Characterization of subclinical ectasia with integrated corneal tomography and biomechanics assessments

Guilherme Garcia Criado1 https://orcid.org/0000-0003-1105-8622
Nelson Batista Sena Júnior1,2,4 https://orcid.org/0000-0003-4031-017X
Thiago José Muniz Machado Mazzeo2 https://orcid.org/0000-0001-9536-1893
Marcella Quaresma Salomão Hoyer de Carvalho3,4,5 https://orcid.org/0000-0001-8330-6432
Louise Pellegrino Gomes Esporcatte4 https://orcid.org/0000-0002-2353-9442
Guilherme Simões Luz Hilgert4 https://orcid.org/0000-0001-9536-1893
Marcella Quaresma Salomão Hoyer de Carvalho3,4,5 https://orcid.org/0000-0001-8330-6432
Louise Pellegrino Gomes Esporcatte4 https://orcid.org/0000-0002-2353-9442
Guilherme Simões Luz Hilgert4 https://orcid.org/0000-0001-9536-1893
Renato Ambrósio Júnior2,3,4,5 https://orcid.org/0000-0001-6919-4606

1Rio de Janeiro State University, Ophthalmology Medical Residency Program, Rio de Janeiro City, Rio de Janeiro State, Brazil.
2Rio de Janeiro Federal University, Ophthalmology Department Gaffrée and Guinle University Hospital, Rio de Janeiro City, Rio de Janeiro State, Brazil.
3Federal University of São Paulo, Ophthalmology Department, São Paulo City, São Paulo State, Brazil.
4Rio de Janeiro Study Group on Corneal Tomography and Biomechanics, Rio de Janeiro City, Rio de Janeiro State, Brazil.
5Cornea and Refractive Surgery, Renato Ambrósio Eye Institute, Rio de Janeiro City, Rio de Janeiro State, Brazil.

VisareRIO Refracta Personal Laser, Rio de Janeiro City, Rio de Janeiro State, Brazil.

Dr. Renato Ambrósio Jr. is consultant for OCULUS, ALCON, MEDIPHACOS, and ZEI. The other authors state no conflict of interest.

Received for publication 4/11/2019 - Accepted for publication 21/2/2020.
**INTRODUCTION**

Keratoconus (KC) is a non-inflammatory, progressive, bilateral, and asymmetrical disease featured by corneal protrusion and thinning capable of causing optical and refractive changes leading to reversible vision loss in advanced stages. This disease has multifactorial origin and combines intrinsic factors, such as biochemistry and genetics, which determine tissue biomechanical features and extrinsic factors. In addition to the biomechanical weakening of the cornea due to surgical procedure, chronic mechanical trauma also stands out among its causes, mainly eye scratching.\(^{(1,2)}\)

Keratoconus annual incidence is classically described as 13 cases/100,000 inhabitants. However, it is believed that these numbers are larger due to the diagnostic criterion, as well as to other environmental factors.\(^{(3,4)}\) Differentiations must be made, physiological cases of high astigmatism, corneal warpage due to chronic contact lens use, and other acquired ectasias with well-identified cause, must be differentiated from KC, since these cases are usually unilateral and related to traumatic environmental factors, such eye scratching.\(^{(5)}\)

Early diagnosis becomes relevant to the emergence of alternative treatments to the traditional penetrating corneal transplant. Corneal intrastromal ring segments and crosslinking can improve VA and slow disease progression, respectively, when they are recommended at the right time.\(^{(6)}\) Correct diagnosis is also very important to educate patients and their family members about in subclinical cases, so they can be aware of decision-making on paradoxes related to keratoconus treatment.\(^{(7)}\)

By definition and consensus, keratoconus is a bilateral disease; however, it is highly asymmetric. Cases whose eye contralateral to the most affected eye has normal visual acuity and topography have been assessed to develop more sensitive investigation methods for diagnosis. Patients with very asymmetric ectasia (VAE) can have either asymmetric keratoconus or unilateral ectasia caused by exclusively mechanical factors.\(^{(7,8)}\)

The aim of the current article was to report different ectasis treatment scenarios by prospectively describing 3 VAE cases and differentiating subclinical keratoconus forms from unilateral ectasia.

