Ability of corneal biomechanical metrics and anterior segment data in the differentiation of keratoconus and healthy corneas

Estudo da performance diagnóstica de parâmetros biomecânicos e dados anatômicos da câmara anterior na diferenciação de córneas saudáveis e com ceratocone

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ABSTRACT

Purpose: To evaluate the sensitivity, specificity, and test accuracy of corneal biomechanical metrics and anterior segment data in differentiating keratoconus from healthy corneas.

Methods: Comparative case series. Patients with and without keratoconus (gender and age-matched) were submitted for complete eye examinations including corneal hysteresis (CH) and corneal resistance factor (CRF) as measured by the Ocular Response Analyzer and anterior segment data as gathered through Pentacam assessments. The anterior segment data measurement included average central keratometric readings (K-Ave), corneal astigmatism (CA), central corneal thickness (CCT), anterior chamber depth (AC depth) and corneal volume (CV). All parameters were assessed, compared and analyzed. A receiver operating characteristic (ROC) curve was used to identify the best cutoff point by which to maximize the sensitivity and specificity of discriminating keratoconus from normal corneas for each data category.

Results: Seventy seven eyes from forty three patients (24 male, 19 female) with keratoconus and eighty six eyes from forty three (24 male, 19 female) healthy controls were enrolled. ROC curve analysis showed poor overall predictive accuracy for all studied parameters in differentiating keratoconus from normal corneas. The highest sensitivity (79.2%) was obtained for both AC depth and CH (cutoff points 3.22 mm and 9.39 mmHg respectively). The best specificity (89.5%) and test accuracy (80.34%) were obtained for CA (cutoff point of 2.2 D).

Conclusion: When considered together, studied parameters showed statistical differences between groups. However, when considered independently they presented low sensitivity, specificity and test accuracy in differentiating keratoconus from healthy corneas.

Keywords: Cornea; Corneal diseases; Corneal topography; Biomechanics; Keratoconus.

INTRODUCTION

Keratoconus is an ectatic disease of the cornea, with progressive noninflammatory thinning and anterior protrusion that leads to an irregular conical shape. It is usually a bilateral and asymmetric condition that manifests at puberty. Clinical (as corneal stromal thinning, corneal protrusion, Vogt striae and Fleischer ring) and topographic (as irregular astigmatism, inferior steepening and inferior-superior asymmetry) findings are habitually combined for diagnosing and staging the disease.

Recently, new technology in eye imaging such as the Pentacam (Oculus Inc, Wetzlar, Germany) has revealed valuable information regarding corneal and anterior segment anatomy. These developments can be credited, primarily, to progress that leads to an irregular conical shape. It is usually a bilateral and asymmetric condition that manifests at puberty. Clinical (as corneal stromal thinning, corneal protrusion, Vogt striae and Fleischer ring) and topographic (as irregular astigmatism, inferior steepening and inferior-superior asymmetry) findings are habitually combined for diagnosing and staging the disease.
provided by a variety of currently available equipment\textsuperscript{12-16}. However, accurate differentiation of keratoconus from healthy corneas is not yet sufficient, as there is a need to detect concomitant with a higher susceptibility to becoming ectatic after laser photoablative surgery\textsuperscript{15-16}.

In vivo corneal biomechanical evaluation was first described by Luce\textsuperscript{17} in 2005, with the development of the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Depew, New York, USA). A number of researchers published diverse and exciting new data regarding corneal hysteresis (CH) and corneal resistance factor (CRF) in healthy and pathological conditions\textsuperscript{18-22}. If ORA proves that “fragile” corneas are more susceptible than “strong” corneas to developing ectasia in the future, then the best use for such data in refractive surgery would be in preoperative screening.

The present study compared the findings of biomechanical and anterior segment parameters in differentiating keratoconus from healthy corneas, and evaluated the ability of each individual parameter to differentiate them.

METHODS

This was a comparative case series. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Federal University of São Paulo (protocol 0123/06). All subjects were informed about the purpose of the study and gave informed consent before inclusion. Patients were sequentially evaluated from October 2005 to December 2008. Demographic and clinical data were obtained, including date of birth, gender and self-reported race or ethnicity.

