Corneal Biomechanical Changes After Intracorneal Ring Segment Implantation in Keratoconus

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Purpose: To evaluate by means of the Ocular Response Analyzer (ORA) the biomechanical changes that follow intracorneal ring segment (ICRS) implantation and to develop a predicting model for the postoperative visual outcome, considering these biomechanical changes and other clinical parameters.

Methods: A total of 45 consecutive keratoconic eyes of 35 patients aged 18 to 55 years and implanted with ICRS were included in this retrospective study. All patients were implanted with KeraRing using femtosecond laser technology. Visual acuity, refraction, corneal topography, and aberrations were evaluated during a 6-month follow-up. Additionally, corneal biomechanical changes were evaluated with the ORA system.

Results: No significant changes in corneal hysteresis (CH) and corneal resistance factor (CRF) were observed at 1 month postoperatively ($P \geq 0.39$). However, significant changes in these parameters were detected afterward (CH, 3 months, $P = 0.03$; CRF, 6 months, $P = 0.02$). Preoperative corneal biomechanical parameters were significantly correlated with postoperative corneal higher-order aberrations at all visits ($P \leq 0.05$), although these correlations became stronger at the end of the follow-up. Multiple regression analysis revealed that corrected distance visual acuity at 1 month after surgery was significantly correlated with the preoperative mean keratometry and the preoperative difference between CH and CRF ($P < 0.01$, adjusted R^2 of 0.66).

Conclusions: Biomechanical parameters measured with the ORA and mean keratometry are factors allowing a prediction of the postoperative visual outcome in a short term after ICRS implantation in keratoconic eyes. In the long term, corneal biomechanical changes limit the prediction of the ring segment effect.

Key Words: corneal biomechanics, intracorneal ring segment, KeraRing, Ocular Response Analyzer

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Keratoconus is an ectatic corneal disorder characterized by a progressive corneal thinning that results in corneal protrusion, irregular astigmatism, and decreased vision.[1] A variety of options have been described for the management of this pathological condition, such as the use of rigid gas-permeable contact lenses,[2] the implantation of intracorneal ring segments (ICRS),[3–22] or the performance of a keratoplasty procedure.[23] The main objective of all these options of treatment in keratoconus is to restore visual function, which is deteriorated because of the significant increase in all ocular aberrations.[24–27]

ICRS have been demonstrated to be very effective in improving visual acuity and in reducing the refractive error and mean keratometry in keratoconic eyes.[3–22] The addition of these segments at the corneal midperiphery of a healthy cornea induces a displacement of the local anterior surface forward at this area and a flattening of the central portion of the anterior cornea because of the morphological structure of corneal lamellae (arc-shortening effect).[28,29] This flattening effect, which is in direct proportion to the thickness of the implant and in inverse proportion to its diameter,[28] is responsible for a spherocylindrical change. In keratoconus, it is assumed that a similar process occurs after ICRS implantation. However, the well-organized lamellar structure of the cornea is lost when the corneal tissue degenerates, as occurs in keratoconus.[30] The regular orthogonal arrangement of the collagen fibrils is destroyed within the apical scar of the keratoconus.[30] Therefore, the ICRS effect in ectatic corneas may be different from the effect achieved in normal corneas when myopia is corrected because the structural properties of the corneal collagen framework are also different.

There is a need for readjusting the nomograms for ICRS implantation in keratoconus. They should consider the structural properties of the corneal tissue in which the segments are going to be inserted. The human cornea is a viscoelastic tissue[31] that responds to the presence of a force, such as that applied peripherally by ICRS. This response varies depending on the magnitude of force and also on the velocity of the force application, as a consequence of the viscoelastic

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behavior of the cornea. Assuming that the same force is applied to the cornea, changes induced in the corneal profile will be different in corneas with different biomechanical properties. Considering this, the effect of ICRS could be optimized by using the specific biomechanical profile of each individual cornea, and not only the keratorefractive parameters, as a guide for the surgical planning.

The study of the corneal biomechanical properties of the cornea in vivo is not an easy task in clinical practice. To this date, only 1 device has been developed for such purpose, the Ocular Response Analyzer (ORA) from Reichert (Buffalo, NY).[32] This device is an adaptation of a noncontact tonometer, which allows the measurement of the intraocular pressure and 2 new metrics referred to as corneal hysteresis (CH) and corneal resistance factor (CRF). Considering the definition of these 2 biomechanical parameters, the CH may reflect mostly the corneal viscosity, whereas the CRF may predominantly relate to the elastic properties of the cornea.[33] However, the exact difference between these 2 biomechanical parameters, CH and CRF, and the exact contributions of the elastic and viscous components to the magnitude of these parameters are not still completely understood, and more comprehensive research on this is necessary to extract consistent conclusions about the physical meaning of CH and CRF. Both the biomechanical parameters have been demonstrated to be significantly reduced in keratoconic eyes, especially in the most advanced cases.[33,34] These reduced viscoelastic properties may be a limiting factor for the effect of ICRS in some keratoconic cases and then for the predictability of this option of treatment. This could explain in part the significant variability reported by some authors in the outcomes obtained after ICRS implantation. On the other hand, it is still unknown if corneal biomechanics is modified with the implantation of ICRS. Several medium to long term studies have reported a partial regression of the changes achieved with time in sphere and keratometry.[9,10,20,35]

The main objective of the present study was to evaluate by means of the ORA the biomechanical changes occurring in keratoconic corneas after ICRS implantation during a 6-month follow-up. The secondary objective was to develop a predictive model for the postoperative success of the surgery, considering the preoperative visual, refractive, aberrometric, and also biomechanical data. To the best of our knowledge, this is the first study that attempts to define a predictive model for the visual success of this kind of surgical option, considering the preoperative clinical features of the keratoconic patient and also the biomechanical properties of the cornea.

