Cornea

Corneal Biomechanics, Refraction, and Corneal Aberrometry in Keratoconus: An Integrated Study

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Purpose. To evaluate the relationship of corneal biomechanical properties to refraction and corneal aberrometry in keratoconic eyes.

Methods. A total of 81 consecutive keratoconic eyes of 81 patients ranging in age from 11 to 58 years were included in the study. Three groups were differentiated according to the severity of keratoconus: mild (37 eyes), moderate (24 eyes), and severe (20 eyes). Visual acuity, refraction, corneal topography, and corneal aberrations were evaluated. In addition, corneal biomechanics were analyzed in relation to two parameters: corneal hysteresis (CH) and corneal resistance factor (CRF). Correlations between these biomechanical factors and the remaining clinical parameters were investigated.

Results. CH and CRF in the severe keratoconus group were significantly lower than those in the other two groups ($P \leq 0.01$). A significant difference in CRF was found between mild and moderate cases ($P = 0.04$). A moderate correlation was found between the CRF and mean keratometry in the overall sample ($r = -0.564$). In addition, a significant, strong correlation was found between the spherical-like root mean square (RMS) and the CRF only in the severe keratoconus group ($r = -0.655$). Multiple regression analysis revealed that CRF correlated significantly with keratometry and the corneal spherical-like RMS ($R^2 = 0.40$, $P < 0.01$).

Conclusions. The CRF correlates with the magnitude of corneal spherical-like aberrations, especially in severe keratoconus. It should be considered an additional factor in keratoconus grading. (*Invest Ophthalmol Vis Sci.* 2010;51:1948–1955) DOI:10.1167/iovs.09-4177

Keratoconus is an ectatic corneal disorder characterized by progressive corneal thinning that results in corneal protrusion, irregular astigmatism, and decreased vision.[1] Its incidence varies depending on several factors, such as the ethnic group analyzed or the diagnostic criteria used (most estimates are between 50 and 230 per 100,000 in the general population).[1] The hallmark of this ectatic disorder is the presence of an irregular corneal astigmatism. This significant irregularity is the consequence of changes occurring in the anterior corneal geometry, which can be assessed by means of corneal topography: increased area of corneal power surrounded by concentric areas of decreasing power, inferior-superior power asymmetry, and skewing of the steepest radial axes above and below the horizontal meridian.[2,3] For this reason, corneal topography has become an indispensable tool for keratoconus diagnosis. In addition, the anterior corneal aberration analysis has been demonstrated to be an effective tool for detecting and grading keratoconus.[4–8] Higher amounts of vertical coma and larger values of coma-like root mean square (RMS) are usually present in patients with keratoconus or suspected keratoconus.[5–8]

All these topographic and aberrometric alterations in keratoconic eyes appear as a consequence of the biomechanical changes that occur in the corneal structure. Corneal elasticity and rigidity are severely affected in keratoconic eyes,[9,10] due to the structural alterations of the cornea. It should be considered that the keratoconic stromal structure is not based on an orthogonal lamellar matrix, as in normal corneas. In keratoconus, there are regions of highly aligned collagen intermixed with regions in which there is little aligned collagen.[11,12] These structural alterations lead to a weakening of the cornea, which becomes more susceptible to the effect of any pressure on it, such as intraocular pressure. As a consequence, corneal shape can be distorted more easily (corneal steepening and aberrometric increase).

The in vivo study of corneal biomechanical properties is not an easy task. To date, only one clinical device has been developed for the purpose (Ocular Response Analyzer [ORA]; Reichert, DePew, NY).[13] Two biomechanical parameters are provided by this instrument: corneal hysteresis (CH) and the corneal resistance factor (CRF). Other studies have demonstrated that these two parameters are significantly reduced in keratoconic eyes,[9,10] as would be expected. The purpose of the present study was to define the relationship between the biomechanical parameters provided by this system (i.e., CH and CRF), and other clinical data such as refraction, corneal topography, or aberrometry in keratoconus. The knowledge of these relations will allow the clinician to achieve a better understanding of the changes that occur in this ectatic disease and to obtain an integrated criterion for keratoconus diagnosis. In addition, it will provide information about the key clinical parameters representing the severity of this disease.

Methods

Patients

A total of 81 consecutive keratoconic eyes of 81 patients with diagnosed keratoconus were retrospectively analyzed in two Spanish ophthalmology centers: Vissum Instituto Oftalmológico de Alicante and Centro de Oftalmología Barraquer in Barcelona. The age of patients

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ranged from 11 to 58 years (mean, 31.81 ± 10.34); 56.8% were male and 43.2% were female. Keratoconus diagnosis was based on corneal topography and slit lamp observation. In all cases, clinical findings characteristic of keratoconus were evident: corneal topography revealing an asymmetric bowtie pattern, with or without skewed axes and at least one keratoconus sign on slit lamp examination, such as stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae, or anterior stromal scar.[1] Only keratoconus cases with no previous ocular surgery and no other active ocular disease were included in the study. Ethics board committee approval from our institution was obtained for the investigation. All patients were informed about inclusion in the study and signed an informed consent in accordance with the Declaration of Helsinki.

