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Corresponding Author: Dr. Jose Manuel Gonzalez-Meijome, OD, FIACLE

Corresponding Author's Institution: University of Minho

First Author: Jose Manuel Gonzalez-Meijome, OD, FIACLE

Order of Authors: Jose Manuel Gonzalez-Meijome, OD, FIACLE; Cesar Villa, MSc, FAAO; Antonio Queiros, OD; Jorge Jorge, OD, PhD; Manuel Parafita, MD, PhD

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Abstract: Purpose: To investigate the short term response of the cornea to Corneal Refractive Therapy (CRT) for myopia and correlate it with corneal biomechanical properties as measured with a new device, the Ocular Response Analyzer. Methods: Eight eyes from eight young subjects were fitted with a reverse geometry contact lens pursuing a myopic correction of -4.00 D. Corneal resistance factor (CRF) and corneal hysteresis (CH) were measured prior lens fitting with the Ocular Response Analyzer and correlated with the change in the remaining ocular parameters (apical curvature, simulated keratometry and central corneal thickness) after a period of 3 hours of lens wear (progression) and the same time after lens removal (regression). Results: There was a trend towards faster progression and faster regression of the orthokeratologic effect for corneas with less resistance in terms of their biomechanical properties. However, CRF did not correlate significantly with any of the topographic and pachymetric parameters. Conversely, CH was significantly correlated with changes in steep keratometry (0.758; p=0.029) and central corneal thickness (0.755; p=0.030) during lens wearing phase. During the regression phase, CH significantly correlated with changes in steep keratometry (-0.835; p=0.010). Overall, higher values of CH meant slower progression and regression of the orthokeratologic effect. Conclusion: short-term response of the human cornea to CRT is correlated with the biomechanical properties of the cornea. Of the various theories that support such involvement on corneal response to reverse geometry contact lenses, that assuming a faster response and faster regression for corneas with lower resistance seems to be the more likely. Larger studies are necessary to clarify the involvement of corneal biomechanical properties on corneal response to orthokeratology.

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A Pilot Study on the Influence of Biomechanical Properties of the Cornea on Short-term Response to Myopic Corneal Refractive Therapy

Corresponding Author:
Jose Manuel Gonzalez-Meijome

Mailing Address and Telephone/Fax Numbers:
Department of Physics (Optometry)
Campus de Gualtar, University of Minho, 4710-057 Braga – Portugal
Tel.: +351 253 60 4067; Fax : +351 253 67 89 81
e-mail: jgmeijome@fisica.uminho.pt

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Signature	Printed name	Date
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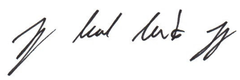	**Jorge Manuel Martins Jorge**	**3rd January 2007**

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A Pilot Study on the Influence of Biomechanical Properties of the Cornea on Short-term Response to Myopic Corneal Refractive Therapy

[1]González-Méijome JM, [2]Villa Collar C, [1]Queirós A, [1]Jorge J, [3]Parafita MA

[1] Department of Physics (Optometry), School of Sciences, University of Minho, Braga, Portugal.

[2] Clínica Oftalmológica Novovision. S.L. Madrid, Spain.

[3] Department of Surgery (Ophthalmology), School of Optics and Optometry. University of Santiago de Compostela, Santiago de Compostela, Spain.

Corneal Biomechanical Properties and Orthokeratology Response

Corresponding Author:

José Manuel González-Méijome
Department of Physics (Optometry)
Campus de Gualtar, University of Minho, 4710-057 Braga – Portugal
Tel.: +351 253 60 4067; Fax : +351 253 67 89 81
e-mail: jgmeijome@fisica.uminho.pt

