DOI 10.5935/0034-7280.20210014

Characterization of subclinical ectasia with integrated corneal tomography and biomechanics assessments

Caracterização de ectasia subclínica com análise integrada da tomografia e biomecânica da córnea

Guilherme Garcia Criado[1] https://orcid.org/0000-0003-1105-8622
Nelson Batista Sena Júnior[1,2,4] https://orcid.org/0000-0003-4031-017X
Thiago José Muniz Machado Mazzeo[2] https://orcid.org/0000-0001-9536-1893
Marcella Quaresma Salomão Hoyer de Carvalho[3,4,5] https://orcid.org/0000-0001-8330-6432
Louise Pellegrino Gomes Esporcatte[4] https://orcid.org/0000-0002-2353-9442
Guilherme Simões Luz Hilgert[4] https://orcid.org/0000-0001-7946-2205
Renato Ambrósio Júnior[2,3,4,5] https://orcid.org/0000-0001-6919-4606

Abstract

The article aims to prospectively describe different cases of highly asymmetric ectasia (very asymmetric ectasia, VAE) to differentiate subclinical or "frustrated" forms of keratoconus (forme fruste keratoconus – FFKC) from cases of unilateral ectatic disease. Case 1 is a 39-year-old patient with unilateral ectasia treated with an intrastromal ring implant. The contralateral eye was normal due to multimodal propaedeutics, stable for more than 3 years, with a TBI of 0.02. The patient admitted to having intensely scratched only his right eye in his youth. In Case 2, a 15-year-old patient with clinical ectasia in the right eye, had a left eye with normal topography and tomographic and biomechanical changes characterizing FFKC. Case 3 is the mother of the case 2 patient, aged 46, who presented with presbyopia, without any relevant ophthalmological history. Uncorrected visual acuity of 20/20 in each eye, Placido topography with slight lower curving, but without definitive signs of ectasia. The biomechanical and tomographic evaluation revealed signs of keratoconus in both eyes. These three cases are in accordance with the definition of the global consensus: keratoconus is a bilateral disease, but ectasia can occur because of strictly mechanical unilateral (in any eye). The relevance of multimodal refractive imaging is highlighted, with a focus on integrating biomechanical and tomographic assessments with Scheimpflug images.

Keywords: *Ectasia; Dilatation, pathologic; keratoconus/diagnosis; Corneal Topography; Tomography; Biomechanics*

Resumo

O artigo tem como objetivo descrever de forma prospectiva diferentes casos de ectasias altamente assimétricas (very asymmetric ectasia, VAE) para diferenciar formas subclínicas ou "frustas" do ceratocone (forme fruste keratoconus – FFKC) de casos de doença ectásica unilateral. O Caso 1 é um paciente de 39 anos, que admitiu ter coçado intensamente apenas o olho direito (OD) na juventude, se apresentando com ectasia unilateral tratada com sucesso por meio de implante de anel intraestromal em OD. O olho esquerdo (OE) apresentou-se normal ao exame completo por meio de propedêutica multimodal e acuidade visual não corrigida (AVsc) de 20/20, estável por mais de 5 anos, com TBI (tomography and biomechanical index) de 0.02. No Caso 2 é um paciente de 15 anos com ectasia clínica em OD, e OE com topografia normal, mas alterações tomográficas e biomecânicas, incluindo o TBI 0,56, caracterizarando a doença subclínica (FFKC). O Caso 3 é a mãe do paciente do Caso 2, de 46 anos, que se apresentou com presbiopia, sem qualquer histórico oftalmológico relevante. A AVsc foi de 20/20 em cada olho, topografia de Placido com leve encurvamento inferior, mas sem sinais definitivos de ectasia. A avaliação biomecânica e tomográfica revelou sinais de ceratocone em ambos os olhos, com TBI de 1,0 e 0,99. Esses três casos estão de acordo com a definição do consenso global e a hipótese de dois acertos (two-hit hypothesis), que ceratocone é uma doença bilateral, mas ectasia pode ocorrer por causa estritamente mecânica unilateralmente (ou em qualquer olho). A relevância da propedêutica multimodal é destacada, destacando-se a integração do estudo biomecânico e tomográfico com imagens de Scheimpflug.