Examination Protocol

A comprehensive examination was performed in all cases and included: logMAR uncorrected visual acuity (UCVA), logMAR best spectacle-corrected visual acuity (BSCVA), manifest refraction, slit lamp biomicroscopy, Goldmann tonometry, fundus evaluation, ultrasonic pachymetry, and corneal topographic analysis. As topographic data were collected from two different centers, two different corneal topography systems were used for corneal examination: the CSO (CSO [Costruzione Strumenti Oftalmici], Firenze, Italy) and the Orbscan IIz (Bausch & Lomb, Rochester, NY). The first 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.[14] 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 the CSO topography system (55 eyes), because this device was the only one of those used in this study with the capability of direct calculation of this specific information. The system analyzes 6144 corneal points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33 mm and an outer radius of 10 mm with respect to corneal vertex. The software of the CSO (EyeTop2005; CSO) automatically performs the conversion of corneal elevation profile into corneal wavefront data by 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: higher order RMS, RMS for corneal astigmatism, 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 was 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 to be the CH. In addition, the software of this instrument provides the CRF, which is calculated by using a proprietary algorithm, and it is said to be predominantly related to the elastic properties of the cornea.[13] These parameters, CH and CRF, were shown to be reproducible in nonsurgical, healthy eyes.[15]

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

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 unpaired data (two samples) or the one-way analysis of variance (ANOVA) with Bonferroni post hoc analysis (more than two samples) was used to compare the outcomes between specific groups (i.e., comparison between keratoconus grades). When parametric analysis was not possible, the Mann-Whitney test (two samples) or the Kruskal-Wallis test (more than two samples) was used for the comparison between groups. Statistical significance was set at a α level of 0.05 (SPSS, ver. 15.0 for Windows; SPSS, Chicago, IL).

Correlation coefficients (Pearson or Spearman depending on whether a normality condition could be assumed) were used to assess the correlation between different variables. In addition, linear regression analysis was performed to obtain a bivariate linear model characterizing the relationship between those pairs of parameters showing good and significant correlation. Furthermore, a multiple regression equation (backward-elimination method) was derived by using different clinical data (visual acuity, refraction, keratometry, and corneal aberrations) to predict the biomechanical properties those measured by the ORA device (CH and CRF). All model assumptions were evaluated by analyzing residuals, normality of unstandardized residuals (homoscedasticity), multicollinearity, and Cook's distance, to detect influential points or outliers.

Results

The contribution of the two participating centers to the present study was as follows: 58 eyes from Vissum Alicante and 23 eyes from Centro de Oftalmología Barraquer. There was a balanced distribution of right and left eyes: 43 versus 38, respectively. Cone opacity was observed in six (7.4%) eyes. According to the Amsler-Krumeich grading system, 37 (45.7%) eyes had cone grade I, 24 (29.6%) cone grade II, 4 (4.9%) cone grade III, and 16 (19.8%) cone grade IV. Considering the corneal aberrations and according to the Alió-Shabayek grading system, 25 (44.6%) eyes had a cone grade I, 12 (21.4%) cone grade II, 7 (12.5%) cone grade III, and 12 (21.4%) cone grade IV. Table 1 shows a summary of the visual, refractive, keratometric, corneal aberrometric, pachymetric, and biomechanical data of the sample of keratoconic eyes analyzed in the study.

A significant but weak correlation was found between the ORA biomechanical parameters and the logMAR BSCVA (CH, $r = -0.354$; CRF, $r = -0.431$; $P < 0.01$). As shown in Figure 1, there was a significant variability in the relationship between biomechanical and visual data, which could explain the limited correlation between them. Regarding keratometry, moderate negative correlations were found between keratometric readings and the CRF (K1, $r = -0.554$; K2, $r = -0.558$; KM, $r = -0.564$; $P < 0.01$; Fig. 2). In addition, weak but significant correlations were found between the CRF and the corneal aberrometric parameters (all $P < 0.01$) higher order ($r = -0.484$), primary coma ($r = -0.487$), spherical-like ($r = -0.482$), and coma-like ($r = -0.487$) RMS (Fig. 3).

Multiple regression analysis revealed that the CRF correlated significantly with K1, higher order RMS, spherical-like RMS, and coma-like RMS ($P < 0.01$). For this relation, a linear model with predictability (R^2) of 0.40 and adjusted R^2 of 0.38 was found (Durbin-Watson statistic = 2.38; multicollinearity tolerance = 1.62):

$$CRF = 15.47 - 0.16 \times \mathrm{K1} - 0.71 \times \mathrm{RMS}_{sph-1}$$

Table 1. Summary of Data from the Sample of Keratoconic Eyes

Parameter	Mean ± SD (Range)
Visual parameters	
LogMAR UCVA	0.97 ± 0.57 (0.01 to 2.78)
LogMAR BSCVA	0.28 ± 0.25 (0.00 to 1.30)
Refractive parameters	
Sphere, D	−3.06 ± 5.22 (−19.75 to +4.00)
Cylinder, D	−4.03 ± 2.98 (−14.00 to 0.00)
Spherical equivalent, D	−5.08 ± 5.13 (−19.75 to +1.12)
Keratometric parameters	
K1, D	47.82 ± 5.04 (39.90 to 68.49)
K2, D	52.59 ± 6.80 (44.95 to 84.61)
KM, D	50.20 ± 5.75 (43.25 to 75.79)
Corneal aberrometric parameters	
Higher-order RMS, μm	3.17 ± 1.86 (0.48 to 10.30)
RMS astigmatism, μm	3.16 ± 2.52 (0.33 to 15.14)
Primary coma RMS, μm	2.72 ± 1.82 (0.33 to 9.01)
Z_4^0, μm	−0.21 ± 0.71 (−1.80 to 1.31)
Residual RMS, μm	1.28 ± 0.78 (0.26 to 4.71)
Spherical-like, μm	0.96 ± 0.62 (0.11 to 3.69)
Comalike, μm	2.98 ± 1.82 (0.47 to 9.62)
Pachymetric parameters	
Central pachymetry, μm	470.13 ± 56.39 (341.00 to 590.00)
Biomechanical parameters	
CH, mm Hg	8.06 ± 1.36 (4.90 to 10.90)
CRF, mm Hg	6.89 ± 1.56 (3.70 to 10.70)

