implants in manifest refraction correlated significantly with the preoperative or baseline refractive status.

Multiple Regression Analysis

According to the correlation analysis, several factors seemed to be implicated in the ring segment's effect, showing the need for a more complex analysis. For this reason, a multiple linear regression was performed to find the appropriate mathematical expression relating all the influencing factors. The purpose was to find a model that predicts the superior and inferior ring segment thicknesses needed to achieve a specific postoperative clinical change with a specific baseline condition. Table 4 summarizes the predictability and goodness of fit of the different models obtained. First, two models were calculated considering only the visual, refractive, and keratometric data, which were available in all the participating centers:

$$\text{Model 1: SST}(\mu\text{m}) = 102.84 - 13.48 \times \text{CYL}_p - 21.27 \times \text{DifKM} - 0.65 \times \text{DifIST}\ (R^2 = 0.84,\ P < 0.01)$$

$$\text{Model 2: IST}(\mu\text{m}) = 102.84 - 13.48 \times \text{CYL}_p - 21.27 \times \text{DifKM} + 0.35 \times \text{DifIST}\ (R^2 = 0.62,\ P < 0.01)$$

where SST is the thickness of the superior segment, IST is the thickness of the inferior segment, CYL_p is the preoperative cylinder, DifKM is the change in mean keratometry after surgery, and DifIST is the difference between the thickness of the inferior and superior ring segments.

TABLE 3. Summary of the Statistically Significant Correlations of the Postoperative Outcome with Preoperative and Ring Segment Parameters

Postoperative Outcome or Change	Correlation	Correlation Coefficient	*P*
Change in sphere, D	IST	0.279	0.02
	Preop sphere	−0.62	<0.01
Change in mean keratometry, D	IST	−0.435	<0.01
	SST	−0.484	<0.01
	IST-SST	0.300	0.02
	Preop LogMAR UCVA	−0.432	<0.01
	Preop sphere	0.537	<0.01
	Preop LogMAR BSCVA	−0.365	0.01
	Preop mean keratometry	−0.480	<0.01
Change in the RMS value for corneal residual HOA, μm	IST	0.501	<0.01
	SST	0.437	<0.01
Change in manifest cylinder, D	Preop cylinder	−0.64	<0.01
Change in spherical-like RMS, μm	Preop primary coma RMS	−0.382	0.01
	Preop coma-like RMS	−0.375	0.01