PATIENTS AND METHODS

Patients

All eyes with the diagnosis of keratoconus and implanted with ICRS were retrospectively analyzed in 2 Spanish ophthalmologic centers: Vissum Instituto Oftalmológico de Alicante and Centro de Oftalmología Barraquer in Barcelona. A total of 45 consecutive keratoconic eyes of 35 patients aged 18 to 55 years old were finally included (mean age, 29.50 ± 9.14 years) in the current analysis. A total of 58.3% of patients included in this study were men and 41.7% were women. In 10 of these keratoconic cases, a bilateral implantation was performed, and in 25 cases, the implantation was unilateral because of the presence of keratoconus in only 1 eye or the presence of a higher rate of severity or progression of keratoconus in 1 eye of some bilateral cases.

Only keratoconus cases implanted with KeraRing using the femtosecond laser technology and with no other previous ocular surgery or active ocular disease were included in this retrospective analysis. 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 1 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 and the Alió–Shabayek[26] classification systems were used for grading keratoconus. In all cases, ICRS implantation was indicated because of the existence of reduced corrected distance visual acuity (CDVA) and/or contact lens intolerance.

Ethical board committee approval of our institution was obtained for this investigation. In addition, permission was granted to later include clinical information in scientific studies during the process of consent for this surgery in all cases.

Examination Protocol

A comprehensive examination was performed in all cases that included uncorrected distance visual acuity (UDVA) [logarithm of the minimum angle of resolution (logMAR) scale], CDVA (logMAR scale), manifest refraction, slit-lamp biomicroscopy, Goldman tonometry, fundus evaluation, ultrasonic pachymetry, and corneal topographic analysis. As topographic data were collected from 2 different centers, a total of 2 different corneal topography systems were used for corneal examination: the CSO (CSO, Firenze, Italy) and the Orbscan II systems (Bausch & Lomb, Rochester, NY). The first device is a Placido-based system, and the Orbscan II is a combined scanning-slit and Placido-disk topography system. Although the agreement between these 2 specific devices has not been reported, Orbscan and Placido-based devices have been proven to provide similar accuracy and precision on calibrated spherical test surfaces.[36] 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 central zone (KM).

Corneal aberrometry was also recorded and analyzed, but only in those patients examined with the CSO topography system (CSO) (25 eyes), because only this device was capable of calculating directly this specific information. This topography system analyzes a total of 6144 corneal points of an area enclosed in a circular annulus defined by an inner and outer radius of 0.33 and 10 mm with respect to corneal vertex, respectively. The software of the CSO, the EyeTop2005, automatically performs the conversion of the corneal elevation profile into corneal wave front 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 following parameters were analyzed and recorded: total RMS, RMS for corneal astigmatism, higher-order 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.

Corneal biomechanics were characterized by means of the ORA (Reichert). This device delivers to the eye an air pulse that causes the cornea to move inward, achieving a specific applanation state or flattening (P1). Milliseconds after the first applanation, the pressure decreases and the cornea passes through a second applanated state (P2) while returning from concavity to its normal convex curvature. Two different pressures are then recorded (P1 and P2), and the difference between them is considered as the CH. In addition, the software of this instrument provides another parameter, the CRF, which is calculated using a proprietary algorithm and it is said to be predominantly related to the elastic properties of the cornea.[32] These parameters, CH and CRF, were proven to be reproducible in nonoperated healthy eyes.[37]

Surgery

Surgical procedures were performed by 2 experienced surgeons (J.L.A. from Vissum Alicante and R.I.B. from Centro de Oftalmología Barraquer). In all cases, an antibiotic prophylaxis before surgery consisting of topical ciprofloxacin (Oftacilox; Alcon Cusí, Barcelona, Spain) every 8 hours for 2 days was prescribed to be applied. All procedures were performed under topical anesthesia.

Corneal incision was placed on the steepest meridian (30 eyes, 66.7%) in the majority of cases. In 15 eyes only, the incision was placed temporally (near the steepest meridian in 4 cases and oblique to the flattest and steepest corneal meridian in the remaining 11 cases). Femtosecond technology was used in all cases for corneal tunnelization (30-kHz IntraLase femtosecond system; IntraLase Corp, Irvine, CA). The disposable glass lens of the laser system was first applanated to the cornea to fixate the eye and help maintain a precise distance from the laser head to the focal point.[7] Then, a continuous circular stromal tunnel was created at approximately 80% of corneal depth within 15 seconds with no corneal manipulation.[7] A tunnel with an inner and outer diameter of 4.8 and 5.7 mm, respectively, was always planned. Ring segments were then inserted manually into the dissected channels.

The selection of the number (1 or 2) and thickness of KeraRing segments was performed following the nomogram defined by the manufacturer, which is based on the topographic pattern, the manifest sphere, and the manifest cylinder. In 17 eyes (37.8%), only 1 ring segment was implanted, whereas in the remaining 28 eyes (62.2%), 2 segments were necessary.