Data are expressed as the mean ± SD (range).

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 zone; aberrometric definitions, primary coma, terms $Z_3^{\pm 1}$; primary spherical aberration, term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like, terms from fourth and sixth order; comalike: terms from third, fifth and seventh orders.

where K1 is the dioptric power in the flattest corneal meridian for the 3-mm central zone measured in diopters and RMS_{sph-l} is the RMS corresponding to the corneal spherical-like aberrations measured in micrometers.

The homoscedasticity of the model was confirmed by the normality of the unstandardized residuals distribution and the absence of influential points or outliers (mean Cook's distance = 0.02 ± 0.04). In this model, 26.71% of unstandardized residuals were higher than 1.5 mm Hg.

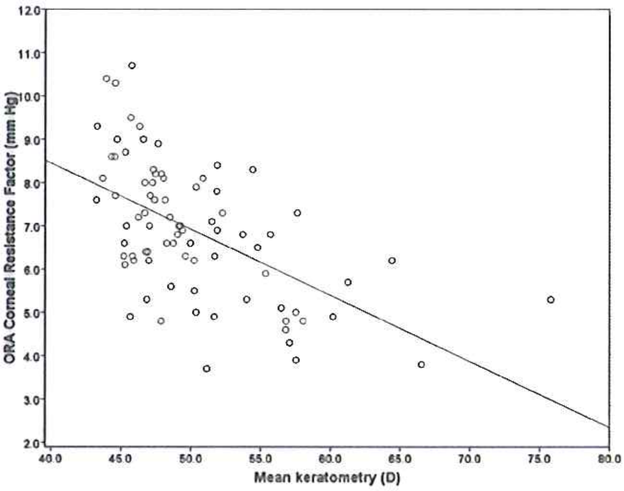

Figure 2. Scattergram showing the relationship between the CRF and KM. The adjusting line to the data obtained by means of the least-squares fit is shown. This linear predicting model showed a limited predictability (*straight line,* R^2 = 0.316).

On the contrary, the multiple regression analysis showed a weaker linear predictive model for the CH parameter (R^2 = 0.21, adjusted R^2 = 0.13). Specifically, the CH was found to correlate minimally with K1 and with higher order, spherical-like, and coma-like RMS values.

Besides this analysis, a comparison between keratoconus grades was performed. As only four eyes with keratoconus grade III (Amsler-Krumeich grading system) were included in our sample, a larger group including keratoconic eyes with either grade III and IV was created. This group was designated as the severe keratoconus group (20 eyes), and it was compared with keratoconic eyes of grades I (37 eyes) and II (24 eyes). No significant differences were present in age among these three groups of eyes (grade I, grade II, and severe keratoconus; P = 0.42, Kruskal-Wallis test). Table 2 summarizes the visual, refractive, and keratometric data obtained for the three