**Case Report**

**CASE 1**

Man, aged 39 years, businessman, referred for KC treatment. The patient complained about low visual acuity associated with intense itching in the RE. Uncorrected distance visual acuity (UDVA) was RE 20/62 and LE 20/32. Distance corrected visual acuity (DCVA) using Wavefront was RE 20/40 (-1.75/-4.00x35°) and LE (-0.50/-0.25x115°). Topography was performed with Placido discs (OCULUS Keratograph®5M) and Scheimpflug corneal tomography (Pentacam HR, Oculus), which presented similar anterior corneal axial curvature maps, with marked irregularity in an asymmetric and inclined bow tie in the RE and relatively normal asphericity in LE. The topographic keratoconus classification (TKC) algorithm indicated grade 2 disease in the RE and absence of ectasia signs in the LE. Belin’s ABCD grading system was observed in RE A2/B2/C0/D1 and A0/B0/C0/D0.

Wavefront aberrometry (iTrace) revealed irregularities compatible to those observed in the anterior axial curvature map in the RE. The total number of high-order aberrations in the cornea (3.2mm central area) was 0.472 µm in the RE and 0.099 µm in the LE. CT scan revealed ectatic pattern and abrupt increase in thickness in the thinnest point of the cornea in the RE. LE findings were within the normal range. Ambrósio relational thickness-max index (ART-max) was 240µm in the RE and 535µm in the LE. Belin/Ambrósio Enhanced Display (BAD-D) was 5.25 in the RE and 0.25 in the LE. Spectral-domain optical coherence tomography (OCT) by RTVue (Optovue; Fremont, CA, USA), the total pachymetry map, and thickness of the thinnest point were similar to those shown by Pentacam HR in both eyes. The epithelial thickness map of the RE showed inferior temporal thinning surrounded by an area of greater thickness that corresponded to the apex of the cone in the elevation maps, suggesting ectasia in this eye. The values of epithelial parameters in the LE were relatively normal. Specular microscopy (Tomy; Nagaya, Japan) revealed endothelium without changes in both eyes. Corneal biomechanical properties were assessed in Ocular Response Analyzer (ORA; Reichert, Buffalo, NY, USA) and Corvis ST (Oculus, Wetzlar, Germany), which showed corneal hysteresis (CH) values of 8.8 in the RE and 12.1 in the LE, as well as corneal resistance factor (CRF) of 8.1 mmHg in the RE and 12.0 in the LE mmHg. Based on this series of exams, the patient was diagnosed with unilateral ectasia; corneal intrastromal ring implant was indicated for the RE. A ring segment (Kerraring Si6 150° with 250µm) was temporarily implanted at a calculated depth, with the aid of the FS-200 femtosecond laser (Alcon-Wavelight; Earlagen, Germany), by respecting 80% of the thinnest thickness to create the tunnel by following the Mediphacos 4.0 nomogram (Beio Horizonte, Brazil). UDVA was 20/50 and DCVA was20/20 (-2.00/-0,50 cil 140°) in the fourth month after the surgery. The topographic map showed improvement in irregularities, corneal astigmatism, and Kmax. Follow-up continued at the London Vision Clinic (United Kingdom), and clinical and complementary tests remained stable in both eyes 1 year after the surgery. Artemis high-frequency digital ultrasound (VHF-US; ArcScan Inc, Golden, CO, USA) was also performed at the time. It detected changes secondary to the intra-stromal ring in the RE and LE epithelial thickness profile within the normal values, which was confirmed by the device keratoconus algorithm.