The keratoconus group consisted of 77 eyes from 43 patients (24 male, 19 female) with a mean age of 34.95 ± 11.95 years (ranging from 18 to 73 years). The control group consisted of 86 eyes from 43 (24 male, 19 female) gender- and age-matched healthy patients, with a mean age of 35.02 ± 12.19 years (ranging from 18 to 72 years-old) (p=1).

Each subject underwent a comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slit lamp biomicroscopy, fundoscopic examination, Placido disc topography (Humphrey ATLAS, Carl Zeiss Meditec Inc. Dublin, USA), Pentacam tomographic evaluation and ORA measurements. Diagnosis of keratoconus 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 (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\textsuperscript{14,15,23-25}) evaluation.

Cases were gender- and age-matched with controls for data comparison\textsuperscript{21}. Exclusion criteria were: less than 18 years-old, any previous corneal or ocular surgery, any eye disease that could possibly interfere with the readings/results (e.g., glaucoma, uveitis, corneal ectatic disease, Fuch’s dystrophy, diabetic retinopathy, etc.) chronic and/or continuous use of topical medications, corneal scars and/or opacities, irregular astigmatism, systemic collagen diseases and refusal to sign an informed consent agreement. Contact lenses were required to be removed at least 72 h before examination. Patients underwent testing with the ORA and Pentacam during the same visit. All measurements were taken between 8:00 AM and 6:00 PM. Two consecutive ORA measurements were performed on both eyes and the results were averaged.

RESULTS

K-Ave was 47.03 ± 5.22 diopters (D) (range 40.4 to 74.15 D) in keratoconus and 43.31 ± 1.53 D (range 39.9 to 46.75 D) in the control group (p<0). CA was 3.46 ± 2.20 D (range 0.7 to 10.9 D) in keratoconus and 43.31 ± 1.53 D in keratoconus and 43.31 ± 1.53 D (range 39.9 to 46.75 D) in the control group (p<0). CCT was 493.17 ± 42.84 μm (range 349 to 568 μm) in keratoconus and 543.90 ± 34.83 μm (range 457 to 627 μm) in the control group (p<0) (Figure 1). AC depth was 3.25 ± 0.38 mm (range 2.41 to 5.21 mm) in keratoconus and 3.07 ± 0.42 mm (range 2.08 to 3.80 mm) in the control group (p<0) (Figure 2).
control group (p=0.012). CV was 57.01 ± 3.53 mm³ (range 49.5 to 66.9 mm³) in keratoconus and 60.19 ± 3.40 mm³ (range 53.7 to 68.5 mm³) in the control group (p=0).

CH was 8.23 ± 1.51 mmHg (range 4.60 to 11.80 mmHg) in keratoconus and 10.13 ± 1.75 mmHg (range 5.95 to 14.58 mmHg) in the control group (p=0) (Figure 2). CRF was 7.46 ± 1.76 mmHg (range 2.80 to 11.20 mmHg) in keratoconus and 10.06 ± 1.97 mmHg (range 5.45 to 15.10 mmHg) in the control group (p=0) (Figure 3). The results are summarized in table 1.

ROC curve analyses showed poor overall predictive accuracy for all studied parameters in differentiating keratoconus from normal corneas. The results are summarized in table 2.

Higher sensitivity in differentiating keratoconus from healthy corneas was 79.2% for AC depth and CH (cutoff point 3.22 mm and 9.39 mmHg respectively); the best specificity and test accuracy for CA (cutoff point 2.2 D; 89.5% and 80.34% respectively). Lowest sensitivity was 62% for CV, with a specificity of 44.2% for AC depth and 69.93% test accuracy for K-Ave.

The cutoff point for K-Ave was 44.35 D with sensitivity of 74%, specificity of 66.3% and test accuracy of 69.93%. For CA, the cutoff point was 2.2 D with sensitivity of 70.1%, specificity of 89.5% and test accuracy of 80.34%. The cutoff point for CCT was 521 μm, with sensitivity of 77.9%, specificity of 80.2% and test accuracy of 79.11%. The cutoff point for AC depth was 3.22 mm, with sensitivity of 79.2%, specificity of 44.2% and test accuracy of 60.72%. The cutoff point for CV was 57.8 mm³, with sensitivity of 62%, specificity of 77.9% and test accuracy of 74.82%.