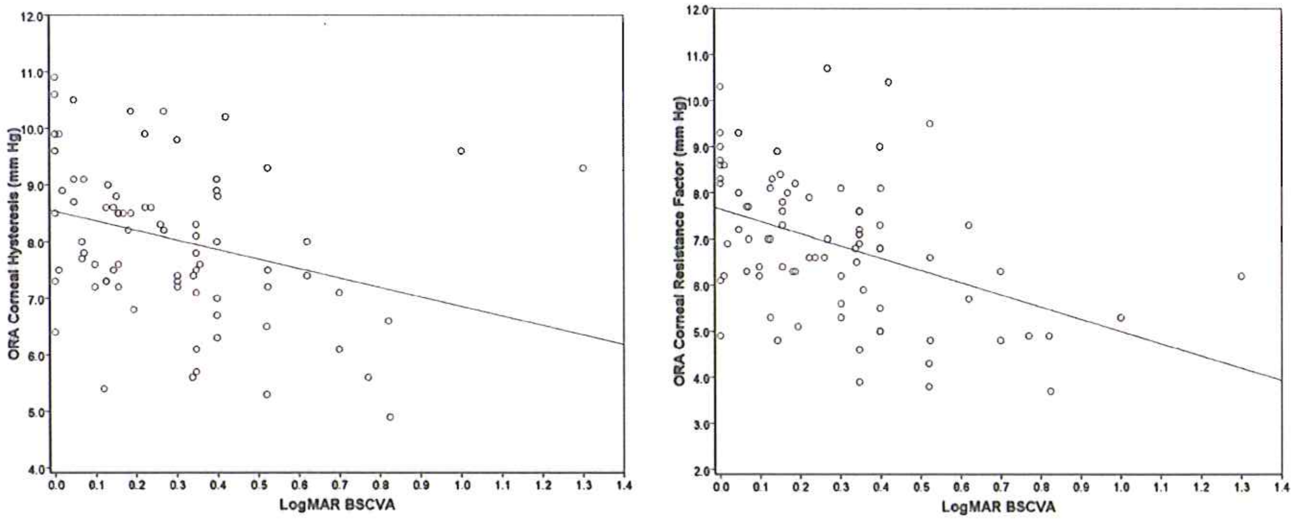

Figure 1. Scattergrams showing the relationship between the ORA biomechanical parameters and the logMAR BSCVA. *Left*: relationship between CH and logMAR BSCVA; *right*: relationship between the CRF and the logMAR BSCVA. In both graphs, the adjusting line to the data obtained by means of the least-squares fit is also shown. The two linear predicting models obtained showed a very low predictability (CH-BSCVA, *straight line,* R^2 = 0.10; CRF-BSCVA, *dotted line,* R^2 = 0.18).

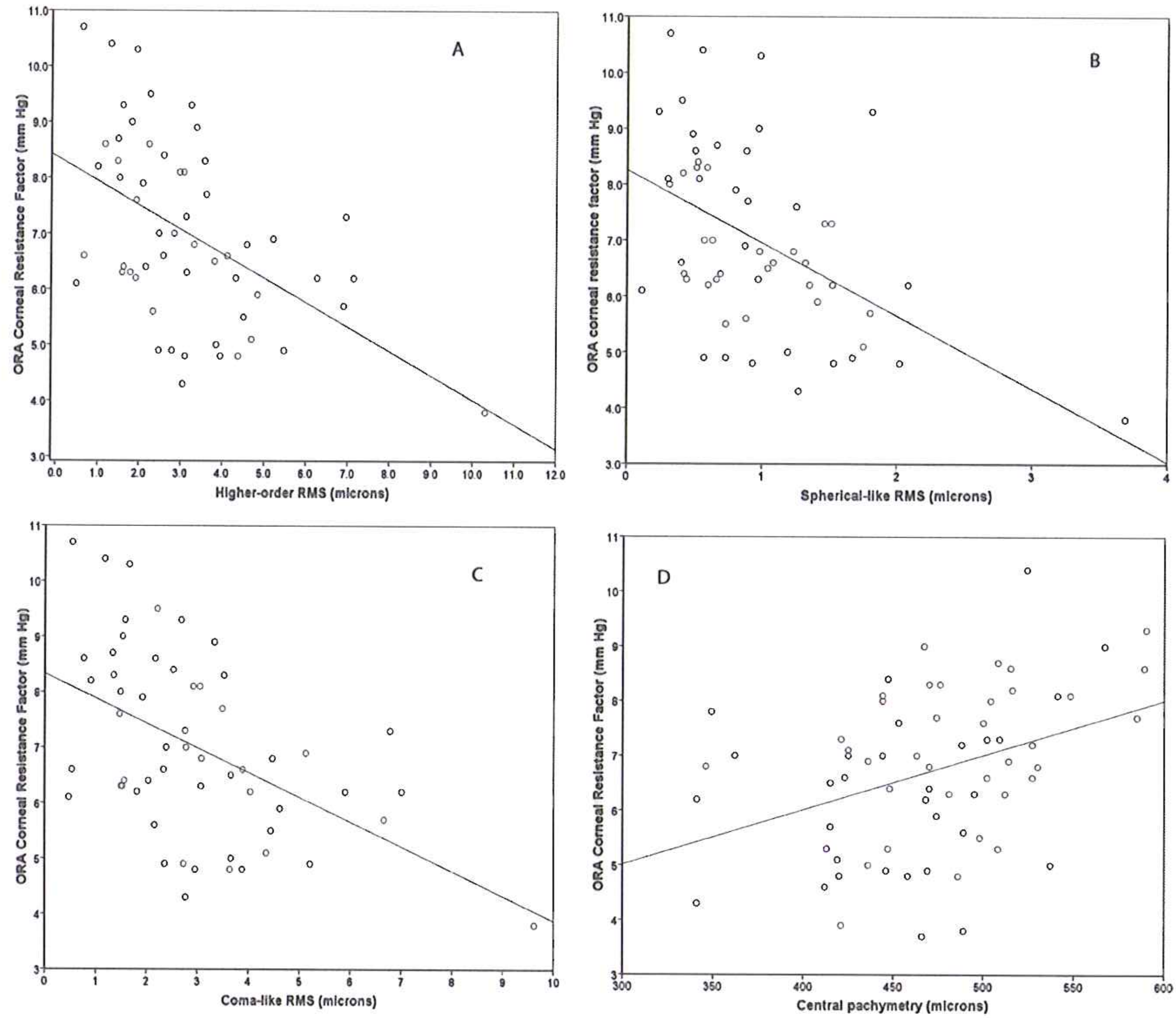

Figure 3. Scattergrams showing the relationship between the CRF and other clinical parameters: (**A**) higher order RMS; (**B**) spherical-like RMS; (**C**) coma-like RMS; and (**D**) central pachymetry. The adjusting line to the data obtained by means of the least-squares fit is shown in the four graphs: (**A**) CRF (mm Hg) = $-0.44 \times$ higher order RMS (μm) + 8.38 ($R^2 = 0.25$); (**B**) CRF (mm Hg) = $-1.30 \times$ spherical-like RMS (μm) + 8.26 ($R^2 = 0.24$); (**C**) CRF (mm Hg) = $-0.45 \times$ coma-like RMS (μm) + 8.33 ($R^2 = 0.24$); and (**D**) CRF (mm Hg) = $0.01 \times$ central pachymetry (μm) + 2.02 ($R^2 = 0.15$).