The case was previously published in 2016 as unilateral ectasia.\(^{(9,10)}\) Stability in both eyes has been confirmed when the patient returned to Brazil, five years after the initial assessment. In this opportunity, all the previously observed parameters were stable. When biomechanical/tomographic integration was performed, the previous diagnosis was confirmed: BAD-D of 4.13 and -0.08 (values lower than 1.50 are considered normal by the device algorithm); TBI of 0.96 and 0.02 (graduated by the device algorithm) and CI of 0.80 and 0.01 (graduated by the device algorithm from 0.0 to 1.00 - 0.5 is the upper normal threshold) and CI of 0.80 and 0.01 (graduated by the device algorithm from 0.0 to 1.00 - 0.5 is the upper normal threshold) in the right and left eyes, respectively (Figures 1 and 2).

**CASE 2**

Men, aged 15 years, student, KC diagnosed in the RE, reported eye itching in both eyes. Family history of KC (in a second cousin). UDVA RE 20/150 and LE 20/60; DCVA RE 20/70 (+1.00/-7.25x12°) and LE 20/20 (-1.00/-0.50x170°). VA potential -0.50/-0.50 cil 140°. Specular microscopy (Tomy; Nagaya, Japan) did not show any change in endothelium in both eyes. Placido topography (OCULUS Keratograph®5M) showed irregular and asymmetric thickness profile within the normal values, which was confirmed by the device keratoconus algorithm.
Characterization of subclinical ectasia with integrated corneal tomography and biomechanics assessments

astigmatism with typical KC pattern in the RE and the lack of apparent ectatic changes in the LE. Biomechanical examinations and corneal tomography (Corvis ST and Pentacam HR, Oculus) were performed and identified KC disease in both eyes: BAD-D RE 6.04 and LE 1.50; Tomographic and Biomechanical Index (TBI) RE 1.0 and LE 0.56; Corvis Biomechanical Index (CBI) RE 0.89 and LE 0.44 (Figures 3 and 4); ART-max RE 183 and LE 348; Kmax RE 55.0 D and LE 41.6 D; thinnest point thickness RE 487 µm and LE 520 µm. The patient was diagnosed with VAE, with TKC value of 3 in the RE and 0 in the LE. Topical treatment for ocular allergy was initiated, and the patient was instructed not to scratch his eyes. The patient was referred to intra-stromal ring implant (Keraring S / 5 160 ° 250 µm) in the RE, performed with FS-200 femtosecond laser (Alcon-WaveLight; Earlagen, Germany) by following the Mediphacos 4.0 nomogram (Belo Horizonte, Brazil). Figure 5 shows the postoperative follow-up and its results after the ring implant. Improvement was noticed in the corneal irregularities in the RE (Figure 6), which presented DCVA 20/30 with refraction +0,75/-1,25x1°.

CASE 3

Woman, aged 46 years, wanted to know if she had KC, based on her child’s recent diagnosis (Case 2). She denied atopy or eye itching. UDVA 20/20 in both eyes; DCVA RE 20/15 (plane/-0.75x70°) and LE 20/20+ (plane/-0.50x22°). J1 with +/-1.50 addition. Biomicroscopy, applanation tonometry, and fundoscopy did not show any changes in both eyes. Placido topography (OCULUS Keratograph®5M) with anterior surface was not suggestive of ectasia - TKC value was 0 in both eyes. Specular microscopy (Tomey; Nagaya, Japan) did not show any changes in both eyes. Tomography (Pentacam HR) showed Kmax RE 42.8 D and LE 42.9 D, thickness at the thinnest point of 496 µm in the RE and 494 µm in the LE, and slight changes in the posterior elevation

Figure 1: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient RE in Case 1: BAD-D 4.13; TBI: 0.96 and CBI 0.80. Assessment carried out after 3-year follow-up after intrastromal ring implantation.

Figure 3: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient LE in Case 2: BAD-D 6.04; TBI 1.0, CBI 0.89.

Figure 2: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient LE in Case 1: BAD-D -0.08; TBI 0.02 and CBI 0.01. Assessment performed after 3-year follow-up

Figure 4: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient LE in Case 2: BAD-D 1.50; TBI 0.56 and CBI 0.44.