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

Follow-up Evaluation

Postoperative visits were scheduled for the first postoperative day and for the postoperative months 1, 3, and 6. On the first postoperative day, measurement of UDVA and slit-lamp examination (ICRS position and corneal integrity) were performed. Visual acuity testing, manifest refraction, slit-lamp examination, and corneal topography were performed in the remaining postoperative examinations. In a total of 9 eyes, ring segments were explanted or repositioned during the follow-up, and then it could not be completed. The postoperative visits after ring reposition or explantation were not included in the analysis to avoid bias.

Statistical Analysis

SPSS statistics software package version 15.0 for Windows (SPSS, Chicago, IL) was used for statistical analysis. Normality of all data samples was first checked by means of the Kolmogorov–Smirnov test. When parametric analysis was possible, the Student *t* test for paired data was used for all parameter comparisons between preoperative and postoperative examinations or consecutive postoperative visits. On the contrary, when parametric analysis was not possible, the Wilcoxon rank sum test was used to assess the significance of differences between preoperative and postoperative data, using in all cases the same level of significance ($P < 0.05$).

Correlation coefficients (Pearson or Spearman, depending on whether a normality condition could be assumed) were used to assess the correlation between different variables. Furthermore, a multiple regression analysis was performed using the backward elimination method, with the aim of obtaining a mathematical expression relating the postoperative visual outcome at 1, 3, and 6 months with several preoperative clinical parameters. Model assumptions were evaluated by analyzing residuals, normality of unstandardized residuals (homoscedasticity), and Cook 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 2 participating centers to the current study was as follows: 25 eyes from Vissum Alicante and 20 eyes from Centro de Oftalmología Barraquer. There was a balanced distribution of right and left eyes (21 eyes vs 24 eyes, respectively). No cone opacity was observed in any case. According to the Amsler–Krumeich grading system, 18 eyes had a cone grade I (40.0%), 13 eyes a cone grade II (28.9%), 5 eyes a cone grade III (11.1%), and 9 eyes a cone grade IV (20.0%). Considering the corneal aberrations and according to the Alió–Shabayek grading system, 9 eyes had

a cone grade I (37.5%), 7 eyes a cone grade II (29.2%), 3 eyes a cone grade III (12.5%), and 5 eyes a cone grade IV (20.8%). Table 1 summarizes the main clinical outcomes of this study.

Visual and Refractive Outcomes

No significant changes were observed in either manifest sphere or cylinder ($P \geq 0.37$, Wilcoxon test), although mean values of these parameters were slightly lower during the initial postoperative period (Fig. 1). In addition, a slight regression of the limited spherical correction achieved was observed between months 3 and 6 after surgery, but this change did not reach statistical significance ($P = 0.39$, Wilcoxon test; Fig. 1).

Regarding the visual outcomes, an improvement in the limit of statistical significance was found in the logMAR UDVA, which changed from a mean preoperative value of 0.99 ± 0.53 to a mean 1-month postoperative value of 0.74 ± 0.37 ($P = 0.05$, Wilcoxon test). No significant changes were found in this parameter during the remaining follow-up ($P \geq 0.07$, Wilcoxon test). LogMAR CDVA changed from a mean preoperative value of 0.28 ± 0.17 to a mean postoperative value of 0.25 ± 0.15. This slight improvement was not statistically significant ($P = 0.42$, Wilcoxon test). In addition, no significant changes were observed in logMAR CDVA during the remaining follow-up ($P \geq 0.90$, Wilcoxon test). At 3 months after surgery, 5 eyes lost lines of logMAR CDVA, whereas at 6 months after surgery, losses of lines were only present in 3 eyes. In 3 of those eyes suffering losses of lines of CDVA, ring segments were explanted because of the poor visual outcome obtained.

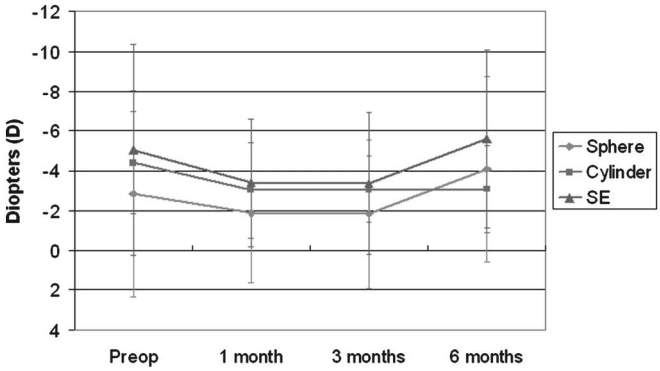

FIGURE 1. Changes in sphere (orange line), cylinder (gray line), and spherical equivalent (SE) (green line) during the 6-month follow-up.

Keratometric and Corneal Aberrometric Outcomes

All keratometric readings were reduced significantly 1 month after surgery [mean change KM = 2.39 diopters (D), K1 = 1.60 D, K2 = 3.26 D; all $P < 0.01$, paired Student *t* and Wilcoxon tests; Fig. 2). This flattening effect was maintained until the third postoperative month, with a nonsignificant regression at 6 months (mean regression KM = 0.11 D, K1 = 0.19 D; both $P \geq 0.18$, paired Student *t* test; Fig. 2). Corneal astigmatism in the 3-mm central zone (K2–K1) changed significantly from a mean preoperative value of 4.84 ± 2.68 D to a mean 1-month postoperative value of 3.16 ± 2.36 D ($P = 0.01$, paired Student *t* test), with

TABLE 1. Summary of the Clinical Outcomes in the Current Series During the Follow-up