groups of eyes analyzed. As expected, significant differences were found between the keratoconus groups in logMAR UCVA, logMAR BSCVA, and keratometry (Kruskal-Wallis test, all $P < 0.01$). In addition, in eyes with keratoconus grade I, cylinder was significantly lower than in eyes with grade II and severe keratoconus (Mann-Whitney, $P \leq 0.03$).

Table 2. Summary of Visual, Refractive, Keratometric, and Pachymetric Data Obtained from the Three Groups of Eyes

Parameter (Range)	Grade I (37 Eyes)	Grade II (24 Eyes)	Grades III and IV Severe Keratoconus (20 Eyes)	*P*
LogMAR UCVA	0.72 ± 0.48 (0.01 to 1.78)	1.01 ± 0.46 (0.02 to 2.00)	1.37 ± 0.64 (0.05 to 2.78)	<0.01
Sphere, D	−2.18 ± 4.51 (−18.00 to +3.50)	−2.46 ± 4.16 (−10.00 to +4.00)	−5.44 ± 6.87 (−19.75 to +3.00)	0.27
Cylinder, D	−2.93 ± 2.47 (−9.50 to 0.00)	−5.05 ± 3.01 (−14.00 to 0.00)	−4.85 ± 3.23 (−12.00 to 0.00)	0.01
SE, D	−3.64 ± 4.48 (−19.50 to +1.12)	−4.98 ± 4.42 (−14.50 to +1.00)	−7.86 ± 6.09 (−19.75 to 0.00)	0.02
LogMAR BSCVA	0.16 ± 0.18 (0.00 to 0.70)	0.30 ± 0.19 (0.02 to 0.82)	0.50 ± 0.29 (0.00 to 1.30)	<0.01
K1, D	44.18 ± 1.72 (39.90 to 47.53)	47.59 ± 1.96 (43.50 to 50.60)	54.83 ± 4.37 (48.31 to 68.49)	<0.01
K2, D	47.72 ± 1.96 (44.95 to 52.35)	52.45 ± 1.50 (49.65 to 56.90)	61.75 ± 7.11 (55.52 to 84.61)	<0.01
KM, D	45.97 ± 1.38 (43.25 to 48.58)	49.95 ± 1.41 (47.64 to 51.88)	58.32 ± 5.40 (52.26 to 75.79)	<0.01
Central pachymetry, μm	499.93 ± 48.16 (413.00 to 90.00)	462.70 ± 53.01 (349.00 to 41.00)	437.35 ± 51.08 (341.00 to 509.00)	<0.01

Data are the mean ± SD (range). Abbreviations are defined in Table 1.

Table 3. Summary of Corneal Aberrometric Data for the Three Groups of Eyes Keratoconic Eyes

Parameter	Grade I (37 Eyes)	Grade II (24 Eyes)	Grades III and IV Severe Keratoconus (20 Eyes)	*P*
Higher order RMS	1.91 ± 0.87 (0.48 to 4.32)	3.69 ± 1.28 (2.08 to 7.14)	5.04 ± 2.01 (3.05 to 10.30)	<0.01
RMS astigmatism	2.10 ± 1.35 (0.48 to 5.36)	2.99 ± 1.48 (0.33 to 5.76)	5.41 ± 3.62 (1.18 to 15.14)	<0.01
Primary coma RMS	1.51 ± 0.88 (0.33 to 3.98)	3.42 ± 1.24 (1.72 to 6.90)	4.31 ± 2.13 (0.37 to 9.01)	<0.01
Z_4^0	+0.06 ± 0.46 (−1.26 to +0.70)	−0.24 ± 0.38 (−1.03 to +0.35)	−0.73 ± 1.06 (−1.80 to 1.31)	<0.01
Residual RMS	0.98 ± 0.43 (0.26 to 1.92)	1.26 ± 0.48 (0.58 to 2.27)	1.90 ± 1.17 (0.60 to 4.71)	0.01
Spherical-like RMS	0.71 ± 0.39 (0.11 to 1.81)	0.79 ± 0.32 (0.30 to 1.35)	1.64 ± 0.71 (0.51 to 3.69)	<0.01
Comalike RMS	1.74 ± 0.84 (0.47 to 4.04)	3.59 ± 1.27 (1.92 to 7.01)	4.75 ± 1.93 (2.76 to 9.62)	<0.01

Data are expressed as mean micrometers ± SD (range). Definitions are defined in Table 1.

Table 3 summarizes the corneal aberrometric data for the three groups of keratoconic eyes. Significantly lower levels of higher order, primary coma, coma-like, and higher order residual aberrations were present in eyes with keratoconus grade I in comparison with levels in the other two groups (Bonferroni and Mann-Whitney test, all $P < 0.01$). The spherical-like RMS was significantly higher in the severe keratoconic eyes compared with mild and moderate cases (Bonferroni test, $P < 0.01$). The primary spherical aberration was significantly more negative in those eyes with severe keratoconus (Mann-Whitney test, all $P < 0.05$). Regarding the RMS for corneal astigmatism, it was significantly higher in moderate and severe cases than in the mild cases (Bonferroni test, $P \leq 0.01$).