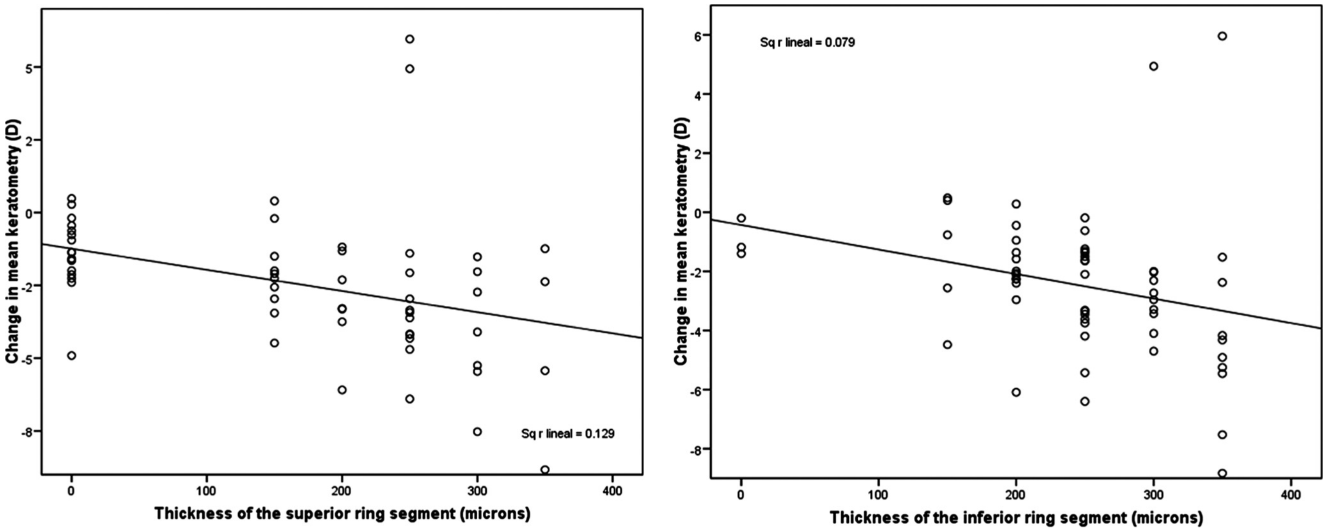

FIGURE 3. Scattergrams showing the relationship between the change in mean keratometry (postop–preop) and the thickness of the superior (*left*) and inferior (*right*) ring segment. The adjusting line to the data obtained by means of the least-squares fit is shown in both graphs: (*left*) change in mean keratometry (D) = −0.007 × superior segment thickness (μm) − 1.239 (R^2 = 0.129); (*right*) change in mean keratometry (D) = −0.008 × inferior segment thickness (μm) − 0.433 (R^2 = 0.079).

These models revealed that the thicknesses of both ring segments correlated inversely with the preoperative manifest astigmatism and the change in mean keratometry. The only difference between these two models was the factor accounting for the difference in thickness between the inferior and superior ring segments.

When the multiple regression analysis was performed, introducing the aberrometric corneal data (59 eyes), two new models with increased predictability were obtained, despite the smaller sample size:

$$\text{Model 3: SST}(\mu\text{m}) = 132.20 - 12.14 \times \text{CYL}_p - 20.47 \times \text{DifKM} + 24.37 \times \text{DifRMSHOA} - 0.74 \times \text{DifIST} \; (R^2 = 0.91, P < 0.01)$$

$$\text{Model 4: IST}(\mu\text{m}) = 132.20 - 12.14 \times \text{CYL}_p - 20.47 \times \text{DifKM} + 24.37 \times \text{DifRMSHOA} + 0.26 \times \text{DifIST} \; (R^2 = 0.64, P < 0.01)$$

where SST, IST, CYL_p, DifKM, and DifIST are as defined for models 1 and 2; and DifRMSHOA is the change in the RMS value for corneal higher order aberrations.

These two newly devised models also revealed an inverse correlation of the thicknesses of both ring segments with the preoperative manifest astigmatism and the change in mean keratometry. In addition, these thicknesses correlated positively with the change in corneal higher order aberrations. The difference in thickness between the inferior and superior ring