ABSTRACT

Purpose: To investigate the short term response of the cornea to Corneal Refractive Therapy (CRT) for myopia and correlate it with corneal biomechanical properties as measured with a new device, the Ocular Response Analyzer. **Methods:** Eight eyes from eight young subjects were fitted with a reverse geometry contact lens pursuing a myopic correction of -4.00 D. Corneal resistance factor (CRF) and corneal hysteresis (CH) were measured prior lens fitting with the Ocular Response Analyzer and correlated with the change in the remaining ocular parameters (apical curvature, simulated keratometry and central corneal thickness) after a period of 3 hours of lens wear (progression) and the same time after lens removal (regression). **Results:** There was a trend towards faster progression and faster regression of the orthokeratologic effect for corneas with less resistance in terms of their biomechanical properties. However, CRF did not correlate significantly with any of the topographic and pachymetric parameters. Conversely, CH was significantly correlated with changes in steep keratometry (0.758; p=0.029) and central corneal thickness (0.755; p=0.030) during lens wearing phase. During the regression phase, CH significantly correlated with changes in steep keratometry (-0.835; p=0.010). Overall, higher values of CH meant slower progression and regression of the orthokeratologic effect. **Conclusion:** short-term response of the human cornea to CRT is correlated with the biomechanical properties of the cornea. Of the various theories that support such involvement on corneal response to reverse geometry contact lenses, that assuming a faster response and faster regression for corneas with lower resistance seems to be the more likely. Larger studies are necessary to clarify the involvement of corneal biomechanical properties on corneal response to orthokeratology.

Key Words: corneal refractive therapy; corneal thickness; corneal topography; corneal biomechanical properties; orthokeratology; corneal hysteresis.

INTRODUCTION

During years, one of the main drawbacks of orthokeratology (OK) was the lack of predictability of results, displaying a large inter-individual variability. Among other ocular parameters as corneal eccentricity, corneal resistance or sometimes called corneal rigidity has been considered as one of the potential factors affecting corneal response.[1] Several theories support the involvement of this property on the corneal response to OK. The first one is based on the overall bending of the cornea during OK treatment. In this case, a cornea with less resistance will show a more rapid response to OK lenses but will also display a rapid regression after lens removal (*figure 1A*). This is the most intuitive theory but changes in the posterior corneal surface seem to be limited to the early phases of the orthokeratologic treatment.[2] The second theory is based on the epithelial tissue distribution under reverse geometry contact lenses, which seems to explain medium and long-term refractive changes in OK.[3;4] According to this theory, and assuming that stiffness of the cornea is primarily given by the structure of Bowman's membrane and stroma, the opposite response will be expected. As a result, the corneal epithelium sandwiched between a reverse geometry rigid gas permeable contact lens and a more resistant Bowman's membrane and stroma will show a more rapid redistribution of epithelial thickness than if a less rigid cornea will be present. Regression will depend on the ability of the epithelium to reverse its new distribution of thickness; in the illustration of *figure 1B* it was assumed that a faster regression will be associated to higher corneal resistance). Two additional mixed scenarios are also possible. One assumes that corneas with higher resistance will display a slower onset of OK effect, and a quicker regression after lens removal (*figure 1C*), and the other assuming that corneas with higher resistance will display a more rapid onset of the OK effect and a slower regression (*figure 1D*). Of the four possibilities, the last one will be the most desirable situation in clinical terms.

However, some studies failed to find any correlation between corneal response to OK and ocular rigidity,[5] while others found that corneal rigidity could be correlated with induced corneal astigmatism.[6] The difficulty to obtain reliable measurements of the corneal biomechanical properties could be responsible for this lack of statistical correlations and confounding effects.

Nowadays new devices that measure the corneal biomechanical response of the human cornea are available.[7;8] The Ocular Response Analyzier (ORA; Reichert Inc, Depew, NY, USA) has been recently launched to the marketplace and has proved its ability to differentiate the biomechanical behavior of keratoconic and post-refractive surgery corneas against normal corneas.[9] Along with corneal thickness, biomechanical properties obtained from ORA have also shown clinical significance in predicting visual damage in glaucomatous patients.[10] The Ocular Response Analyzier (ORA; Reichert Inc, Depew, NY, USA) provides two parameters that are claimed to reflect the biomechanical properties of the eye, corneal hysteresis (CH) and corneal resistance factor (CRF). ORA is a non-contact tonometer (NCT) that registers two pressure readings. The first reading, so called "inward pressure" is registered when the increasing air pressure applanates the cornea; after that the pressure continues to increase until the cornea becomes slightly concave at the apex and beyond this point the air pressure begins to decrease rate, and the cornea again applanates in the way back to its original shape, and a second measurement the "outward reading" is taken. If the cornea will be a perfectly elastic tissue, the inward and outward reading will be equal to each other. However, because of the viscoelastic nature of the cornea, the outward reading is usually lower, what means a delay of the cornea to reach the original shape after the applanation. In other words, the pressure need to applanate the cornea during the increasing pressure phase, is not the same that allows the cornea to remain flat again when the pressure is decreasing. The difference in mmHg between inward and outward readings is called hysteresis and is claimed to represent the resistance of the cornea to change its shape due to absorption of energy from the air impulse that causes time delays in the occurrence of the applanation events.[11] The higher the difference between both readings, the higher the hysteresis parameter and the higher the resistance. An electro optical system detects inward and outward applanation over the central 3 mm of the cornea in about 20 ms.[12]