Figure 4 shows the differences in the corneal biomechanical parameters provided by the ORA between keratoconus groups. No significant differences in CH were found between mild and moderate keratoconus cases (Bonferroni, $P = 0.86$) or between moderate and severe cases (Bonferroni test, $P = 0.07$). However, significant differences in the CRF were found between all keratoconus groups (Bonferroni test; mild-moderate, $P = 0.04$; mild-severe, $P < 0.01$; moderate-severe, $P = 0.02$), with the lowest values in the most advanced cases (Fig. 4). Regarding corneal pachymetry, mild keratoconus corneas were significantly thinner than those with the diagnosis of moderate and severe keratoconus (Bonferroni test, $P \leq 0.04$).

Several correlations were found to be significant (although not all of them strong) when the relationship between different visual, refractive, keratometric, pachymetric, and aberrometric parameters and the ORA biomechanical parameters was investigated. In the mild keratoconus group, a positive correlation was found between the ORA biomechanical parameters and central pachymetry (CH, $r = 0.530$; CRF, $r = 0.481$; $P = 0.01$). However, in the moderate keratoconus group, a negative correlation was found between the ORA biomechanical parameters and logMAR BSCVA (CH, $r = -0.610$; CRF, $r = -0.587$; $P < 0.01$). In addition, a moderate correlation was found between the CRF and the RMS for spherical-like aberrations ($r = -0.502$, $P = 0.05$; Fig. 5). This correlation between CRF and spherical-like RMS became statistically significant and stronger in the severe keratoconus group ($r = -0.655$, $P = 0.01$; Fig. 5). Besides these correlations, in this group of eyes, a moderate and significant negative correlation was found between the steepest keratometric reading and the CRF ($r = -0.501$, $P = 0.03$).

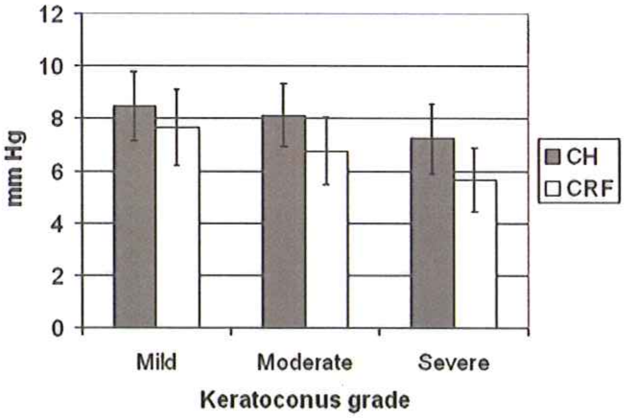

Figure 4. Differences in the biomechanical parameters provided by the ORA between keratoconus grades. CH and CRF were significantly lower in the group of eyes with severe keratoconus.

Discussion

The human cornea is a viscoelastic tissue[13,16] that responds to the presence of any force. This response is not only dependent on the magnitude of the force, but also on the velocity of the force application. As a viscoelastic element, two main properties can be identified in corneal tissue: static resistance or elasticity and viscous resistance or damping.[13] The first property describes the proportionality between the magnitude of tissue deformation and the applied force. The second property represents the dependence on time of the relationship between deformation and applied force. These properties describing the viscoelasticity of the cornea are in relation with its biomechanical behavior.[17]

Many studies have been conducted in an attempt to characterize corneal biomechanics,[13,18–22] but to do it in vivo is not an easy task. Invasive techniques have been described for this purpose, such as the injection of saline solution into the anterior chamber[18] or corneal imaging by central indentation.[19] However, Luce[13] presented in 2005 a noninvasive device for characterizing the corneal biomechanics in vivo, the ORA (Bausch & Lomb). This instrument uses a dynamic bidirectional applanation process to provide a new two measurements of corneal biomechanics: CH and the CRF.[13] Several studies have been performed with the ORA, most of them attempting to define the changes induced in corneal biomechanics after different kinds of surgeries[10,23–25] as well as in some pathologic processes.[9,13,26,27] Specifically, a reduction in the ORA biomechanical parameters was found in keratoconic corneas.[9,10] As commented before, this biomechanical limitation seems to be the consequence of those changes occurring in the collagen lamellar structure of these kinds of corneas (distortion of the orthogonal lamellar matrix).[11,12] Besides this biomechanical limitation, a corneal steepening and an aberrometric corneal increase can also be observed in keratoconic corneas.[1–8] The purpose of the present study was to analyze the degree of correlation between the biomechanical parameters provided by the ORA (CH and CRF) and other clinical data such as refraction, corneal topography, and aberrometry in keratoconus. In addition, we investigated whether there are visual, refractive, keratometric, pachymetric, or aberrometric param-