	Mean (SD); Median (Range)				*P* (Preoperative to 6 mo)
	Preoperative	1 mo	3 mo	6 mo	
LogMAR UDVA	0.99 (0.53); 1.00 (0.10 to 2.78)	0.74 (0.37); 0.70 (0.15 to 1.48)	0.78 (0.31); 0.70 (0.19 to 1.48)	0.77 (0.36); 0.70 (0.30 to 1.30)	0.19 (Wilcoxon)
Sphere (D)	−2.84 (5.20); −1.00 (−18.00 to +4.00)	−1.88 (3.51); −0.75 (−13.50 to +3.00)	−1.81 (3.72); −1.00 (−13.50 to +4.00)	−4.08 (4.67); −3.00 (−13.00 to +2.50)	0.35 (Wilcoxon)
Cylinder (D)	−4.40 (2.57); −4.50 (−9.50 to 0.00)	−3.03 (2.39); −2.00 (−9.00 to 0.00)	−3.05 (1.67); −2.75 (−6.00 to 0.00)	−3.08 (2.17); −2.25 (−7.50 to 0.00)	0.05 (Student *t*)
LogMAR CDVA	0.28 (0.17); 0.30 (0.00 to 0.70)	0.25 (0.15); 0.22 (0.00 to 0.52)	0.25 (0.20); 0.22 (0.00 to 0.70)	0.28 (0.15); 0.30 (0.00 to 0.52)	0.12 (Student *t*)
K1 (D)	47.72 (4.54); 46.50 (39.90 to 57.64)	46.12 (3.55); 45.16 (41.50 to 54.00)	45.64 (3.67); 45.82 (38.80 to 53.97)	46.31 (4.03); 46.02 (40.19 to 53.60)	<0.01 (Wilcoxon)
K2 (D)	52.55 (5.19); 52.10 (44.48 to 63.79)	49.29 (3.87); 48.81 (43.20 to 57.01)	48.79 (4.92); 48.22 (41.80 to 59.78)	49.42 (4.70); 49.50 (42.82 to 57.99)	<0.01 (Student *t*)
KM (D)	50.12 (4.67); 49.05 (43.25 to 60.30)	47.73 (3.55); 47.05 (42.70 to 54.50)	47.23 (4.10); 46.71 (40.30 to 56.46)	47.84 (4.15); 48.06 (42.12 to 54.55)	<0.01 (Wilcoxon)
Spherical-like RMS (μm)	1.00 (0.51); 0.98 (0.24 to 2.02)	0.98 (0.41); 1.12 (0.26 to 1.45)	1.00 (0.40); 1.10 (0.24 to 1.54)	1.27 (0.38); 1.29 (0.46 to 1.96)	0.42 (Student *t*)
Coma-like RMS (μm)	3.20 (1.81); 2.77 (0.68 to 8.53)	2.66 (1.58); 2.17 (0.45 to 6.07)	2.66 (1.59); 2.25 (1.12 to 6.27)	2.99 (1.23); 2.99 (1.16 to 5.25)	0.12 (Student *t*)
CH (mm Hg)	8.01 (1.01); 8.00 (5.90 to 10.30)	8.12 (1.06); 8.00 (6.30 to 10.30)	8.25 (0.77); 8.10 (6.50 to 9.50)	8.32 (0.86); 8.30 (6.60 to 9.70)	0.13 (Student *t*)
CRF (mm Hg)	6.71 (1.30); 6.80 (4.00 to 9.80)	6.33 (1.06); 6.20 (4.50 to 8.90)	6.44 (0.98); 6.50 (4.50 to 8.40)	6.38 (1.16); 6.40 (4.20 to 8.60)	0.98 (Student *t*)

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 power in the 3-mm central zone.

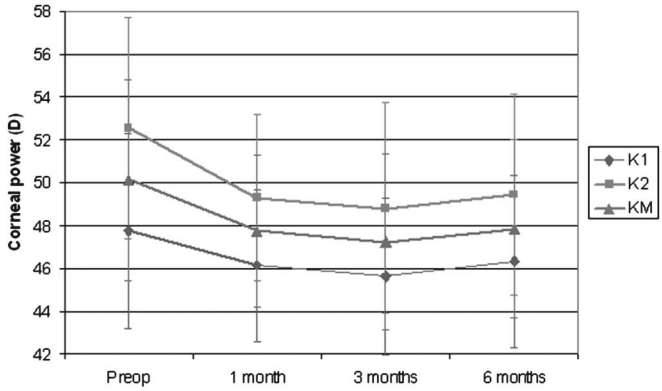

FIGURE 2. Changes in keratometric parameters during the 6-month follow-up: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1) (green line), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2) (orange line), and mean corneal power in the 3-mm zone (KM) (gray line).

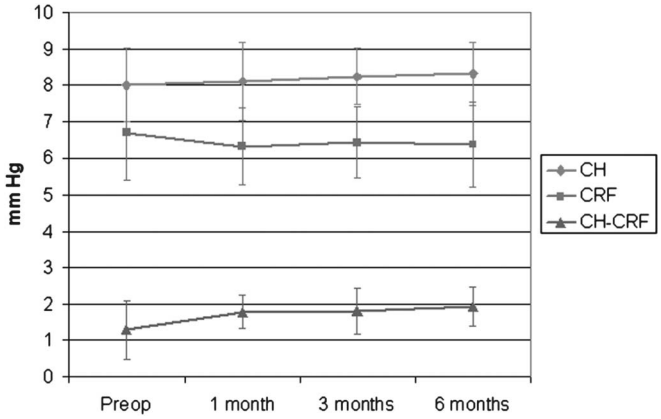

FIGURE 4. Changes in the biomechanical parameters provided by the ORA during the 6-month follow-up: CH, orange line; CRF, gray line; CH-CRF, difference between CH and CRF, green line.

no significant changes during the remaining follow-up ($P \geq 0.28$, paired Student t test).