Figure 5: Biomicroscopic examination of patient LE in Case 2 in recent postoperative period after corneal intrastromal ring implantation.
Discussion

It is important highlighting the essential concepts regarding keratoconus and corneal ectatic diseases: 1) consensus among specialists lies on the fact that keratoconus is a bilateral disease, but it can also be highly asymmetric; 2) ectasia can exceptionally be acquired by purely mechanical factors and it can occur in one or both eyes in the same individual; 3) advanced propaedeutics can increase sensitivity to detect subclinical diseases that can also be called forme frustre; 4) the term forme frustre is (literally) controversial without consensus on its definition.(7,11,12)

Keratoconus is a multifactorial disease whose causes include several genetic factors. Numerous genes are currently being studied because they are associated with KC. However, many patients have positive family history; there is a high disease correspondence between identical twins. Assumingly, KC is a bilateral pathology, since genes are the same in the two eyes of the same individual. Asymmetry is common in this disease since it is also influenced by extrinsic environmental and mechanical factors related to trauma (surgical or not), which can happen differently in each eye.(2,13-15)

The term forme fruste was first described by Amsler in 1961,(16) and has French origin; it is translated into “unfinished” or “abortive”. Such term regards incomplete disease - that may, or may not, evolve to its “full” or complete form. It is also commonly found as "subclinical", "subsymptomatic" or "pre-topographic", depending on the author or adopted criterion. Therefore, it refers to as non-manifest subclinical disease that cannot be identified by general eye examination, nor by complementary tests considered necessary to diagnose it at this stage, such as corneal topography.(17,18)

Classically, forme fruste keratoconus presents itself through asymmetric ectasia (VAE) cases when one eye has defined KC diagnosis and the contralateral eye has regular A V based on biomicroscopic examination and corneal topography. KISA<60, Kmax<47.2, and I-S<1.4(7) are among the objective criteria to indicate topographic normality. Subjective criteria includes lack of asymmetric irregularities and astigmatism. However, this is a less sensitive diagnostic method than can fail to diagnose early cases of the disease. In addition, evaluator-dependent exams reach widely different interpretations among experts, as confirmed by Ramos et al.(19) More accurate diagnostic methods and objective indices created by artificial intelligence based on Scheimpflug tomography and analysis of corneal biomechanics have been used to improve diagnostic and screening capacity, mainly before corneal refractive procedure recommendation.(20,21) Table 1 briefly summarizes the diagnostic tests used in the corneal assessment.

Increasingly sensitive and accurate diagnostic methods for keratoconus come from the study applied to very asymmetrical cases.(22) However, it is important highlighting that unilateral non-KC ectasia cases do exist, and they can lead to confuse diagnosis in the contralateral eye. Differentiation between these two scenarios is often facilitated by longitudinal assessments: parameters’ stabilization and their maintenance within the normal range indicates likely disease absence.

Scheimpflug tomography analysis integration evaluated through Pentacam HR and biomechanics assessment with Corvis ST resulted in Tomographic Biomechanical Index (TBI) creation, which is quite accurate in identifying ectasias in comparison to all other previously evaluated parameters. Ambrósio et al. developed this index by using artificial intelligence techniques in a study composed of 4 groups: 480 eyes randomly selected from patients with normal corneas; 204 eyes randomly selected from patients...
with bilateral ectatic disease defined as keratoconus; 72 ectatic eyes of patients with very asymmetric ectasia (VAE-E), and their contralateral eyes with normal topographies based on objective criteria (VAE-NT). TBI showed 100% sensitivity and specificity to detect ectatic eyes (keratoconus group and VAE-E) at cut-off value of 0.79. It continued to demonstrate high accuracy to assess eyes with normal topography; it reported sensitivity of 90.4% and specificity of 96% at cut-off value optimized to 0.29. TBI demonstrated its usefulness in diagnosing frustrated ectasias in VAE-NT cases, it corroborated the ratio of these results considered normal; these cases can be true unilateral ectasias caused by exclusively mechanical factors.(23-26)