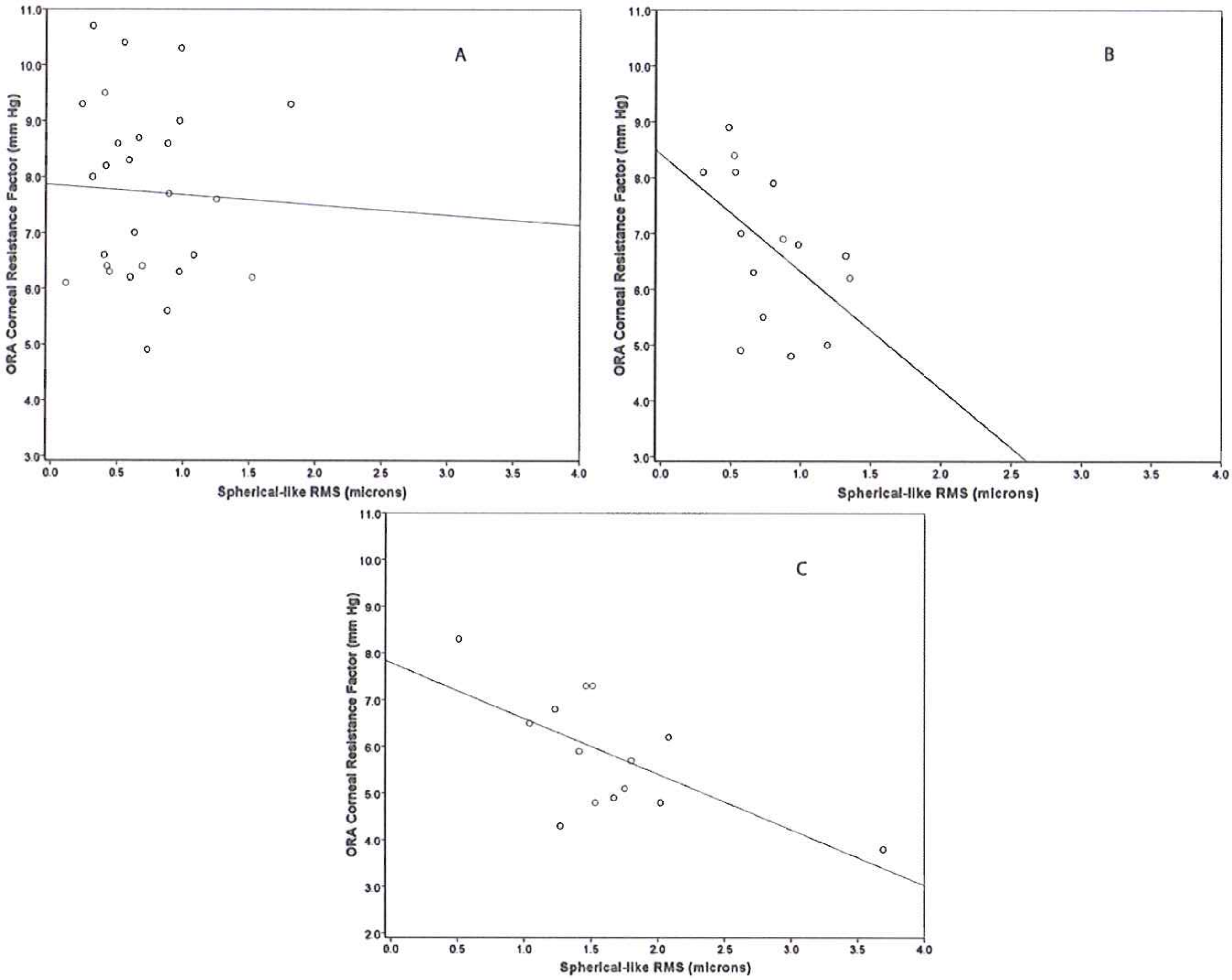

FIGURE 5. Scattergrams showing the relationship between the CRF and the RMS for spherical-like aberrations in the three groups of keratoconic eyes analyzed: (A) Mild keratoconus (grade I). (B) Moderate keratoconus (grade II) group. (C) Severe keratoconus (grades III and IV). The adjusting line to the data obtained by means of the least-squares fit is shown in the three graphs: (A) CRF (mm Hg) = $-0.18 \times$ spherical-like RMS (μm) + 7.86 ($R^2 < 0.01$); (B) CRF (mm Hg) = $-2.10 \times$ spherical-like RMS (μm) + 8.41 ($R^2 = 0.25$); and (C) CRF (mm Hg) = $-1.19 \times$ spherical-like RMS (μm) + 7.79 ($R^2 = 0.43$).

eters that enable prediction of the corneal biomechanical properties of keratoconic eyes. The knowledge of these relations will allow the clinician to achieve a better understanding of the changes that occur in this ectatic disease and to obtain an integrated criterion for keratoconus diagnosis. Furthermore, it will provide information about the key clinical parameters representing the severity of the disease.