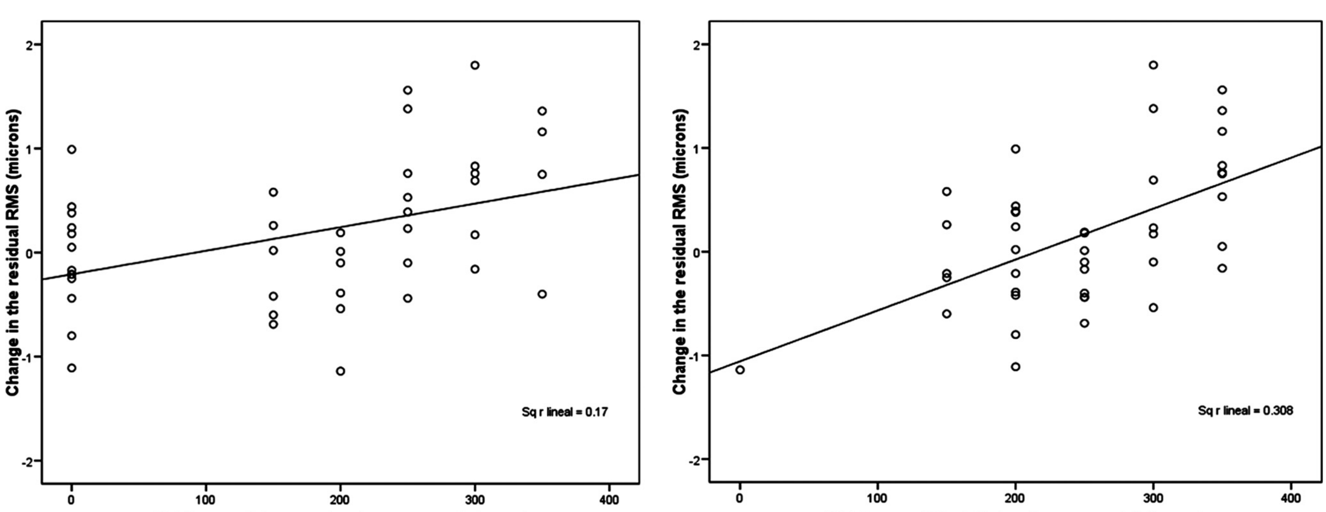

FIGURE 4. Scattergrams showing the relationship between the change (postop–preop) in the value for the corneal residual higher order aberrations (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration) and the thickness of the superior (*left*) and inferior (*right*) ring segment. The adjusting line to the data obtained by means of the least-squares fit is shown in both graphs: (*left*) Change in residual RMS (μm) = 0.002 × superior segment thickness (μm) −0.209 (R^2 = 0.17); (*right*) change in residual RMS (μm) = 0.005 × inferior segment thickness (μm) − 1.057 (R^2 = 0.308).

TABLE 4. Summary of the Outcomes of the Multiple Linear Regression Analysis

Models	R^2	Adjusted R^2	P	Cook's Distance	Residuals Statistics	Durbin-Watson Test	Multicolinearity Tolerance
Model 1	0.84	0.83	<0.01	0.09 ± 0.26	≤100 μm 91.23% ≤50 μm 63.16%	1.75	0.84–0.88
Model 2	0.62	0.59	<0.01	0.09 ± 0.26	≤100 μm 87.72% ≤50 μm 63.16%	1.75	0.84–0.88
Model 3	0.91	0.90	<0.01	0.12 ± 0.31	≤100 μm 92.68% ≤50 μm 75.61%	1.96	0.57–0.77
Model 4	0.64	0.59	<0.01	0.12 ± 0.31	≤100 μm 90.24% ≤50 μm 68.29%	1.96	0.57–0.77

The predictability and those parameters useful for evaluating the goodness of fit of each model are shown.

segments was also the differential factor between these two predictive models.

The homoscedasticity of these models was confirmed by the normality of the unstandardized residuals distribution ($P \geq 0.09$) and the absence of influential points or outliers. The lack of multicollinearity and the independence of the residuals were also confirmed (Table 4).

A statistically significant negative correlation was found between the unstandardized residuals for the four developed linear models and the magnitude of the preoperative sphere (models 1 and 2, $r = -0.32$, $P = 0.04$; models 3 and 4, $r = -0.47$, $P < 0.01$). In addition, statistically significant differences in some corneal aberrometric coefficients were found between cases with residuals >50 μm and those with residuals ≤50 μm for the first two models (model 1 and 2, RMS for astigmatism $P = 0.02$, RMS for residual higher order aberrations $P = 0.01$, RMS for coma-like aberrations $P = 0.02$; Wilcoxon test). In the two linear models that involved corneal higher order aberrations, differences between cases with residuals >50 μm and those with residuals ≤50 μm were near the limit of statistical significance for the RMS values corresponding to corneal astigmatism and spherical-like aberrations ($P = 0.06$, Wilcoxon tests; Fig. 5). It should be noted that only 13 cases had residuals >50 μm, whereas the remaining cases had lesser residuals. This trend observed for corneal astigmatism and spherical-like aberrations was also observed in the other two linear models.