Regarding corneal aberrations, no significant changes were detected in the total RMS ($P \geq 0.60$, Wilcoxon test) and in the RMS value for corneal astigmatism ($P \geq 0.60$, Wilcoxon test). A significant decrease in the higher-order, primary coma, and coma-like RMS values was observed during the initial follow-up (3 months, $P \leq 0.03$, Wilcoxon test; Fig. 3). However, a nonsignificant regression of this aberrometric correction was observed between months 3 and 6 after surgery ($P \geq 0.74$, Wilcoxon test). In addition, the primary spherical aberration term became progressively more positive with time during the follow-up (6 months, $P = 0.03$, Wilcoxon test; Fig. 3). Finally, the magnitude of spherical-like aberrations experienced an increase in the limit of statistical significance between the third and sixth postoperative month ($P = 0.05$, paired Student t test).

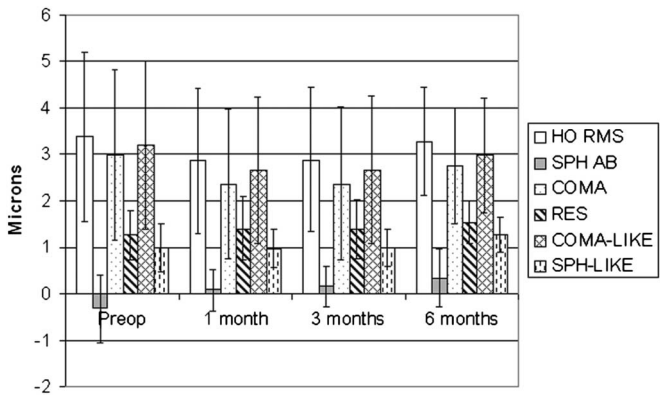

FIGURE 3. Bar diagram showing changes in corneal higher-order aberrations during the 6-month follow-up. HO, higher order; SPH AB, primary spherical aberration; COMA, primary coma; RES, higher-order residual; SPH-LIKE, spherical-like. Definitions of each kind of corneal aberration: primary coma, Zernike terms $Z_3^{\pm 1}$; primary spherical aberration, Zernike term Z_4^0; residual higher-order aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like aberrations, fourth- and sixth-order Zernike terms; coma-like aberrations, third- and fifth-order Zernike terms.

Corneal Biomechanical Changes

No significant changes in CH and CRF were observed at 1 month after surgery ($P \geq 0.39$, paired Student t test; Fig. 4). At 3 months, a slight but statistically significant increase was only found in CH ($P = 0.03$, paired Student t test). In addition, a slight but significant decrease in CRF was found at 6 months after surgery ($P = 0.02$, paired Student t test). The difference between CH and CRF increased significantly during the follow-up, with statistically significant changes at all time intervals (1 month preoperatively, $P = 0.01$; 1–3 months postoperatively, $P = 0.03$; 3–6 months postoperatively, $P = 0.05$; paired Student t test; Fig. 4).

Predictive Model for the Visual Outcome

At 1 month, the following statistically significant correlations between the postoperative visual outcome and the preoperative data were found: preoperative CDVA–postoperative CDVA ($r = 0.59$, $P < 0.01$), preoperative KM–postoperative CDVA ($r = 0.68$, $P < 0.01$), preoperative higher-order RMS–postoperative CDVA ($r = 0.54$, $P = 0.03$), and preoperative coma RMS–postoperative CDVA ($r = 0.55$, $P = 0.02$) (Fig. 5). However, no significant correlations were found at 6 months between the postoperative visual outcome and any preoperative parameter (Fig. 5).

Preoperative ORA biomechanical parameters and postoperative corneal higher-order aberrations were correlated significantly at all visits (preoperative CRF–1-month postoperative higher-order RMS, $r = -0.49$, $P = 0.05$; preoperative CRF–1-month postoperative coma RMS, $r = -0.54$, $P = 0.03$), although these correlations became stronger at the final follow-up (preoperative CRF–6-month postoperative higher-order RMS, $r = -0.73$, $P = 0.01$; preoperative CRF–6-month postoperative coma RMS, $r = -0.62$, $P = 0.03$; Fig. 5).