Descritores: Ectasia; Dilatação patológica; Ceratocone/diagnóstica; Topografia; Tomografia; Biomecânica

[1]Rio de Janeiro State University, Ophthalmology Medical Residency Program, Rio de Janeiro City, Rio de Janeiro State, Brazil.
[2]Rio de Janeiro Federal University, Ophthalmology Department Gaffrée and Guinle University Hospital, Rio de Janeiro City, Rio de Janeiro State, Brazil.
[3]Federal University of São Paulo, Ophthalmology Department, São Paulo City, São Paulo State, Brazil.
[4]Rio de Janeiro Study Group on Corneal Tomography and Biomechanics, Rio de Janeiro City, Rio de Janeiro State, Brazil.
[5]Cornea 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 ZEISS. 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 using, 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 treatments. 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 (Tomey; 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 (Keraring 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 (Belo 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 from 0.0 to 1.00 - 0.3 is the threshold for abnormality) and CBI 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 20/20 with McIntyre super pinhole in both eyes. Biomicroscopy, applanation tonometry, and fundoscopy without changes in both eyes. Specular microscopy (Tomey; Nagaya, Japan) did not show any change in endothelium in both eyes. Placido topography (OCULUS Keratograph®5M) showed irregular and asymmetric

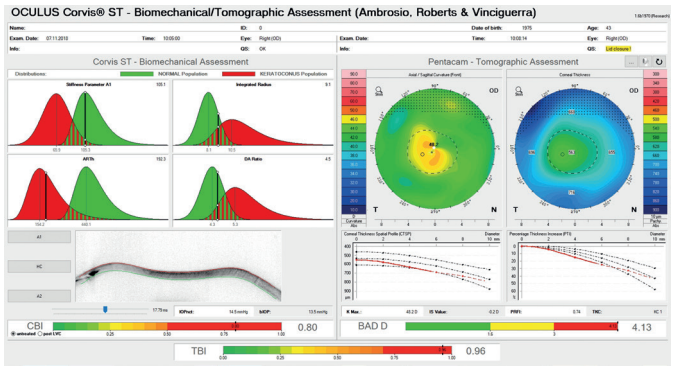

Figure 1: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient RE in Case 1: BAD-D 4.13; TBI: 0.96 and CBI 0.80. Assessment carried out after 3-year follow-up after intrastromal ring implantation.

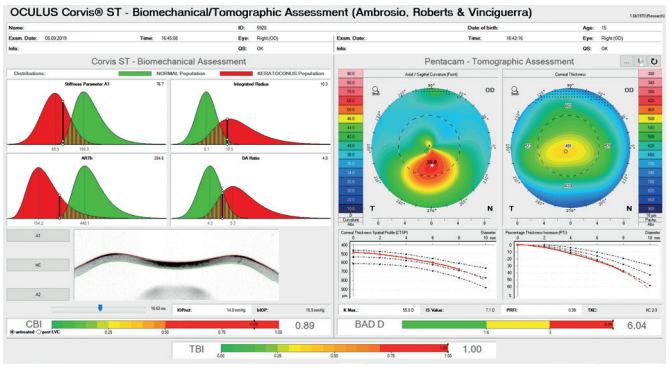

Figure 3: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient LE in Case 2: BAD-D 6.04; TBI 1.0, CBI 0.89.

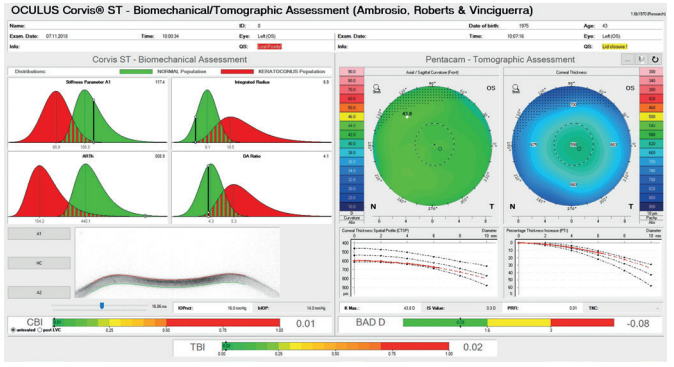

Figure 2: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient LE in Case 1: BAD-D -0.08; TBI 0.02 and CBI 0.01. Assessment performed after 3-year follow-up

