DOI 10.5935/0034-7280.20200092

A review of keratoconus diagnosis

Diagnóstico do ceratocone: um artigo de revisão

Guilherme Simões Luz Hilgert[1] https://orcid.org/0000-0001-7946-2205
Nelson Batista Sena Júnior[1,2,4] https://orcid.org/0000-0003-4031-017X
Louise Pellegrino Gomes Esporcatte[1] https://orcid.org/0000-0002-2353-9442
Ricardo Sturzeneker[1] https://orcid.org/0000-0003-4177-5788
Thiago José Muniz Machado Mazzeo[2] https://orcid.org/0000-0001-9536-1893
Marcella Quaresma Salomão Hoyer de Carvalho[1,3,5] https://orcid.org/0000-0001-8330-6432
Guilherme Garcia Criado[4] https://orcid.org/0000-0003-1105-8622
Renato Ambrósio Júnior[1,2,3,5] https://orcid.org/0000-0001-6919-4606

Abstract

Objective: *To Perform a review on the diagnosis of keratoconus, focusing on the available propaedeutic methods.* ***Methods:*** *A search was performed in the PubMed database using the key words: Keratoconus, diagnosis, topography and tomography. As it is a review, there was no restriction regarding the publication period of the selected articles. Furthermore, both the preferred practice pattern(PPP) manual of the American Academy of Ophthalmology, as well as the website "eyewiki.aao.org" were used as reference. The project was submitted to the research ethics committee of the Federal University of São Paulo / UNIFESP / SP 2018 (# 2,568,770).*
Results: *Out of the 641 papers found in PubMed, in adition to those used as a reference for PPP, 36 were selected while considered more relevant to the adopted theme. The website "eyewiki.aao.org" was used as a reference for the images.*
Conclusion: *The diagnosis of keratoconus has evolved considerably since it was first described. It is desirable to diagnose it on the early stages due to its high potential of morbility. A possibility of an integration between the various diagnostic indices, genetic research, molecular biology and artificial intelligence is recommended for greater diagnostic accuracy.*
Keywords: *Ectasia; Keratoconus; Corneal topography; Tomography; Biomechanics*

Resumo

Objetivo: Realizar uma revisão sobre o diagnóstico do ceratocone, com enfoque nos métodos propedêuticos disponíveis. **Métodos:** Foi realizada uma pesquisa no banco de dados PubMed com as palavras chave: Keratoconus, diagnosis, topography e tomography. Por se tratar de uma revisão, não houve restrição de período para a publicação dos artigos selecionados. Foram também utilizados o manual Prefered Practice Pattern(PPP) da academia americana de oftalmologia, assim como o site "eyewiki.aao.org". **Resultados:** Dos 641 artigos encontrados no PubMed, assim como os usados como referência para o PPP, 36 foram selecionados por serem considerados mais relevantes para o tema proposto. O site "eyewiki.aao.org" foi utilizado como referência para as figuras. **Conclusão:** O diagnóstico do ceratocone evoluiu consideravelmente desde quando foi primeiramente descrito. É desejável que seja feito em suas fases precoces devido ao alto potencial de morbidade desta doença. Uma possível integração entre os múltiplos índices diagnósticos, investigação genética, biologia molecular e inteligência artificial é almejado para uma maior acurácia diagnóstica.
Descritores: Ectasia; Ceratocone; Topografia da córnea; Tomografia; Biomecânica

[1]Rio de Janeiro Study Group on Corneal Tomography and Biomechanics, Rio de Janeiro City, Rio de Janeiro State, Brazil.
[2]Rio de Janeiro Federal University, Ophthalmology Department, Rio de Janeiro City, Rio de Janeiro State, Brazil.
[3]São Paulo Federal University, Ophthalmology Department, São Paulo City, São Paulo State, Brazil.
[4]Rio de Janeiro State University, Ophthalmology Medical Residency Program, Rio de Janeiro City, Rio de Janeiro State, Brazil.
[5]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 14/5/2020 - Accepted for publication 14/7/2020

Introduction

Dr. John Nottingham made the first keratoconus (KC) description in 1854. His study approached several relevant aspects for the description of this disease, despite the technological constraints of the time. [1] Keratoconus is currently defined as progressive bilateral corneal ectasia, which can be asymmetric. Its development causes the thinning and changes in the corneal structure, without any inflammatory cause. [2] It often manifests itself in the second decade of life. Keratoconus can be developed at any moment, but its progression after the age of 40 years is rare. [3] KC prevalence in the world population is 50 to 230 cases per 100,000; both sexes are equally affected. [4,5]

Genetic diseases related to keratoconus include connective tissue disorders with collagen changes such as Ehlers-Danlos syndrome, Osteogenesis imperfecta, congenital hip dysplasia, Nail-Patella syndrome, Pseudoxanthoma Elasticum, immunoglobulin E syndrome with eczema and atopy, oculodentodigital dysplasia and ichthyosis. KC is also related to diseases that decrease cognition and increase the habit of scratching the eyes such as Down syndrome, Noonan syndrome and Angelman syndrome. [6] Keratoconus is a disease associated with corneal biomechanical instability, which is justified by changes in the orthogonal arrangement of collagen fibers. [7] There is imbalance between environmental trauma and corneal biomechanical resistance.