The cutoff point for CH was 8.68 mmHg, with sensitivity of 77.9%, specificity of 75.6% and test accuracy of 76.69%.

**DISCUSSION**

Biomechanical study of the cornea is crucial for refractive surgery progress not only for better preoperative screening, but also for prediction of individual outcomes. As Ethier et al.(24) stated, material properties of the cornea are heterogeneous, highly anisotropic, nonlinear, and viscoelastic. In a broad review, Torres et al.(25) described CCT and corneal collagen fiber density as the most important intrinsic factors determining corneal biomechanics. We would include corneal hydration (and its control by the endothelium), corneal thickness regional variation, collagen fibril orientation and distribution.

Kida et al.(26), and Laiquuzzaman et al. (27) found that CH remained almost constant throughout the day, whereas CCT and intraocular pressure showed statistically significant variations (higher values during the nocturnal period) in young adults. The small number of patients in both studies might restrict their findings to these specific populations. Previous studies, including ours(27), indicate a through relation between CRF and CH with CCT and an inverse relation with age. The present data, in agreement with previous research(28-30), show that biomechanical metrics are statistically lower in keratoconus than in normal corneas. However, the big overlap of the results of both groups involves the issue of accuracy in discriminating normal from abnormal corneas. New data presented recently by David Luce (ASCRS 2009 meeting, San Francisco - CA) regarding waveform parameters provided from the ORA signal may turn out to be more sensitive than CH and CRF in discriminating abnormal corneas.

Anterior segment tomography has been the subject of several papers(28-30,31-32), and has shown its accuracy in corneal and anterior segment mapping. New parameters, such as corneal volume, pachymetric progression and elevation maps are of...
Table 1. Summary of the anterior segment parameters and biomechanical metrics results of studied population

<table>
<thead>
<tr>
<th></th>
<th>Keratoconus</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-Ave (D)</td>
<td>47.03 ± 5.22</td>
<td>40.40 - 74.15</td>
<td>0.0012</td>
</tr>
<tr>
<td>CA (D)</td>
<td>3.46 ± 2.20</td>
<td>0.70 - 10.90</td>
<td>0.0012</td>
</tr>
<tr>
<td>CCT (μm)</td>
<td>493.17 ± 42.84</td>
<td>349.00 - 568.00</td>
<td>0.0012</td>
</tr>
<tr>
<td>AC depth (mm)</td>
<td>3.25 ± 0.38</td>
<td>2.41 - 5.21</td>
<td>0.0012</td>
</tr>
<tr>
<td>CV (mm³)</td>
<td>57.01 ± 3.53</td>
<td>49.50 - 66.90</td>
<td>0.0012</td>
</tr>
<tr>
<td>CH (mmHg)</td>
<td>8.23 ± 1.51</td>
<td>4.60 - 11.80</td>
<td>0.0012</td>
</tr>
<tr>
<td>CRF (mmHg)</td>
<td>7.46 ± 1.76</td>
<td>2.80 - 11.20</td>
<td>0.0012</td>
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</tbody>
</table>

Table 2. Receiver operating characteristic (ROC) identified the best cutoff point of studied parameters to maximize sensitivity and specificity in differentiating keratoconus and healthy corneas

<table>
<thead>
<tr>
<th>Cutoff point</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Test accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-Ave</td>
<td>44.35 D</td>
<td>74.0</td>
<td>66.3</td>
</tr>
<tr>
<td>CA</td>
<td>2.2 D</td>
<td>70.1</td>
<td>89.5</td>
</tr>
<tr>
<td>CCT</td>
<td>521 μm</td>
<td>77.9</td>
<td>80.2</td>
</tr>
<tr>
<td>AC depth</td>
<td>3.22 mm</td>
<td>79.2</td>
<td>44.2</td>
</tr>
<tr>
<td>CV</td>
<td>57.8 mm³</td>
<td>62.0</td>
<td>77.9</td>
</tr>
<tr>
<td>CH</td>
<td>9.39 mmHg</td>
<td>79.2</td>
<td>70.9</td>
</tr>
<tr>
<td>CRF</td>
<td>8.68 mmHg</td>
<td>77.6</td>
<td>75.6</td>
</tr>
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REFERENCES