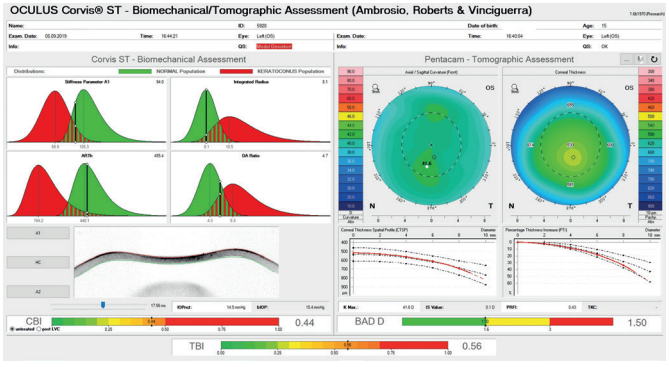

Figure 4: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient LE in Case 2: BAD-D 1.50; TBI 0.56 and CBI 0.44.

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 RE183 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°.

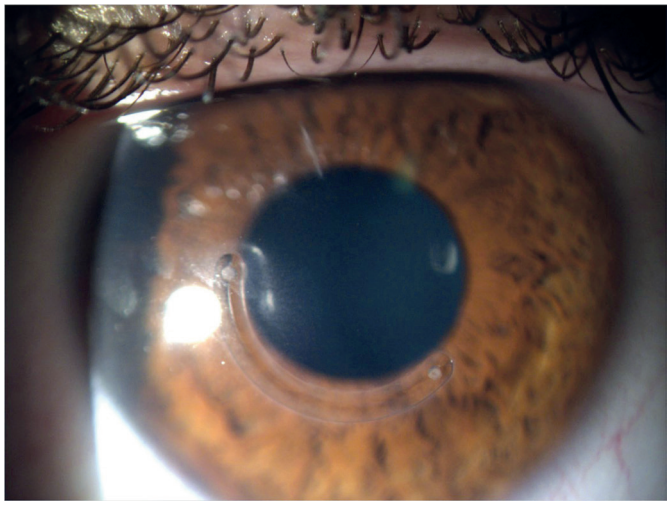

Figure 5: Biomicroscopic examination of patient LE in Case 2 in recent postoperative period after corneal intrastromal ring implantation.

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

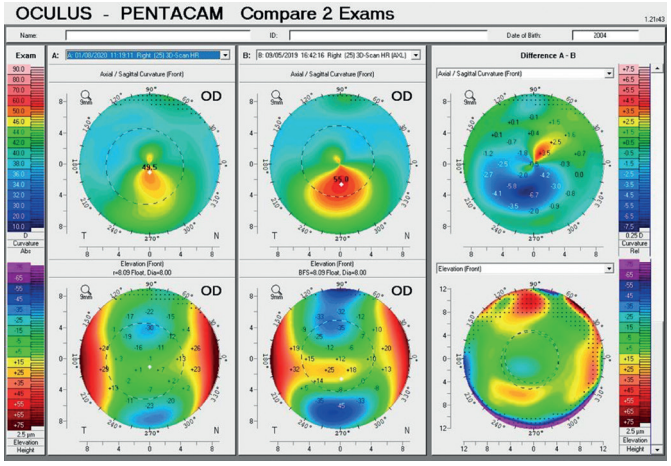

Figure 6: Differential tomographic map of axial curvature and anterior elevation maps comparing the postoperative state to that prior to the corneal intrastromal ring implant in patient RE in Case 2

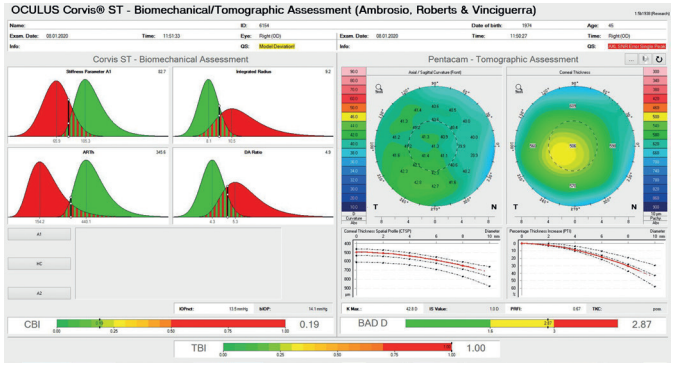

Figure 7: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient RE in Case 3: BAD-D 2.87; TBI 1.0 and CBI 0.19.