DISCUSSION

A significant central flattening was observed after KeraRing implantation with a mean change of ~2.5 D. This outcome supports the findings reported after implantation of KeraRing (Mediphacos) and Intacs (Addition Technology Inc., Des Plaines, IL), showing also a significant flattening effect.[1–15,20,28] This keratometric reduction was the main reason for the change in refraction and the increase in UCVA. However, this keratometric change was dependent on several preoperative factors as keratometry and BSCVA. As mentioned, the ring segments implanted in the midperiphery have been shown to induce a shortening of the central arc length (arc shortening effect [Silvestrini T, et al. *IOVS* 1994;35:ARVO Abstract 2023]) and then a flattening of the central portion of the anterior corneal surface.[23,24] Regarding corneal aberrometric changes, significant changes were found in corneal astigmatism and coma-like aberrations. This aberrometric improvement could be in relation with the significant improvement found on average in logMAR BSCVA. It should be remembered that primary coma has been demonstrated to have a very negative impact on visual acuity due to the optical blur that it induces.[33] In a study by our research group, a significant reduction of higher order aberrations was found after KeraRing implantation, using the femtosecond laser technology in keratoconus, but only in those eyes with a magnitude of coma aberration larger than 3 μm.[8] In addition, it should be mentioned that a nonsignificant change in the primary spherical aberration toward less negative values was observed. This change in primary spherical aberration and also the reduction in coma-like errors were consistent with the reduction of the localized corneal steepening that was present in the keratoconic eyes.

Correlations between the ring segment thicknesses and the refractive, keratometric, and corneal aberrometric changes were also investigated. As described in the Methods section, a specific criterion was used for defining the concept of superior and inferior ring segments, to simplify the statistical analysis: A superior segment was any segment with a geometric center located on the superior half of the cornea and an inferior segment was any segment with a geometric center located on the inferior half of the cornea. In addition, a nonimplanted ring segment (superior or inferior) was regarded as an implant with a thickness of 0. Several statistically significant weak and moderate correlations were found between the thickness of the superior and inferior ring segments, and some clinical changes (Table 3). For example, these thicknesses correlated inversely with the change in mean keratometry and positively with the change in the RMS value corresponding to the corneal higher order residual aberrations. As mentioned earlier, a nearly linear relationship between the degree of central corneal flattening and ring thickness was found in normal corneas.[25,26] Besides these moderate relationships, we found that some clinical changes also correlated significantly with some preoperative conditions, as the magnitude of the spherocylindrical error or the corneal curvature. Therefore, it seems clear that some factors influence the visual and refractive outcomes achieved with the KeraRing segments. In other words, this process

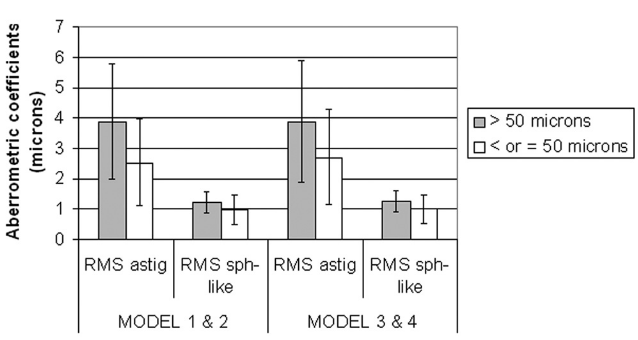

FIGURE 5. Differences in corneal astigmatism and spherical-like aberrations between cases with unstandardized residuals >50 μm and cases with residuals ≤50 μm for the four linear models developed in the present study: model 1 and 2, models for the superior and inferior ring segment thickness without regard for corneal aberrations; models 3 and 4, models for the superior and inferior ring segment thickness with regard for the corneal aberrometric factor.