Back to the OK field, a recent study showed that older corneas respond less to OK in the short term[13] and the authors attributed this effect to a limited ability of the corneal epithelium to be remodeled, thus achieving the desired central corneal flattening necessary to reduce myopia. Nevertheless, older corneas have demonstrated to change their biomechanical properties, displaying higher rigidity.[14] If biomechanical properties of the cornea have any involvement on corneal response to OK this could help to understand the inter-individual response to this method of refractive correction.

The present study was designed to investigate the involvement of corneal biomechanical properties as measured with ORA on the short-term corneal response to OK with Paragon CRT. If any significant correlation does exists between biomechanical properties of the cornea and corneal response to orthokeratology it will be interesting to know which corneal parameters are most likely to reflect such a connection in order to plan future studies on this unknown field.

MATERIAL AND METHODS

Eight volunteers (2 males, 6 females) aged 21.9±1.1 years were fitted with Paragon CRT® rigid gas permeable contact lenses according to the fitting recommendations of the manufacturer. A treatment effect of -4.00 myopic correction was attempted in all eyesin the right or left eye according to a random assignment. After the ideal fit was achieved on a trial, the patients attended on a separate day early in the morning (at least 3 hours after awaking) and baseline measurements of corneal topography using Medmont E300 (Medmont Pty. Ltd., Melbourne, Victoria, Australia), biomechanical properties with ORA (Reichert Inc., Depew, NY) and central corneal thickness (CCT) with US pachymeter SP-100 Handy (Tomey, Nagoya, Japan) were taken. Subsequent topographic and pachymetric readings were obtained after 180 minutes of lens wear and 180 minutes after lens removal. Instruments were calibrated prior to data acquisition.

The research protocol followed the tenets of the Declaration of Helsinki and was reviewed and approved by the Scientific Committee of the School of Sciences of Minho University (Portugal). After explaining the nature of the experimental procedures, a signed informed consent was obtained from each subject prior to data acquisition.

Base curve radius (BCR), return zone depth (RZD) and landing zone angle (LZA) for the first diagnostic lens were derived from monograms in the form of sliding tables produced by the manufacturer.[15] Fitting evaluation was based on fluorescein assessment, lens centration and movement followed by over-refraction. The parameters of RZD and LZA were manipulated until a satisfactory fluorescein fitting pattern was achieved with good centration, light apical bearing over a central 4-mm zone, a paracentral tear reservoir free of air bubbles, tangent peripheral zone and adequate axial edge clearance with an over-refraction between plano and +0.50 D.

Data were analyzed using the statistical package SPSS version 14.0. Descriptive statistics of biomechanical properties of the cornea as well as corneal topographic and pachymetric information at baseline, after 3 hours of lens wear and 3 hours after lens removal were obtained. Thus, progression (*P*) and regression (*R*) values are presented in units of change against baseline or corneal parameters after 180 minutes of lens wear, respectively. Normal distribution of variables was assessed by Kolmogorov-Smirnov normality test. Differences between average progression and regression response (in absolute value for comparison purposes only) were assessed by Paired Samples T-test. Onset of the orthokeratologic effect or "progression" (*P*) after 3 hours with lenses and "regression" (*R*) and 3 hours after lens removal, were correlated with corneal biomechanical properties provided by ORA (CH and CRF). The level of statistical significance was set at α=0.05. Regression analysis was also used in order to graphically illustrate the nature of those correlations.

RESULTS

Table 1 presents the descriptive statistics of the progression (*P*) and regression (*R*) response for apical radius (r_0_P, r_0_R), flat keratometric curvature (K_f_P,K_f_R), steep keratometric curvature (K_s_P, K_s_R), and central corneal thickness (*CCT_P*, *CCT_R*). Differences between progression and regression response (as the absolute value of differences against baseline and against 180 minutes of lens wear, respectively) were statistically significant for all parameters ($p<0.05$) except apical radius ($p=0.862$) which recovered almost completely 3 hours after lens removal. Results are shown in *table 2*.