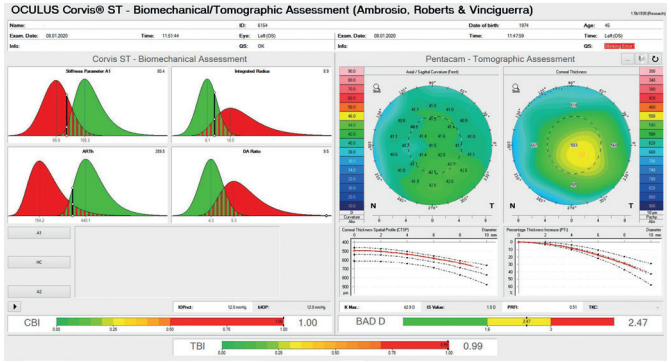

Figure 8: Biomechanical and tomographic assessment (Corvis ST and Pentacam HR, Oculus) of patient RE in Case 3: BAD-D 2.47; TBI 0.99 and CBI 1.0.

map in both eyes. Objective assessment of pachymetry progression showed changes in both eyes: BAD-D 2.87 in the RE and 2.47 in the LE. Subclinical ectasia was confirmed through biomechanic assessment (Corvis ST, Oculus), which revealed TBI RE 1.0 and LE 0.99 and CBI RE 0.19 and LE 1.0 (Figures 7 and 8).

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 frustre 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 AV 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

Table 1
Corneal diagnosis exams

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

Table 2
Diagnostic tests for each eye of each of the 3 patients

	1OD	1RE	2LE	2RE	3LE	3LE
Kmax (D)	51,0	43,5	55,0	41,6	42,8	42,9
Thinnest point pachymetry (μm)	537	590	487	520	496	494
TKC*	2	0	2-3	0	0	0
ART-max	240	535	183	348	303	361
BAD-D**	4,13	- 0,08	6,04	1,50	2,87	2,47
TBI**	0,96	0,02	1,0	0,56	1,0	0,99
CBI**	0,80	0,01	0,89	0,44	0,19	1,0

* 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

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]

References

1. Gordon-Shaag A, Millodot M, Shneor E, Liu Y. The genetic and environmental factors for keratoconus. BioMed Res Int. 2015;2015:795738.
2. Mas Tur V, MacGregor C, Jayaswal R, O'Brart D, Maycock N. A review of keratoconus: Diagnosis, pathophysiology, and genetics. Surv Ophthalmol. 2017;62(6):770–83.
3. Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM, Wisse RP. Age-specific Incidence and Prevalence of Keratoconus: A Nationwide Registration Study. Am J Ophthalmol. 2017;175:169–72.
4. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998 ;42(4):297–319.
5. Stein R, Salim G. False corneal ectasia in patients referred for corneal crosslinking, topography-guided photorefractive keratectomy, and intrastromal corneal rings. Can J Ophthalmol. 2019;54(3):374-381
6. Parker JS, van Dijk K, Melles GR. Treatment options for advanced keratoconus: A review. Surv Ophthalmol. 2015;60(5):459–80.
7. Ambrósio R Jr, Lopes B, Amaral J, Correia FF, Canedo AL, Salomao M, et al. Ceratocone: quebra de paradigmas e contradições de uma nova subespecialidade. Rev Bras Oftalmol. 2019;78(2):81–5.
8. Belin MW, Duncan JK. Keratoconus: The ABCD Grading System. Klin Monatsbl Augenheilkd. 2016;233(6):701–7.