cannot be represented by means of a simple linear model with two variables. The effect achieved with each KeraRing segment is a multifactorial process depending on the ocular preoperative conditions and on the thickness of the implant. It should be remembered that all segments were implanted according to the same surgical criteria (inner and outer diameters of 4.8 and 5.7 mm, respectively, and ring placement at ~80% of the depth of the cornea). The diameter and the depth of the implant are also factors in the final effect achieved with the ring segments,[24] but these factors have not been modified in the present study. It should be considered that corneal changes induced by the ICRS must be in relation to the structural properties of the collagen framework in the corneal stroma. The stroma accounts for 90% of corneal thickness, and evidently its mechanical properties define, for the most part, the mechanical properties of the whole corneal structure. In the normal cornea, there is a preferred orientation of collagen lamellae along the horizontal and vertical directions, but this trend is maintained to within approximately 1 mm from the limbus, where a circular or tangential disposition of fibrils occurs.[34] However, this well-organized lamellar structure is lost when the corneal tissue degenerates, as happens in keratoconus.[27] The regular orthogonal arrangement of the collagen fibrils is destroyed within the apical scar of the keratoconus.[27] Therefore, the ICRS effect in keratoconus seems to be a more complicated phenomenon that needs a more complex mathematical model. The current investigation was conducted to define an approach to devising such a model through multiple linear regression analysis. A more accurate model should be defined in the future, considering clinical parameters and also accurate measurements of the structural and mechanical properties of the corneal tissue.

A consistent linear model relating the thickness of superior and inferior ring segments with the achieved clinical changes and the ocular preoperative conditions was obtained. This analysis was first performed considering only the visual, refractive, and keratometric data that were available in all the participating centers. We found that the thicknesses of the inferior and superior ring segments were significantly correlated with the preoperative manifest cylinder, the change in mean keratometry and the difference in thickness between the inferior and superior segments. Thicknesses correlated inversely with the preoperative cylinder and the keratometric change, which means that the thicker the segment, the higher the keratometric change, consistent with previous findings in normal eyes.[25,26] However, this effect was limited by the preoperative manifest cylinder of the eye, which seems to be in relation with the instability of the keratoconic cornea. The third implicated factor, the difference in thickness between the inferior and superior segments, represents the interaction between both ring segments, and it correlated positively with the thickness of the inferior ring segment, but inversely with the thickness of the superior ring segment. This result means that the most positive combination for KeraRing consists of a superior ring segment that is thinner than the inferior implant. The goodness of fit of these models was confirmed by testing the homoscedasticity of the models, the correlation between residuals and the multicollinearity. The predictability of the superior ring segment thickness model was good, with 91.23% of unstandardized residuals <100 μm and 63.16% ≤ 50 μm. However, the predictability of the inferior ring segment thickness model was moderate, with 87.72% of unstandardized residuals <100 μm and 63.16% ≤ 50 μm.

Furthermore, a new multiple regression analysis was performed including only the sample of eyes with examination of corneal aberrations, which was smaller because this kind of examination was performed in only two of the participating centers. Despite the smaller sample, the predictability of the models of the thicknesses of the superior and inferior ring segments improved. In both models the same influencing factors were detected (preoperative cylinder, keratometric change, and difference in thickness between inferior and superior ring segments), but an additional aberrometric parameter was included: the change in the RMS value corresponding to the corneal higher order aberrations (negative correlation). Thinner segments would be necessary in those cases in which the required reduction in corneal higher order aberrations is lower (cases with lower preoperative levels of higher order aberrations). In contrast, thicker segments would be necessary in the corneas with the highest aberrations. It has been demonstrated that the visual outcome of ICRSs implanted according to a standard nomogram, in all cases correlated inversely with the magnitude of some corneal higher order aberrations.[2,35] It should be considered that larger amounts of corneal higher order aberrations are present in the more advanced keratoconic corneas.[31,36] In such cases, the biomechanical alteration seems to be more pronounced. Indeed, in previous work, our research group found a significant correlation between the corneal resistance factor (CRF) parameter measured with the ocular response analyzer (ORA; Reichert) and the magnitude of corneal spherical-like aberrations.[36] All the topographic and aberrometric alterations in keratoconic eyes are the consequence of the biomechanical changes that occur in the corneal structure. Therefore, the improvement in the predictability of the models for the ring segment thicknesses, when the corneal higher order aberrations are included, could be the consequence of introducing an additional factor in relation to the corneal biomechanical status. In other words, the introduction of the aberrometric factor could be an indirect manner of considering part of the corneal biomechanical factor. In any case, this indirect contribution of aberrometry to corneal biomechanics is limited, and it does not account for the total biomechanical effect. The predictability of the superior ring segment thickness model including corneal aberrations was quite good, with 92.68% of unstandardized residuals <100 μm and 75.61% ≤ 50 μm. The predictability of the model for the thickness of the inferior segment was also good but a little bit more limited, with 90.24% of unstandardized residuals <100 μm and 68.29% ≤ 50 μm.