Correlations of biomechanical properties (CRF and CH) with topographic (r_0_P, r_0_R K_f_P, K_f_R, K_s_P and K_s_R) and pachymetric (*CCT_P* and *CCT_R*) parameters were explored and presented in *table 2*. *Figure 2* shows the graphical representation of those relationships. All progression values displayed a positive correlation with CRF and CH. Considering that progression of the orthokeratologic effect would result in negative values for r_0_P, K_f_P, K_s_P, *CCT_P*, this result means that faster progression is observed as CRF and CH decrease. Conversely, regression values displayed a negative correlation with CRF and CH. Considering that regression of the orthokeratologic effect will give positive values for r_0_R, K_f_R, K_s_R, *CCT_R*, this means that faster regression is observed for eyes with lower CRF and CH. *Figure 2* confirms those facts.

Despite trends observed in *figure 2*, CRF did not correlate significantly with the remaining parameters either in the progression or regression phases. Conversely, CH was significantly correlated with K_s_P (Pearson coefficient= 0.758; p=0.029) and K_s_R (Pearson coefficient=-0.835; p=0.010), as well as with *CCT_P* (Pearson coefficient= 0.755; p=0.030). Overall, faster progression and regression response is somehow associated with lower higher values of CRF and CH, and vice-versa.

DISCUSSION

The present study is in agreement with previous studies showing rapid changes in corneal curvature and thickness with reverse geometry contact lenses for orthokeratology under open-eye[16] and closed-eye conditions.[17] In addition to the present knowledge, it has also been shown how regression effect after short periods of time of lens wear under open-eye studies are almost as rapid as changes produced in a similar timeframe.

Several empirical facts support the assumption that corneal biomechanical properties could play a role on corneal response to OK. Different corneal responses to same contact lens geometries on eyes with similar corneal topography and corneal thickness are usual observations in clinical practice. Moreover, recent investigations have demonstrated that corneas from older patients are not as good responders to orthokeratology as young corneas.[18] Despite, other factors as epithelial physiology, lid pressure or tear function could be involved, corneal resistance and viscoelastic properties should not be ignored as a recent investigation has concluded that the human eye becomes more rigid with age.[19] Also, in the short term, corneal bending with flattening of the posterior corneal surface could be implicated in the early corneal change in response to orthokeratology.[20] In such conditions, the involvement of corneal resistance on corneal response to OK seems to be reasonable.

For the sample included in the present study, biomechanical parameters, CRF and CH varied within the range of normality previously reported.[21] Nevertheless, we have found significant correlations between biomechanical properties of the cornea and the rate of change in corneal parameters during the progression of the OK effect with the contact lenses in place and regression of the effect after lens removal.

This study provides the first objective evidence that biomechanical properties of the cornea measured with the ORA play a significant role in corneal response to corneal refractive therapy with contact lenses for myopia correction. This is an important issue that will help to explain different patient's response to this modality of lens wear. Moreover, we think that present results provide valuable information on the corneal biomechanical response to external forces acting on the human corneal tissue with therapeutic or diagnostic purposes (refractive surgery, orthokeratology, intraocular pressure measurement,…). Some clinically interesting conclusions can be derived from the results of the present study related to the ability of normal corneas with biomechanical properties within the range of normality to change their topographic parameters in a different way under the effect of OK lenses with the same target treatment.

To do so, we have to go back to the theories that could potentially explain the involvement of biomechanical properties of the cornea on corneal response to OK. In this sense our results suggest that the most likely link between corneal biomechanical properties and corneal response to OK would be an inverse relationship. In such a relationship, the higher the resistance and/or viscoelastic nature of the cornea would mean a slower corneal response to myopic OK, but also a slower regression of the effect. Conversely, those corneas showing the faster response in the present study are those with a lower corneal resistance and hysteresis, the former being statistically significant when correlated with steepest keratometric curvature and corneal thinning. Physically, this assumes that corneas with a lower resistance will respond faster and this perhaps assumes some bending of the cornea in addition to the central epithelial thickness, at least in the short-term. Such a bending effect of the posterior surface has been demonstrated recently by Owens et al using a video Purkinje image method during the first adaptation period to overnight orthokeratology.[22] This could be partially explained due to posterior edema within the first minutes/hours of wear,[23] exacerbated by the limited swelling response in the anterior direction due to central compression.[24] However, the effect of mechanical compression of the cornea through the tear film under reverse geometry contact lenses could also be a principal factor being responsible for such changes. According to our results the biomechanical behavior of the cornea seems to play a significant role in this effect. So, the results from the present study, despite not measuring the curvature of posterior corneal surface, are not inconsistent with the posterior corneal changes in response to orthokeratology in the short-term.[25]