In the present study, we found significant but weak correlations between the CRF and the various aberrometric coefficients (higher order, primary coma, spherical-like, and coma-like aberrations). All the correlation coefficients corresponding to these relationships were negative, indicating that the higher the aberration, the lower the CRF. One factor that could explain the weakness of these correlations was the high variability observed, especially in those eyes with moderate CRF (6–7 mm Hg; Fig. 3). In addition, a moderate negative correlation between CRF and mean curvature was found. It should be remembered that mean keratometric measures have always been used as a parameter for classifying the level of severity in keratoconus.[6] Curiously, the CH did not correlate significantly with any refractive, keratometric, pachymetric, or aberrometric parameters. Therefore, it seems that the CH is a parameter with less ability to characterize the clinical changes occurring in keratoconic corneas. This finding is consistent with a previous experience in which a viscoelastic biomechanical model of the cornea was used to describe the effect of viscosity and elasticity on CH and showed that the CH was a more variable parameter, with theoretically less diagnostic ability.[17] A low CH value could be present in a cornea with a high or low elastic modulus, depending on the associated viscosity.[17] Shah et al.[9] demonstrated that a clear separation of normal and keratoconic eyes was not possible with CH used as a screening criterion, because the ranges overlapped.

The manufacturer stated that CH may reflect mostly corneal viscosity, whereas the CRF may predominantly relate to the elastic properties of the cornea.[10] However, the exact physical meaning of these parameters is still not well understood. They are said to represent the viscoelastic properties of the cornea, but there is no study proving whether these parameters correlate with the standard mechanical properties used for the description of the elastic materials (Young's modulus). The CRF is calculated as a linear function of the two pressures recorded during the ORA measurement procedure (P1 and P2). It is said to be an indicator of the overall resistance of the cornea. From a mathematical point of view, the CRF places more emphasis on P1, and so it is more heavily weighted by the underlying corneal elastic properties.[17] However, despite not knowing the exact physical meaning of the parameters CH and CRF, they have been very useful for characterizing the biomechanical properties of the cornea.

Multiple regression analysis revealed that 40% of the variance in the CRF could be explained by the corneal flattest curvature and the levels of corneal spherical-like aberrations. Therefore, changes in the viscoelastic properties of the cornea seem to be in part responsible for the keratometric and aberrometric changes in keratoconus. This finding supports previous ones stating that the keratometric and aberrometric analysis are crucial for keratoconus diagnosis.[5-7] For example, our research group developed a keratoconus grading system in which mean keratometric measurements and the coma-like RMS were used as the main discriminating factors (Alió-Shabayek classification).[6] Regarding visual and refractive data, no correlations of these factors with the ORA biomechanical parameters were found. An explanation of this fact is the variability of these subjective measurements in keratoconus patients due to the difficulty in finding a clear focus in such patients.[28] It should be considered that the spherocylindrical refraction in keratoconus can be easily biased by the loss of retinal image quality induced by the significant aberrometric increase.

When the sample was divided into mild (grade I), moderate (grade II), and severe (grade III and IV) keratoconus cases, significant differences were found in the ORA biomechanical parameters, as expected. Significantly lower values of CH were found only in the severe ectatic cases. Regarding the CRF, the higher the keratoconus grade, the lower the CRF was, with significant differences between all keratoconus groups. It seems that the corneal elastic component, theoretically represented by the CRF, is greatly affected in severe keratoconus as a consequence of the structural changes. However, it seems that changes in the general viscoelastic properties (viscosity+elasticity), theoretically represented by CH, are more variable in keratoconic corneas.

A strong correlation was found between the magnitude of spherical-like aberrations and the CRF in severe keratoconic eyes. This correlation was negative and then, the higher the CRF, the lower the magnitude of spherical-like aberrations was. Therefore, corneas with lower CRF values were associated with a more aberrant corneal profile. We cannot find a simple explanation of this fact in our results, because the ectatic process is multifactorial, with several interacting variables. Probably, this biomechanical alteration represented by the low CRF makes the cornea more susceptible to deformation by intraocular pressure or the eyelid effect, leading to a more significant level of corneal irregularity. More studies on this issue are necessary, to obtain more precise information about the ectatic procedure and how the biomechanical alterations can affect the corneal profile. This study is preliminary, but it shows a potential relationship between corneal irregularity and corneal biomechanical changes. Our results support the previous scientific evidence that there are more levels of higher order corneal aberrations in keratoconic corneas.[4-8]

The correlation between the CRF and corneal higher order aberrations was limited in moderate keratoconus and very weak in mild keratoconus cases. In these cases, the CRF can be reduced, but with few alterations in corneal topography and aberrations. This fact indicates that a biomechanical alteration could be present before topographic and clinical changes become apparent and would explain the significant variability in topographic and aberrometric alterations that could be observed, especially in mild keratoconus, which make the detection of the most incipient cases sometimes difficult.

In summary, the ORA biomechanical parameters are significantly reduced in severe keratoconus, with significant differences between mild and moderate cases only for the CRF. Keratometry and the magnitude of corneal spherical-like aberrations are factors in relation with the biomechanical changes that occur in keratoconus. Therefore, all these factors should always be considered when diagnosing this ectatic corneal condition. Furthermore, it was demonstrated that corneas with a more reduced CRF (measured by the ORA system) were more irregular, with higher levels of corneal higher order aberrations, especially of spherical-like aberrations. This reduction in the CRF represents the biomechanical change that occurs in keratoconus. This parameter seems to correlate with changes in the elastic component of the cornea according to the manufacturer and previous studies, but the relation should be proven with accuracy in the future.

In future studies, the role of the CRF as a predictive parameter for keratoconus progression and the success of intracorneal ring segment implantation for the management of keratoconus should be evaluated. A better understanding of the CH and CRF and their exact contribution to the elastic and viscous components is necessary to achieve a more comprehensive characterization of the ectatic process of the cornea.

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