Finally, we performed the analysis of the residuals for the four developed multiple linear models. Although the predictability was acceptable for all models, there were a few cases with residuals of 100 μm or more. In such cases, the use of this nomogram would not be appropriate, leading to poorly predictable results. Specifically, we found that those cases with residuals >50 μm presented higher levels of corneal higher order aberrations. Higher RMS values for corneal spherical-like aberrations were found in those cases with the highest residuals. This aberrometric parameter was found to correlate inversely with one biomechanical parameter provided by the ORA system, the CRF.[36] Therefore, it seems clear that the corneal biomechanical status is a limiting factor for the developed nomogram and would have significant relevance in more advanced keratoconus. Currently, there is no nomogram for ICRS implantation that takes into account the specific biomechanical properties of the cornea. One reason for this is that the analysis of the corneal biomechanical properties of the cornea in vivo is not an easy task in clinical practice. To this date, only one device has been developed for the clinical evaluation of corneal biomechanics: the ORA (Reichert).[37] This device is an adaptation of a noncontact tonometer, which allows the measurement of the intraocular pressure as well as two new metrics referred to as corneal hysteresis (CH) and CRF. The exact differences between these two biomechanical parameters, as well as the exact contributions of the elastic and viscous components to the magnitude of these parameters are not yet completely understood. However, although we do not know the exact physical meaning of these parameters, CH and CRF have been shown to be very useful for characterizing the biomechanical properties of the cornea in the clinical practice.[38] Indeed, as previously mentioned, the keratometry and the magnitude of corneal higher order aberrations have been shown to correlate inversely with the CRF in keratoconus.[36]

Limitations of the current investigation should be also mentioned. One limitation is its retrospective nature, with no possibility of including cases with the same controlled postoperative protocol of measurements. For example, as mentioned, corneal aberrations were not obtained in all cases because different topographic devices were used and one of them was not able to derive aberrations directly. This fact limited the sample size available for the analysis of some clinical parameters. A second limitation was the two different incision criteria used in the study. It should be noted that there is no general agreement about which location for corneal incision is the better option. Different reference points have been described in the literature, such as the temporal position, the 12 o'clock position (superior), the axis of positive cylinder if it is not 90° away from topographic axis, and the steepest topographic meridian.[39] To this date, there are no published studies in which the visual, refractive, and keratometric outcomes were compared after ICRS implantation via some of these incision locations. Theoretically, the ideal location would be the steepest corneal meridian, as most surgeons do currently, because this kind of incision would reduce the corneal power of the steepest meridian, and it would increase the flattest keratometric reading. This solution would minimize the corneal and manifest astigmatism. However, significant reductions in manifest cylinder have also been achieved in eyes with the incision located elsewhere.[39] In our study, an incision on the steepest corneal meridian was used in most of the cases, with very few cases with the incision distant from the steepest corneal meridian. We think that this factor caused very little variability in the outcome. Indeed, we have obtained predictable models for the selection of the ring segments according to the intended corneal change and the preoperative conditions of the eye. Furthermore, the most important issue was the position of the ring segments, and that was always parallel to the flattest corneal meridian.