Present results also support the assumption that older patients will respond to at a lower rate to OK, at least in the short term.[26] Jayakumar and Swarbrick speculated with the possibility that a limited ability of the older epithelium to migrate could explain such a limited response. However, on the view of the present results and considering that older corneas have in fact shown an increase in rigidity,[27] other factors related with the biomechanical behavior of the cornea could be involved on the limited response of the older corneas to OK. Aging changes in the corneal biomechanical properties could be related to the alterations described on collagen fibrils.[28]

One potential limitation of this study could be the fact that CCT had been measured by US pachymetry that needs topical anesthesia. Changes in epithelial barrier function have been documented with some anesthetic agents, particularly when they contain some preservatives as benzalkonium chloride (BAK) and chlorhexidine.[29] This could potentially induce a confounding factor in the corneal response observed here as the OK effects depend on the redistribution of the epithelium. However other study did not showed any impairment in epithelial permeability after installation of oxybuprocaine in normal healthy patients.[30] The protocol of our study considered fluorescein staining at the 180 minute controls after lens wear and after lens removal, and no corneal staining was observed.

Other concern with the administration of anesthetics is the potential effect of these eyedrops on corneal thickness and topography measurement because of the potential effect of the drops on epithelial homeostasis. However, according to our protocol it is not expected that anesthetic will affect topographic or pachymetric data as it was performed after corneal topography and a recent study found that both tetracaine and oxybuprocaine will increase CT by 8 microns immediately after instillation, falling again to baseline after

80 minutes with another transient period of thickness increase after 5 minutes.[31] In this study, CCT measurements were taken within this period of corneal changes for all patients. Also, despite changes were observed on some cases, Asensio and co-workers did not observed significant changes in corneal thickness after the instillation of two drops of 0.4% oxybuprocaine.[32]

In summary, the present study showed for the first time evidences that at least in the short-term, corneal flattening response to myopic OK and regression of the effect occur more rapid in eyes with lower corneal resistance factor and corneal hysteresis within normal ranges. Despite the limited sample size, the findings of this study support the involvement of biomechanical properties of the cornea in the short-term response to orthokeratology. In our opinion this is a very important finding. Further studies considering larger samples are needed in order to confirm this hypothesis in the medium-term progression and consolidation of the orthokeratologic effect and its regression after long-term periods of wear, particularly under closed-eye conditions.

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Figure 1.- Graphic representation of the potential involvement of biomechanical properties on corneal response to orthokeratology. Higher resistance associated to slower onset and slower regression of OK effect (a); higher resistance associated to faster onset and faster regression of OK effect (b); higher resistance associated to slower onset and faster regression of OK effect (c); and higher resistance associated to faster onset and slower regression of OK effect (b). Values are arbitrary units, only the increase or decrease direction matters.

Figure 2.- Relationship of 3 hour changes in apical curvature, simulated keratometry (flattest and steepest meridians) and central corneal thickness with corneal biomechanical properties