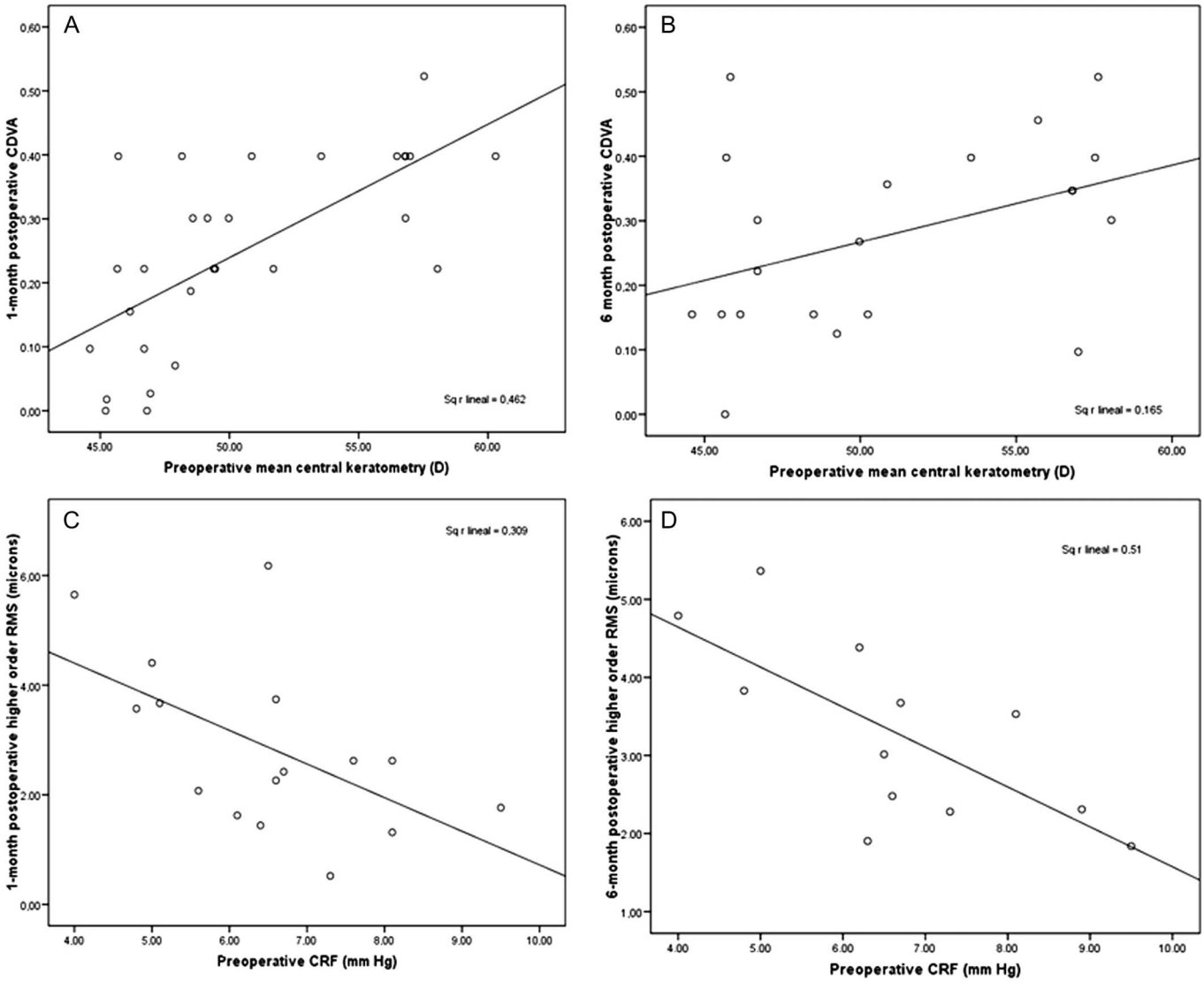

FIGURE 5. Scattergrams showing 2 different relationships, postoperative best spectacle–corrected distance visual acuity–preoperative mean central keratometry (upper figures) and postoperative higher-order RMS–preoperative CRF (lower figures), at 2 different time points of the follow-up (A and C, 1 month postoperatively; B and D, 6 months postoperatively). The adjusting line to the data obtained by means of the least squares fit is shown in the 4 graphs: 1-month postoperative logMAR CDVA = 0.02 × KM (D) − 0.80 (R^2 = 0.47); 6-month postoperative logMAR CDVA = 0.01 × KM (D) − 0.33 (R^2 = 0.17); 1-month higher-order RMS (micrometers) = −0.61 × CRF (millimeters of mercury) + 6.86 (R^2 = 0.31); 6-month higher-order RMS (micrometers) = −0.51 × CRF (millimeter of mercury) + 6.69 (R^2 = 0.51).

As several factors seemed to be implicated in the effect of ring segments, a multiple regression analysis was performed to find the appropriate mathematical expression relating all the factors influencing the postoperative visual outcome. This analysis was first performed considering only visual, refractive, and keratometric data, which were available in all the participating centers. This multiple regression analysis revealed that 1-month postoperative CDVA was significantly correlated with the preoperative mean keratometry and with the difference between ORA biomechanical parameters (CH-CRF) ($P < 0.01$). For this relation, a predicting model with predictability (R^2) of 0.69 and adjusted R^2 of 0.66 was found (Durbin–Watson statistic = 1.44):

$$\mathrm{CDVA_{post}} = -1.05 + 0.03 \times \mathrm{KM_p} - 0.12 \times \mathrm{CHCRF_p},$$

where $\mathrm{CDVA_{post}}$ (logMAR) is the 1-month postoperative CDVA, $\mathrm{KM_p}$ the preoperative mean keratometry, and $\mathrm{CHCRF_p}$ the preoperative difference between CH and CRF.

Homoscedasticity of the model was confirmed by the normality of the unstandardized residuals distribution ($P = 0.20$) and the absence of influential points or outliers (mean Cook distance = 0.04 ± 0.07). With this model, 68.97%

of unstandardized residuals were lower than 0.1% and 100% less than or equal to 0.17. The poor correlation between residuals (Durbin–Watson test = 1.44) and the lack of multicollinearity (tolerance, 0.74; VIFs between 1.36) was also confirmed.