In conclusion, KeraRings are useful for corneal modeling in keratoconus, but their effect is not the same in all cases. The thickness of the implants are related to the keratometric change, but there are other factors that account for the final effect, as the preoperative astigmatism or the preoperative level of corneal higher order aberrations. The selection of the ring segment to implant should not be based only on refraction and the subjective appearance of the corneal topographic pattern. Corneal aberrometry is an additional factor that should be considered in the selection of the ring segments to implant. Specifically, the thicknesses of the superior and inferior 160° arc length KeraRing segments that should be implanted in a keratoconic eye correlated significantly with the preoperative manifest cylinder, the intended changes in the mean keratometry, and the RMS value for corneal higher order aberrations and also with the selected difference in thickness between the inferior and superior ring segments. We have devised a consistent multiple linear model relating all these factors that only fails in corneas with the highest aberrations—that is, in the most advanced cases. The predictability in these advanced cases was limited with the proposed nomograms and it seems the underlying significant biomechanical alteration necessitates a more complex mathematical model for characterizing the ring segment effect. In future studies, a precise factor should be included in the ICRS model that accounts for real biomechanical status. To achieve this end, further developments in the field of corneal biomechanics are necessary to obtain an accurate instrument for evaluating corneal biomechanics, using the standard physical concepts used for the description of the viscoelastic materials. In addition, the applicability of this model for the development of a new optimized nomogram for the clinical practice should be addressed in the future.

References

1. Torquetti L, Fabri Berbel R, Ferrara P. Long-term follow-up of intrastromal corneal ring segments in keratoconus. *J Cataract Refract Surg.* 2009;35:1768–1773.
2. Piñero DP, Alió JL, El Kady B, et al. Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures. *Ophthalmology.* 2009;116:1675–1687.
3. Ferrara P, Torquetti L. Clinical outcomes after implantation of a new intrastromal corneal ring with a 210-degree arc length. *J Cataract Refract Surg.* 2009;35:1604–1608.
4. Coskunseven E, Kymionis GD, Tsiklis NS, et al. One-year results of intrastromal corneal ring segment implantation (KeraRing) using femtosecond laser in patients with keratoconus. *Am J Ophthalmol.* 2008;145:775–779.
5. Shetty R, Kurian M, Anand D, Mhaske P, Narayana KM, Shetty BK. Intacs in advanced keratoconus. *Cornea.* 2008;27:1022–1029.
6. Ertan A, Ozkilic E. Effect of age on outcomes in patients with keratoconus treated by Intacs using a femtosecond laser. *J Refract Surg.* 2008;24:690–695.
7. Ertan A, Kamburoglu G. Intacs implantation using femtosecond laser for management of keratoconus: comparison of 306 cases in different stages. *J Cataract Refract Surg.* 2008;34:1521–1526.
8. Shabayek MH, Alió JL. Intrastromal corneal ring segment implantation by femtosecond laser for keratoconus correction. *Ophthalmology.* 2007;114:1643–1652.
9. Zare MA, Hashemi H, Salari MR. Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy. *J Cataract Refract Surg.* 2007;33:1886–1891.
10. Kymionis GD, Siganos CS, Tsiklis NS, et al. Long-term follow-up of Intacs in keratoconus. *Am J Ophthalmol.* 2007;143:236–244.
11. Alió JL, Shabayek MH, Artola A. Intracorneal ring segments for keratoconus correction: long-term follow-up. *J Cataract Refract Surg.* 2006;32:978–985.
12. Alió JL, Shabayek MH, Belda JI, Correas P, Feijoo ED. Analysis of results related to good and bad outcomes of Intacs implantation for keratoconus correction. *J Cataract Refract Surg.* 2006;32:756–761.
13. Ertan A, Kamburoglu G, Bahadir M. Intacs insertion with the femtosecond laser for the management of keratoconus: one-year results. *J Cataract Refract Surg.* 2006;32:2039–2042.
14. Colin J. European clinical evaluation: use of Intacs for the treatment of keratoconus. *J Cataract Refract Surg.* 2006;32:747–755.
15. Kanellopoulos AJ, Pe LH, Perry HD, Donnenfeld ED. Modified intracorneal ring segment implantations (INTACS) for the management of moderate to advanced keratoconus: efficacy and complications. *Cornea.* 2006;25:29–33.
16. Hellstedt T, Mäkelä J, Uusitalo R, Emre S, Uusitalo R. Treating keratoconus with Intacs corneal ring segments. *J Refract Surg.* 2005;21:236–246.
17. Miranda D, Sartori M, Francesconi C, Allemann N, Ferrara P, Campos M. Ferrara intrastromal corneal ring segments for severe keratoconus. *J Refract Surg.* 2003;19:645–653.
18. Siganos CS, Kymionis GD, Kartakis N, Theodorakis MA, Astyrakakis N, Pallikaris IG. Management of keratoconus with Intacs. *Am J Ophthalmol.* 2003;135:64–70.
19. Boxer Wachler BS, Christie JP, Chandra NS, Chou B, Korn T, Nepomuceno R. Intacs for keratoconus. *Ophthalmology.* 2003;110:1031–1040.
20. Siganos D, Ferrara P, Chatzinikolas K, Bessis N, Papastergiou G. Ferrara intrastromal corneal rings for the correction of keratoconus. *J Cataract Refract Surg.* 2002;28:1947–1951.