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Figure
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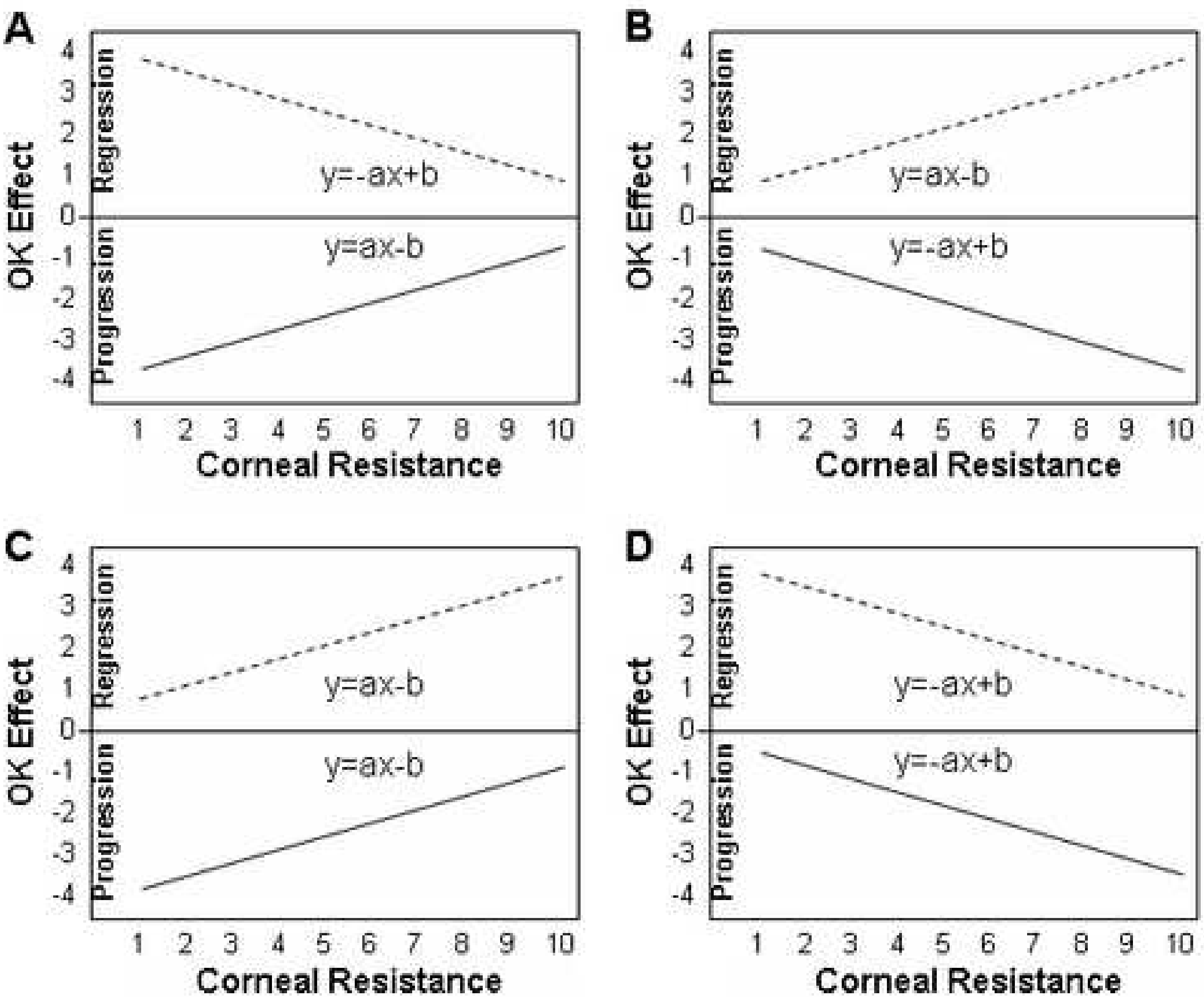

