Biomechanical and Tomographic Analysis of Unilateral Keratoconus

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ABSTRACT

PURPOSE: To evaluate and compare tomographic, clinical, and biomechanical data of patients with unilateral keratoconus and healthy controls.

METHODS: Observational, case-control study. Complete clinical eye examination was followed by topographic (ATLAS), tomographic (Pentacam), and biomechanical (Ocular Response Analyzer) evaluation. Cases were sex- and age-matched with healthy individuals for controls.

RESULTS: Four patients had unilateral keratoconus, and eight healthy patients served as controls. Central corneal thickness was 508±16 μm in the keratoconus group, 531±12.7 μm in the fellow eye group, and 528.6±40.7 μm in the control group ($P>.125$, all comparisons). Central keratometry was 43.70±2.70 diopters (D) in the keratoconus group, 42.84±1.43 D in the fellow eye group, and 43.81±1.94 D in the control group ($P>.45$, all comparisons). Corneal astigmatism was 3.30±2.24 D in the keratoconus group, 1.38±1.49 D in the fellow eye group, and 1.34±1.13 D in the control group ($P=.037$ between the keratoconus and control groups; $P=.25$ between the keratoconus and fellow eye groups). Corneal hysteresis was 8.13±2 mmHg in the keratoconus group, 8.96±0.86 mmHg in the fellow eye group, and 9.89±1.33 mmHg in the control group ($P>.064$, all comparisons). Corneal resistance factor was 7.96±2.43 mmHg in the keratoconus group, 8.92±1.39 mmHg in the fellow eye group, and 9.90±2.24 mmHg in the control group ($P>.33$, all comparisons).

CONCLUSIONS: Corneal hysteresis and corneal resistance factor values were not statistically different among the groups; however, a trend for lower values was found for keratoconus and fellow eyes compared to controls. Data should be interpreted with caution because of the small sample. [*J Refract Surg*. 2010;26(9):677-681.]

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Keratoconus is an ectatic disorder in which thinning and protrusion of the cornea causes it to assume a conical shape. It is most commonly a bilateral and asymmetric condition with no sex or race predilection, with typical onset at puberty.[1] Unilateral cases are rarely described, with an estimated incidence of 1% to 4%.[2-7] A number of cornea specialists believe that patients initially diagnosed with unilateral keratoconus will develop the disease in the fellow eye over time. Currently, no test reliably detects anatomic or functional abnormality predicting disease progression in these eyes.

The ability to detect initial and subclinical (forme fruste) keratoconus has greatly improved with the use of new corneal imaging technology. The latest corneal topographers and tomographers are widely available, and new indices are described frequently.[8] Most improvements are due to the refractive surgery process, in which candidates are carefully screened preoperatively to avoid complications such as postoperative LASIK ectasia.[9,10] Corneal refractive surgery should not be performed in keratoconus suspects or on apparently normal corneas in cases of unilateral keratoconus.

Since the first publication by Luce in 2005,[11] in vivo corneal biomechanics evaluation using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, New York) has been the subject of several publications.[12-20] The ORA records corneal inward and outward applanation after delivery of a metered collimated air pulse and gives two

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corneal biomechanic metrics: corneal hysteresis and corneal resistance factor. In the present study, we evaluated and compared tomographic, clinical, and biomechanical findings in patients with unilateral keratoconus and healthy control individuals.

PATIENTS AND METHODS

An observational, case-control study was performed. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee from Federal University of São Paulo. All study participants were informed about the purpose of the study and gave informed consent before inclusion. Patients were sequentially evaluated from October 2005 to December 2006.

Patients were diagnosed as having unilateral keratoconus during complete eye examination. Diagnosis of keratoconus (keratoconic eyes) was made by clinical (corneal stromal thinning, Vogt's striae, Fleischer ring, scissoring of the red reflex, or oil droplet sign identified by retinoscopy) and topographic evaluation (an 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[21]).

Each patient underwent a comprehensive ophthalmologic examination including review of medical history, corrected distance visual acuity, slit-lamp microscopy, funduscopic examination, Placido disk topography (Humphrey ATLAS; Carl Zeiss Meditec, Jena, Germany), Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) tomographic evaluation, and ORA measurements. Cases were sex- and age-matched with healthy individuals serving as controls. Patients were divided into three groups for data comparison: keratoconus group, fellow eye group, and control group.

Exclusion criteria were patient age <18 years, previous corneal or ocular surgery, eye disease other than keratoconus, chronic and/or continuous use of topical medications, corneal scars and/or opacities, and objection to signing an informed consent. Contact lenses had to be removed at least 72 hours before examination.