For the remaining postoperative visual parameters (UDVA at 1, 3, and 6 months; CDVA at 3 and 6 months), poor linear predicting models were obtained, showing reduced predictability, multicollinearity, or a significant correlation of errors. When the multiple regression analysis was performed introducing also corneal aberrometric data (25 eyes), a predictive model for the postoperative CDVAs with higher predictability could be obtained but also with higher correlation between residuals (Durbin–Watson: 0.68, CDVA at 1 month) and a more significant level of multicollinearity (VIF $>$ 9), which was therefore less accurate. This seemed logical because the sample was significantly smaller.

Complications

Ring segment explantation was performed in a total of 3 eyes (6.67%). In all these cases, ring segments were explanted because of significant visual deterioration during the follow-up. In addition, ring segment reposition was performed in 1 case (2.22%) with the aim of maximizing the segment effect. No ring extrusion or migrations were observed during the follow-up.

DISCUSSION

In the current study, a mean reduction in sphere and cylinder was found in the initial postoperative period, but these changes did not reach statistical significance. This trend of ICRS to reduce manifest sphere and cylinder supports the previous findings of other authors also using KeraRing segments.[3,7] This reduction in spherocylindrical error was also reported by several authors using other types of ring segments, such as Intacs segments.[4,5,7,10,12–14,21,38] The absence of statistical significance in refractive changes in the current series could be explained by the large variability that was present in the refractive parameters preoperatively and postoperatively. It should be considered that early, moderate, and advanced keratoconus were included in this study. The slight and nonsignificant reduction in spherocylindrical error was associated with a significant improvement in logMAR UDVA. On the other hand, the large variability in the postoperative refractive outcomes was an indicative sign of the presence of a limited outcome in some cases and a very successful outcome in others. This fact shows the poor predictability of the nomogram used in the current series in some keratoconic corneas, which should be identified before ICRS implantation using a guideline, such as a specific nomogram. Another curious finding was the slight but nonsignificant regression of the achieved spherical correction in our series at 6 months after surgery. This slight variability in sphere in a medium term was also reported with Intacs in keratoconic eyes.[9,10,13,17]

Regarding corneal curvature, central keratometric readings (mean, steepest, and flattest Ks) were reduced significantly in the initial postoperative period. This outcome supports previous findings reported with KeraRing and Intacs segments, showing also a significant flattening effect.[3–14,20,38] This keratometric reduction is responsible for the change in spherocylindrical refraction and the increase in UDVA. Furthermore, a regression of the achieved central corneal flattening was observed between months 3 and 6 after surgery. This change did not reach statistical significance, but it was consistent with the nonsignificant regression of the myopic spherical correction also observed at 6 months after surgery. Therefore, it seems that in some keratoconic cases, corneal biomechanical changes could still occur despite the implantation of the ring segments. Significant changes were also observed in corneal higher-order aberrations. Specifically, a significant decrease was observed in coma-like aberrations, especially in the primary coma aberration. This aberrometric improvement could be in relation with the small and nonsignificant improvement found on average in the logMAR CDVA. It should be noted that primary coma has been demonstrated to have a very negative impact on visual acuity because of the optical blur that it induces.[39] In a previous study of our research group, a significant reduction of higher-order aberrations was also found after KeraRing implantation in keratoconus using the femtosecond laser technology but only in those eyes with a magnitude of coma aberration larger than 3 μm.[7] At 6 months after surgery, a nonsignificant regression of the achieved aberrometric correction was found and an increase in the magnitude of spherical-like aberrations was found as well. These medium-term changes suggest that biomechanical changes are still occurring in some keratoconic corneas, leading to spherocylindrical and higher-order aberrometric changes. These changes are able to limit in some cases the predictability of ICRS outcomes in the medium to long term and could be one of the factors accounting for the significant variability in the outcomes reported in different studies using ICRS.

Besides visual, refractive, and aberrometric outcomes, in the current study, we have analyzed the biomechanical changes occurring after KeraRing implantation by means of the ORA system. As noted before, this instrument provides 2 measures of corneal biomechanics at the central cornea, CH and CRF. The CH is calculated as the difference between the 2 pressures associated with the applanation processes during the measurement with the ORA system. This numerical value is assumed to represent the viscoelastic corneal tissue response to a dynamic deformation.[40] However, the CRF is calculated as a linear function of the 2 pressures recorded during the ORA measurement procedure (P1 and P2). From a mathematical standpoint, CRF places more emphasis on P1, so it should be more heavily weighted by the underlying corneal elastic properties.[40] For this reason, the manufacturer states that the CH may reflect mostly corneal viscosity, whereas the CRF may predominantly relate to the elastic properties of the cornea.[33] The exact difference between these 2 biomechanical parameters, CH and CRF, and the exact contributions of the elastic and viscous components to the magnitude of these parameters are still not completely understood. However, despite not knowing the exact physical meaning of these parameters, CH and CRF have been proven to be very useful for characterizing the biomechanical properties of the cornea

in clinical practice. As noted before, it has been proven that these parameters are altered in some pathological conditions, such as in keratoconus.[9,10] CH and CRF are usually reduced in this corneal condition, especially in the most severe cases.[9,10]