Figure

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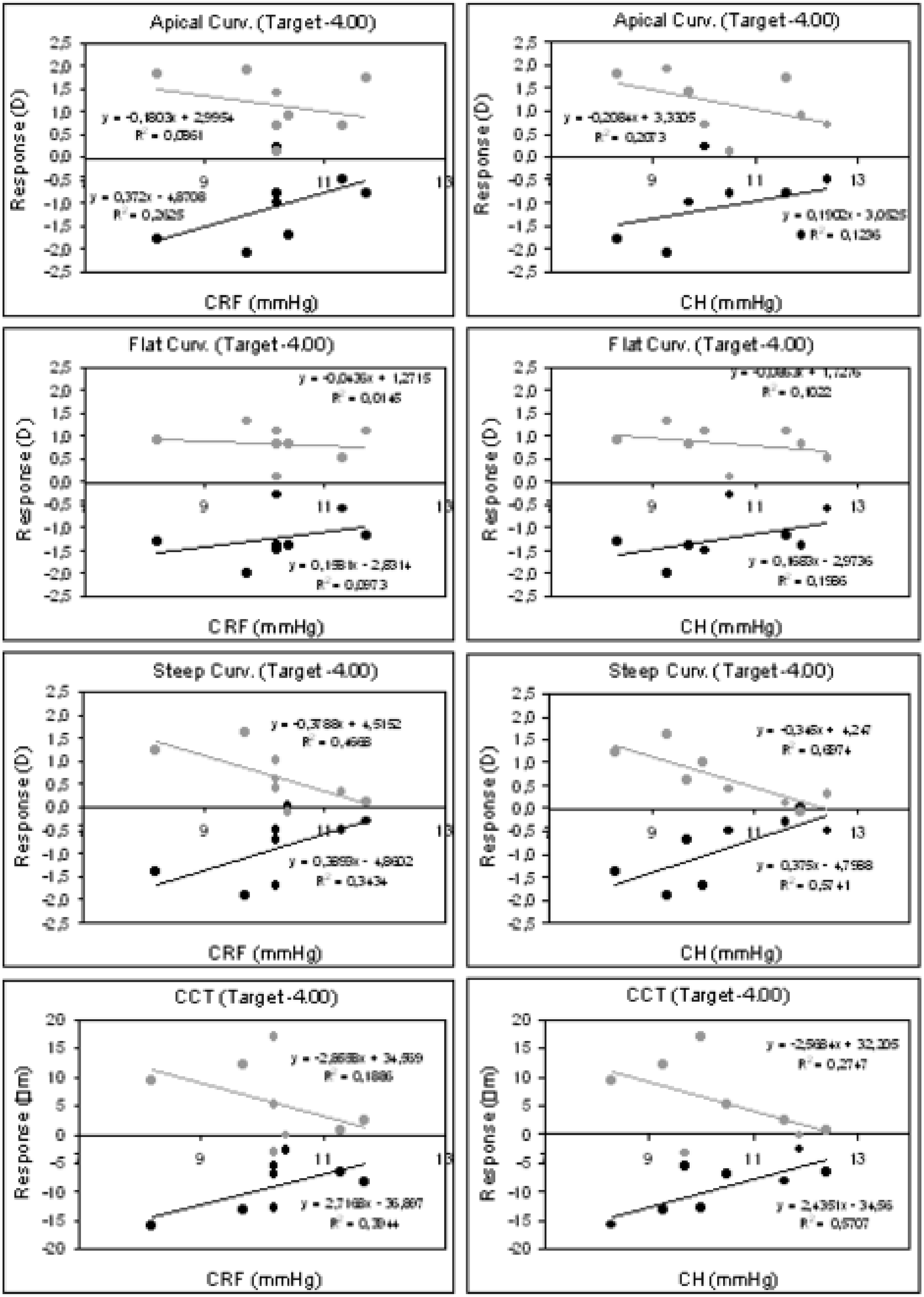

Table 1. Descriptive statistics (mean±SD) and intervals [maximum, minimum] for progression and regression rates for different corneal parameters under study. Significance values are for comparison of absolute value of average progression and regression parameters

	Progression (180min-Baseline)*	Regression (180 min nCL-180min CL)*	Sig. p§
Apical curvature (*r_0*)	-1.06±0.76	1.15±0.65	N.S
Flat keratometry (*K_f*)	-1.21 ±0.53	0.83 ±0.38	0.002
Steep keratometry (*K_s*)	-0.88±0.70	0.64 ±0.58	0.012
Central corneal thickness (*CCT*)	-9.08 ±4.55	5.33±6.91	0.035

* nCL: after CL removal; CL: after CL wear; § Student T-test

Table 2. Correlations of the biomechanical parameters with the

		Progression (180min-Baseline)*	Regression (180 min nCL-180min CL)*
Apical curvature (*r_0*) vs	**CRF**	0.512 (p=0.194)	-0.293 (p=0.481)
	CH	0.352 (p=0.393)	-0.455 (p=0.257)
Flat keratometry (*K_f*) vs	**CRF**	0.312 (p=0.452)	-0.120 (p=0.776)
	CH	0.446 (p=0.268)	-0.320 (p=0.440)
Steep keratometry (*K_s*) vs	**CRF**	0.586 (p=0.127)	-0.683 (p=0.062)
	CH	0.758 (p=0.029)§	-0.835 (p=0.010)§
Central corneal thickness (*CCT*) vs	**CRF**	0.628 (p=0.095)	-0.434 (p=0.282)
	CH	0.755 (p=0.030)§	-0.524 (p=0.182)

* nCL: after CL removal; CL: after CL wear; §Statistically significant