Patients underwent testing with the ORA and Pentacam by two trained ophthalmologists (R.A., M.S.) during the same visit. All measurements were taken between 8 AM and 6 PM. Two consecutive ORA measurements were performed on both eyes (only good quality readings, as defined by the manufacturer, were recorded), and results averaged. Spherical equivalent refraction was obtained by dynamic refraction during the clinical examination. Central keratometry (average central K), central corneal thickness, corneal astigmatism, and anterior chamber depth were assessed by the Pentacam.

A detailed description of the Pentacam system was published in a previous study by our group[12] and other investigators.[22-24] Briefly, a rotating camera was set to take 25 slit images of the anterior eye segment in approximately 2 seconds with 500 true elevation points incorporated in each slit image. The central corneal thickness, average central keratometry, corneal astigmatism, and anterior chamber depth are measured in each of the single images of a scan.

The ORA determines corneal biomechanical properties using an applied force-displacement relationship. Details have been described previously.[11,13,14,16,18] Corneal hysteresis is an indication of viscous damping in the cornea, reflecting the capacity of corneal tissue to absorb and dissipate energy. Corneal resistance factor is a measurement of the cumulative effects of both the viscous and elastic resistance encountered by the air jet while deforming the corneal surface, and is an indicator of the overall resistance of the cornea. Although corneal hysteresis and corneal resistance factor are related, in some instances they can be significantly different, each providing distinct information about the cornea.

Statistical analysis was performed with BioEstat 5.0 software (Belém, PA, Brazil). Data are expressed as mean±standard deviation. The Wilcoxon test (signed-rank or rank-sum, where indicated) was used to compare results among the groups.

RESULTS

During the study period, 77 patients were diagnosed as having keratoconus, all of whom had presented for refractive surgery preoperative evaluation. Four patients (2 men and 2 women, corresponding to 5.2% of the total evaluated keratoconus patients) were diagnosed as having unilateral keratoconus, and 8 healthy patients (4 men and 4 women, 16 eyes) were used as controls. Mean age for the keratoconus and control groups was 32±12.8 years and 33.9±12.5 years, respectively. At slit-lamp examination, all eyes in the keratoconus group had corneal thinning and mild iron deposit (Fleischer ring) with no visible scar. Biomicroscopic examination of the remaining groups was within normal limits. Spherical equivalent refraction was −4.40±3.80 diopters (D) in the keratoconus group, −4.50±4.40 D in the fellow eye group, and −2.31±2.58 D in the control group.

Central corneal thickness was 508±16 µm in the keratoconus group, 531±12.7 µm in the fellow eye group, and 528.6±40.7 µm in the control group (P>.125, all comparisons). Average central keratometry was 43.70±2.70 D in the keratoconus group, 42.84±1.43 D in the fellow eye group, and 43.81±1.94 D in the control

TABLE 1

Demographic, Clinical, Tomographic, and Biomechanical Data in Patients With and Without Unilateral Keratoconus

	Keratoconus Group	Fellow Eye Group	Control Group
Gender (M/F)	2/2	2/2	4/4
Age (y)	32±12.8 (18 to 49)	32±12.8 (18 to 49)	33.9±12.5 (19 to 48)
SE (D)	−4.40±3.80 (−9.75 to −1.75)	−4.50±4.40 (−10.75 to −1.25)	−2.31±2.58 (−7.25 to +1.00)
Slit-lamp findings (all eyes)	Corneal thinning, Fleischer ring	None	None
K-Ave (D)	43.70±2.70 (40.40 to 46.20)	42.84±1.43 (40.85 to 44.00)	43.81±1.94 (39.90 to 46.20)
Corneal astigmatism (D)	3.34±2.20 (1.20 to 6.40)	1.38±1.49 (0.20 to 3.50)	1.34±1.13 (0.30 to 3.70)
ACD (mm)	3.3±0.2 (3.07 to 3.63)	3.26±0.28 (2.94 to 3.55)	3.12±0.39 (2.55 to 3.7)
CCT (μm)	508±16 (487 to 521)	531±12.7 (517 to 542)	528.6±40.7 (457 to 597)
CRF (mmHg)	7.96±2.43 (5.2 to 10.7)	8.92±1.39 (7.8 to 10.6)	9.90±2.24 (6.8 to 14.4)
CH (mmHg)	8.13±2.0 (6.6 to 11.1)	8.96±0.86 (8.1 to 10.1)	9.89±1.33 (7.8 to 12.3)

SE = spherical equivalent refraction, K-Ave = average central keratometry, ACD = anterior chamber depth, CCT = central corneal thickness, CRF = corneal resistance factor, CH = corneal hysteresis

TABLE 2

Comparative, Statistical Analysis of Patients With and Without Unilateral Keratoconus