In the current study, we found no significant changes in the ORA biomechanical parameters in the initial postoperative period. It seems logical because the structural and mechanical properties of the central cornea were not modified with the insertion of the midperipheral implants. A previous article on this issue was recently published by Dauwe et al.[41] They also did not find significant changes after Intacs implantation in the CH and CRF 6 months after surgery, but they did not study the changes in the ORA biomechanical parameters between different time intervals of follow-up (1 month, 3 months, and 6 months).[41] Indeed, we have found significant changes in the ORA biomechanical parameters between months 1 and 3 after surgery and also between months 3 and 6. Regarding CRF, it decreased progressively during the follow-up, with a significant change at 6 months. In contrast, the CH progressively became higher during the follow-up, with a significant increase at 3 months. Furthermore, the difference between CH and CRF experienced a progressive significant increase during the follow-up. According to the definition of CH and CRF and from a theoretical point of view, because CRF is more heavily weighted by elasticity and it derives from the CH value that represents the global viscoelastic behavior, the difference between CH and CRF could be more affected by the viscous component of the cornea. However, this has not yet been proven, and there is no scientific evidence of it. All these corneal biomechanical changes with time are consistent with our refractive and aberrometric findings: slight regression of the refractive, keratometric, and aberrometric correction between months 3 and 6 after surgery suggesting that corneal biomechanics is not stable after ICRS implantation in all keratoconic corneas. This should be confirmed in future studies using larger samples of eyes and specific devices, allowing an analysis of corneal biomechanics using the standard properties defining the viscoelastic systems. In addition, we found a significant correlation between the preoperative CRF and the postoperative magnitude of higher-order aberrations. This correlation became progressively stronger with time, and it was negative; the higher the CRF, the less aberrated the cornea was postoperatively. Therefore, those corneas with a low CRF preoperatively (theoretically representing an altered elastic component of the cornea) seem to be more susceptible to becoming more aberrated with time after ICRS implantation.

We also attempted to define those factors allowing the clinician to identify keratoconus cases with a potentially poor visual outcome after KeraRing implantation using the nomogram defined by the manufacturer. At 1 month, visual outcomes were significantly correlated with several preoperative parameters, such as the mean keratometry, the CDVA, or the magnitude of higher-order aberrations. However, these correlations became weaker at 6 months after surgery. Therefore, no significant preoperative predictive factors for the 6-month postoperative visual outcome were detected. Possibly, the predictability for the visual outcome at 6 months after surgery was poorer because there were cases in which some corneal biomechanical changes occurred during the follow-up despite the ring segment effect, as suggested previously. These biomechanical changes were responsible for some alterations in the optical properties of the cornea and then of the eye, limiting the potential visual benefit of ring segments. In addition, we found an inverse correlation between the preoperative CRF and the postoperative magnitude of higher-order aberrations, as previously described.

A predictive model was obtained by means of a linear multiple regression analysis, with the aim of correlating all these predictive factors for a good visual outcome after KeraRing implantation. Two parameters were identified as predictive factors for the early postoperative visual outcome (1 month after surgery): the difference between CH and CRF and the mean keratometry. This means that a worse visual outcome can be expected in steeper corneas with a high biomechanical alteration, as determined by the difference between CH and CRF (larger differences). In such corneas, the effect of ICRS seems to be variable, limited, and difficult to predict. This predictive model for the visual outcome after KeraRing implantation including these 2 factors, KM and CH-CRF, showed sufficient precision, with a predictability of 66%. In a previous work, Levinger and Prokroy[42] found a predicting model for the postoperative UDVA after Intacs implantation, with the following predicting factors: the preoperative CDVA, manifest astigmatism, and manifest sphere. This model showed a very limited predictability (36%), which was consistent with our findings because we also found a poor predicting model for the postoperative UDVA. This limitation in the prediction of UDVA shows that the predictability for the correction of spherocylindrical errors is still limited. Several factors could account for this fact, such as the use of inaccurate nomograms or the errors in the determination of preoperative refraction because of the difficulty of finding the most appropriate focus in these highly aberrated eyes.[43] Other authors have also attempted to define some factors that could lead to a limited visual outcome after Intacs implantation, but they do not develop a specific predicting model. Examples of these limiting factors were the keratoconus severity,[6,11] mean keratometry,[11] spherical equivalent,[11] or manifest astigmatism.[42] Some of them were also identified by our predicting model. Therefore, the immediate best-corrected visual outcome after KeraRing implantation can be predicted from 2 preoperative parameters with an acceptable precision. However, the predictions for the visual outcome in the medium to long term are not so precise. We found difficulties in finding a predicting model for the uncorrected and best-corrected visual outcomes at 3 and 6 months after surgery from preoperative parameters. This was consistent with the relative instability of refraction, keratometry, and aberrations found in some keratoconic patients at 3 and 6 months postoperatively. Therefore, it seems that the modeling effect of the ring segments may be limited by biomechanical changes occurring in the postoperative medium term. The use of UV-A–collagen cross-linking could be considered as an additional advisable tool to maintain the modeling effect achieved, with the ring segments in those cases showing signs of biomechanical instability.

In conclusion, KeraRing segments are safe and useful for corneal modeling in keratoconus, but their effect is not maintained in a medium to long term in all cases. Some keratoconic corneas can suffer some biomechanical alterations, leading to a deterioration of corneal optics despite the ring segment effect. This fact is one factor that accounts for the variability in the outcomes obtained with KeraRing in the long term. The mean keratometry and the biomechanical parameters measured with the ORA system are factors that allow a prediction for the postoperative visual outcome in a short term. In the long term, corneal biomechanical changes can still occur, and these changes seem to be responsible for the limitation of the ring segment effect in some cases. Corneal collagen cross-linking could be a useful option of treatment for stabilizing the ring segment effect 1 month after ICRS implantation, but this is something that should be addressed in future studies.

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