Cases reported in the current article show some of the aforementioned scenarios. Case 1 is a true unilateral ectasia mainly caused by traumatic factors; it was confirmed by disease absence in the contralateral eye, which was subjected to propaedeutic comprising the entire diagnostic arsenal currently available for such longitudinal assessments. (27) Multimodal exams allowed reaching the correct diagnosis in case 2, which reported subclinical KC in the contralateral eye of a patient who, at first, only had ectasia in one eye. Broader understanding of the bilaterality of the disease in VAE cases can educate the patient to avoid circumstances that can contribute to worsening the conditions of the lesser affected eye. Case 3 highlights the multifactorial etiology of KC by exposing the genetic and environmental component at non-manifest ectasia in a patient susceptible to the disease but lacking the extrinsic factors for its development. Table 2 organizes the diagnostic exams for each of the 3 exposed cases.

Multimodal approach and advanced propaedeutic are necessary to clarify ectasia.7 It is also important highlighting that KC screening is not the same as screening to detect greater susceptibility to develop ectasia after refractive surgery corneal, which is better evaluated by retrospective studies of corneal evaluations. (28-30)

### Table 1
**Corneal diagnosis exams**

<table>
<thead>
<tr>
<th>Diagnosis exam</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topography</td>
<td>Assesses the curvature of the anterior corneal anterior surface and expresses it in color graphic</td>
</tr>
<tr>
<td>Tomography</td>
<td>Provides 3D reconstruction of the cornea, assesses anterior and posterior surface and pachymetry map</td>
</tr>
<tr>
<td>Biomechanical (Corvis ST)</td>
<td>Assesses corneal applanation response to air impulse stimulus</td>
</tr>
<tr>
<td>Biomechanical/tomographic assessment</td>
<td>Uses both technologies to create objective indices, increase diagnosis sensibility and specificity</td>
</tr>
<tr>
<td>Wavefront</td>
<td>Shows features of high and low order aberrations in patients with ectasia</td>
</tr>
<tr>
<td>Segmented tomography by OCT or VHFU</td>
<td>Assesses individual corneal layers such as epithelium and Bowman membrane</td>
</tr>
<tr>
<td>Segmented tomography by OCT or VHFU</td>
<td>Identifies changes at cell level based on high-resolution images</td>
</tr>
<tr>
<td>Confocal and specular microscopy</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Diagnostic tests for each eye of each of the 3 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOD</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Kmax (D)</td>
</tr>
<tr>
<td>Thinnest point pachymetry (µm)</td>
</tr>
<tr>
<td>TKC*</td>
</tr>
<tr>
<td>ART-max</td>
</tr>
<tr>
<td>BAD-D**</td>
</tr>
<tr>
<td>TBI**</td>
</tr>
<tr>
<td>CBI**</td>
</tr>
</tbody>
</table>

* TKC 0 means no signs indicative of ectasia. ** BAD-D, TBI, and CBI indices of patient 1 were calculated after 3-year follow-up after corneal intrastromal ring implantation in RE.

Kmax = maximum keratometry; Thinnest point pachymetry = thickness at the cornea thinnest point; TKC = topographic keratoconus classification; ART-max = Ambrósio relacional thickness-max; BAD-D = Belin/Ambrósio Enhanced Display; TBI = Biomechanic Topographic Index; CBI = Corvis Biomechanic Index

### References


Corresponding author
Renato Ambrósio Jr., Rio de Janeiro State University, Ophthalmology Department, Rio de Janeiro Study Group on Corneal Topography and Biomechanics, Rio de Janeiro City, Rio de Janeiro State, Brazil, E-mail: dr.renatoambrsio@gmail.com

Rev Bras Oftalmol. 2021; 80 (1): 71-6