	P Value					
Groups	**K-Ave**	**CA**	**ACD**	**CCT**	**CRF**	**CH**
Keratoconus vs fellow eye	.4576	.25	.25	.125	.375	.375
Keratoconus vs control	.8499	.0374*	.3947	.2902	.3352	.064
Fellow eye group vs control group	.2326	.3575	.0721	.2326	.2102	.1018

K-Ave = average central keratometry, CA = corneal astigmatism, ACD = anterior chamber depth, CCT = central corneal thickness, CRF = corneal resistance factor, CH = corneal hysteresis
**Statistical difference.*
Note. Results should be interpreted with caution because of the small sample size. An optimal sample would be composed of 20 individuals with unilateral keratoconus.

group ($P>.45$, all comparisons). Corneal astigmatism was 3.30±2.24 D in the keratoconus group, 1.38±1.49 D in the fellow eye group, and 1.34±1.13 D in the control group ($P=.037$ between the keratoconus and control groups; $P=.25$ between the keratoconus and fellow eye groups; $P=.3575$ between the fellow eye and control groups). Anterior chamber depth was 3.3±0.2 mm in the keratoconus group, 3.26±0.28 mm in the fellow eye group, and 3.12±0.39 mm in the control group ($P>.072$, all comparisons).

Corneal hysteresis was 8.13±2 mmHg in the keratoconus group, 8.96±0.86 mmHg in the fellow eye group, and 9.89±1.33 mmHg in the control group ($P>.064$, all comparisons). Corneal resistance factor was 7.96±2.43 mmHg in the keratoconus group, 8.92±1.39 mmHg in the fellow eye group, and 9.90±2.24 mmHg in the control group ($P>.33$, all comparisons). Demographic, clinical, tomographic, and biomechanical data are summarized in Table 1.

A statistically significant difference ($P<.05$) was only found in regards to corneal astigmatism between the keratoconus and control groups. Statistical analysis of all groups is presented in Table 2. Results should be interpreted with caution because of the small sample size. We used a power analysis statistical program to estimate the optimal sample to draw conclusive results regarding the present variables. To have a test power of 0.95 with alpha 0.01, an optimal sample would be composed of 20 individuals with unilateral keratoconus.

DISCUSSION

New biomechanical metrics (corneal hysteresis and corneal resistance factor) may be useful when determining corneal stiffness by indicating a "more fragile" tissue that is at greater risk for developing corneal ectasia. In addition, they could be used to differentiate mild (and forme fruste) keratoconus from healthy corneas before manifestation of typical topographic signs.

In the present study, we found a trend of lower biomechanical metric values in keratoconus and fellow eyes compared with controls. However, a great scatter in values was seen and a statistical difference was not shown. A possible explanation is the small sample size. An ideal sample of 20 patients with unilateral keratoconus would provide a better understanding and more conclusive results. As unilateral keratoconus is an unusual condition,[3-7] it is difficult to obtain a large population.

Unilateral chronic eye rubbing or ocular trauma and greater asymmetry in corneal curvature have been shown to be associated with unilateral keratoconus in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study.[4] It is a common belief among cornea specialists that patients at greater genetic risk for developing keratoconus may progress to corneal ectasia depending on certain risk factors (eg, corneal surgery, eye rubbing, or trauma) during their lifetime.[3] Li et al[3] and Holland et al[5] studied the incidence and fellow-eye disease progression in unilateral keratoconus and concluded that, if observed for a sufficient period of time, most cases developed the disease in the fellow eye. Currently, no method exists to identify these high-risk patients, as they often have normal ocular and topographic examinations.

Artificial intelligence "keratoconus detection indices" provided by both corneal topography and tomography were able to detect keratoconic eyes and discriminate from healthy corneas. New biomechanical metrics should not be relied on as a stand-alone method for keratoconus diagnosis, but may improve the sensitivity of its screening when combined with current corneal topographers and tomographers. Also, new data presented recently by Luce[25] regarding waveform parameters provided by the ORA signal may be more sensitive than corneal hysteresis and corneal resistance factor in discriminating abnormal corneas.

Biomechanical metrics were not statistically different among the study groups; however, a trend for lower values was found for keratoconus and fellow eyes compared to controls. Data should be interpreted with caution because of the small sample. Prospective studies with larger samples are warranted.

AUTHOR CONTRIBUTIONS

Study concept and design (B.M.F., R.A., G.C.V., W.N.); data collection (B.M.F., R.A., M.S.); analysis and interpretation of data (B.M.F., R.A., G.C.V., W.N.); drafting of the manuscript (B.M.F.); critical revision of the manuscript (B.M.F., R.A., M.S., G.C.V., W.N.); statistical expertise (G.C.V.); administrative, technical, or material support (B.M.F., R.A.); supervision (B.M.F., R.A., W.N.)

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