21. Colin J, Cochener B, Savary G, Malet F, Holmes-Higgin D. INTACS inserts for treating keratoconus: one-year results. *Ophthalmology.* 2001;108:1409–1414.
22. Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. *J Cataract Refract Surg.* 2000;26:1117–1122.
23. Fleming JF, Lee Wan W, Schanzlin DJ. The theory of corneal curvature change with the intra-stromal corneal ring. *CLAO J.* 1989;15:146–150.
24. Patel S, Marshall J, Fitzke III FW. Model for deriving the optical performance of the myopic eye corrected with an intracorneal ring. *J Refract Surg.* 1995;11:248–252.
25. Burris TE, Baker PC, Ayer CT, Loomas BE, Mathis ML, Silvestrini TA. Flattening of central corneal curvature with intrastromal corneal rings of increasing thickness: an eye-bank eye study. *J Cataract Refract Surg.* 1993;19(suppl):182–187.
26. Nosé W, Neves RA, Schanzlin DJ, Belfort Júnior R. Intrastromal corneal ring–one-year results of first implants in humans: a preliminary non-functional eye study. *Refract Corneal Surg.* 1993;9:452–458.
27. Daxer A, Fratzl P. Collagen orientation in the human corneal stroma and its implication in keratoconus. *Invest Ophthalmol Vis Sci.* 1997;38:121–129.
28. Alió JL, Artola A, Hassanein A, Haroun H, Galal A. One or 2 Intacs segments for the correction of keratoconus. *J Cataract Refract Surg.* 2005;31:943–953.
29. Levinger S, Prokroy R. Keratoconus managed with Intacs: one-year results. *Arch Ophthalmol.* 2005;123:1308–1314.
30. Rabinowitz YS. Keratoconus. *Surv Ophthalmol.* 1998;42:297–319.
31. Alió JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg.* 2006;22:539–545.
32. González Pérez J, Cerviño A, Giraldez MJ, Parafita M, Yebra-Pimentel E. Accuracy and precision of EyeSys and Orbscan systems on calibrated spherical test surfaces. *Eye Contact Lens.* 2004;30:74–78.
33. Applegate RA, Sarver EJ, Khemsara V. Are all aberrations equal? *J Refract Surg.* 2002;18:S556–S562.
34. Aghamohammadzadeh H, Newton RH, Meek KM. X-ray scattering used to map the preferred collagen orientation in the human cornea and limbus. *Structure.* 2004;12:249–256.
35. Piñero DP, Alió JL, Uceda-Montanes A, El Kady B, Pascual I. Intracorneal ring segment implantation in corneas with post-laser in situ keratomileusis keratectasia. *Ophthalmology.* 2009;116:1665–1674.
36. Piñero DP, Alió JL, Barraquer RI, Michael R, Jiménez R. Corneal biomechanics, refraction and corneal aberrometry in keratoconus: an integrated study. *Invest Ophthalmol Vis Sci.* 2010;51:1948–1955.
37. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg.* 2005;31:156–162.
38. Ortiz D, Piñero D, Shabayek MH, Arnalich-Montiel F, Alió JL. Corneal biomechanical properties in normal, post-laser in situ keratomileusis, and keratoconic eyes. *J Cataract Refract Surg.* 2007;33:1371–1375.
39. Piñero DP, Alió JL. Intracorneal ring segments in ectatic corneal disease-a review. *Clin Exp Ophthalmol.* 2010;38:154–167.