9. Ramos IC, Reinstein DZ, Archer TJ, Gobbe M, Salomao MQ, Lopes B, et al. Unilateral ectasia characterized by advanced diagnostic tests. Int J Ker Cor Ect Dis. 2016; 5(1):40–51.
10. Silverman RH, Urs R, Roychoudhury A, Archer TJ, Gobbe M, Reinstein DZ. Epithelial remodeling as basis for machine-based identification of keratoconus. Invest Ophthalmol Vis Sci. 2014;55(3):1580–7.
11. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, et al.; Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34(4):359–69.
12. Ambrósio R, Jr BM, Perez VL, Abad JC. Gomes JAP. Definitions and concepts on keratoconus and ectatic corneal diseases: panamerican Delphi Consensus – a pilot for the global consensus on ectasias. Int J Ker Ect Cor Dis. 2014;3(3):99–106.
13. Loukovitis E, Sfakianakis K, Syrmakesi P, Tsotridou E, Orfanidou M, Bakaloudi DR, et al. Genetic Aspects of Keratoconus: A Literature Review Exploring Potential Genetic Contributions and Possible Genetic Relationships with Comorbidities. Ophthalmol Ther. 2018;7(2):263–92.
14. Mahroo OA, Oomerjee M, Williams KM, O'Brart DP, Hammond CJ. High heritability of posterior corneal tomography, as measured by Scheimpflug imaging, in a twin study. Invest Ophthalmol Vis Sci. 2014;55(12):8359–64.
15. Tuft SJ, Hassan H, George S, Frazer DG, Willoughby CE, Liskova P. Keratoconus in 18 pairs of twins. Acta Ophthalmol. 2012;90(6):e482–6.
16. Amsler M. [The "forme fruste" of keratoconus]. Wien Klin Wochenschr. 1961;73:842–3.
17. Ambrósio Jr R RI, Lopes B, Canedo ALC, Correa R, Guerra F, Luz A, Price Jr FW, Price MO, Schallhor S, Belin MW. . Assessing ectasia susceptibility prior to LASIK: the role of age and residual stromal bed (RSB) in conjunction to Belin-Ambrósio deviation index (BAD-D). Rev Bras Oftalmol. 2014;73(2):75-80.
18. De Oliveira Correa RC, Beildeck R, Salomão MQ, de Politis PB, Ambrósio R Jr. Longterm stability of ectasia in a young patient with asymmetric keratoconus. Int J Kerat Ect Cor Dis. 2015;4(2):66–8.
19. Ramos IC, Correa R, Guerra FP, Trattler W, Belin MW, Klyce SD, et al. Variability of subjective classifications of corneal topography maps from LASIK candidates. J Refract Surg. 2013;29(11):770–5.
20. Valbon BF, Ramos I, Canedo AL, Nogueira L, Ambrósio R Jr. Importância da tomografia de córnea para o diagnóstico de ectasia. Rev Bras Oftalmol. 2012;71(5):302–8.
21. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. Invest Ophthalmol Vis Sci. 2010;51(11):5546–55.
22. Elham R, Jafarzadehpur E, Hashemi H, Amanzadeh K, Shokrollahzadeh F, Yekta A, et al. Keratoconus diagnosis using Corvis ST measured biomechanical parameters. J Curr Ophthalmol. 2017;29(3):175–81.
23. Salomão M, Hoffling-Lima AL, Lopes B, Belin MW, Sena N, Dawson DG, et al. Recent developments in keratoconus diagnosis. Expert Rev Ophthalmol. 2018;13(6):329–41.
24. Ambrósio R Jr, Lopes BT, Faria-Correia F, Salomão MQ, Bühren J, Roberts CJ, et al. Integration of Scheimpflug-Based Corneal Tomography and Biomechanical Assessments for Enhancing Ectasia Detection. J Refract Surg. 2017;33(7):434–43.
25. Esporcatte LP, Salomão MQ, Lopes BT, Vinciguerra P, Vinciguerra R, Roberts C, et al. Biomechanical diagnostics of the cornea. Eye Vis (Lond). 2020;7(1):9.
26. Salomão MQ, Hofling-Lima AL, Gomes Esporcatte LP, Lopes B, Vinciguerra R, Vinciguerra P, et al. The Role of Corneal Biomechanics for the Evaluation of Ectasia Patients. Int J Environ Res Public Health. 2020;17(6):17.
27. Reinstein DZ, Gobbe M, Archer TJ, Silverman RH, Coleman DJ. Epithelial, stromal, and total corneal thickness in keratoconus: three-dimensional display with artemis very-high frequency digital ultrasound. J Refract Surg. 2010;26(4):259–71.
28. Ambrósio R Jr, Faria-Correia F, Ramos I, Valbon BF, Lopes B, Jardim D, et al. Enhanced screening for ectasia susceptibility among refractive candidates: the role of corneal tomography and biomechanics. Curr Ophthalmol Rep. 2013;1(1):28–38.
29. Ambrósio R Jr, Randleman JB. Screening for ectasia risk: what are we screening for and how should we screen for it? J Refract Surg. 2013;29(4):230–2.
30. Klyce SD. Chasing the suspect: keratoconus. Br J Ophthalmol. 2009;93(7):845-7.

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