Keratoconus diagnosis starts with detailed clinical history and careful examination with the aid of slit lamp. However, using and associating data from new technologies to increase diagnostic accuracy is still challenging. [8] Corneal topography with Placido rings, 3-D corneal tomography, segmental tomography, Wavefront analysis, stromal cell count and the study of corneal nerves, corneal biomechanical assessment, genetics and molecular biology tests are the most relevant diagnosis methods. [8]

Keratoconus clinical development causes irregular astigmatism and progressive visual acuity loss. [9] Subclinical changes can be likely diagnosed due to improved detection methods that suggest susceptibility to ectasia. [10] KC treatment is constantly evolving and depends on disease stage.

Patients must understand all disease stages, allergy and ocular surface inflammation control and glasses' prescription for visual rehabilitation. [11] Contact lenses can be used in case of irregular astigmatisms. Using intrastromal ring segments can be an option when other strategies are not enough to improve visual quality. Penetrating corneal transplantation was the only therapeutic option before treatments to stabilize corneal biomechanical failure were developed.[5]

The cross-linking procedure (CXL) based on riboflavin/UVA using described by Spoerl et al. in 1998 is a strategy to stabilize keratoconus progression. The action mechanism of this procedure lies on stiffening corneal collagen fibers to hinder their structural change.[12]

Methods

Search carried out in the PubMed database based on the following keywords: keratoconus, diagnosis, topography, tomography. There was no restriction on publication date for the selected articles, since the current research is a literature review. The Prefered Practice Pattern (PPP) manual, by the American Academy of Ophthalmology, and the website "eyewiki.aao.org", were also used as publication sources. The Ethics Committee of São Paulo Federal University approved the current project (São Paulo Federal University /UNIFESP/SP 2018 protocol n. 2.568.770).

Results

Forty-five articles were found in PubMed database based on the aforementioned keywords, of which thirty-seven were selected after article review and the application of relevant references found in PPP. The inclusion included was the brief description of general diagnostic aspects of keratoconus. Emphasis was given on diagnostic indices for ectasia described in Pentacam and Corvis, since they have a solid basis with external validation. Routinely used propaedeutic methods, such as specular microscopy, wavefront and genetic features were also cited.

Discussion

Early Keratoconus diagnosis became more relevant given the consecration of refractive surgery as new ophthalmology subspecialty. These cases present higher progression risk to ectatic disease after laser visual correction (LVC).[8]

Initial clinical signs of Keratoconus are asymmetric refractive error with progressive or high astigmatism, keratometry suggesting high astigmatism and irregularity (axis does not add up to 180 degrees), scissor effect on red reflex on ophthalmoscopy or retinoscopy, values of lower inclination, inclined axis or high keratometry in K reading and in computerized corneal topography, and corneal thinning (mainly inferior). Some signs of it are observed through biomicroscopy - the region presenting greater thinning corresponds to that with greater protrusion. Rizutti sign is a conical reflex close to the nasal limbus; it is observed when the light beam hits the temporal cornea. Fleischer ring is an iron reservoir often observed in the epithelium, around the basis of the cone - its brown color is best seen with the aid of cobalt blue filter. Vogt striae in the stroma are thin and vertical, they usually disappear when firm pressure is applied to the eyeball and reappears when the pressure stops.

Advanced clinical signs are Munson's sign, which is the protrusion of the lower eyelid when looking down; superficial scars; rupture in Bowman's membrane; acute dropsy, when Descemet's membrane rupture allows aqueous humor to enter the stoma, which leads to corneal thickening, decreased vision and pain and stromal scars - after the resolution of the acute dropsy condition. Paradoxically, the resolution of the acute dropsy condition can improve vision since it changes corneal curvature and reduces irregular astigmatism.

In addition to clinical aspects, objective methods are used to classify and assess keratoconus development. The ABCD grading system proposed by Belin (Figure 1, Table 2) gives individual grades to 4 parameters: (A) the radius of the anterior corneal curvature, (B) the radius of the posterior corneal curvature, (C) corneal pachymetry at the thinnest point and (D) visual acuity with better correction. The (-) sign is added for absence of corneal scars or (+) for the presence of a scar allowing the visualization of iris details (++) of a scar that does not allow visualizing iris details.[12] The 4 parameters are graphically presented to depict radial curvature and pachymetry values, and the 5–stage classification ranging from 0 to 5. The examiner needs to add visual acuity, the presence or absence of corneal scarring, so the software can automatically classify the cornea based on ABCD criteria.

It is important clarifying the nomenclature applied to image

Table 1
Exams to help keratoconus diagnosis.

EXAME DIAGNÓSTICO	CARACTERÍSTICAS
Topografia	Analisa a curvatura da superfície anterior da córnea e a expressa em gráfico de cores
Tomografia	Proporciona reconstrução 3D da córnea analisando superfícies anterior e posterior e mapa paquimétrico
Biomecânica (Corvis ST)	Analisa a resposta de aplanação corneana a um estímulo de pulso de ar
Avaliação biomecânica/tomográfica	Une as duas tecnologias criando índices objetivos e aumentando a sensibilidade e especificidade diagnóstica
Wavefront	Caracteriza as aberrações de baixa e alta ordem que acompanham o paciente com ectasia
Tomografia segmentar por OCT ou VHFU (ultrassom de altíssima frequência)	Avalia camadas individuais da córnea como epitélio e membrana de bowman
Microscopia confocal e especular	Identifica alterações em nível celular a partir de imagens de alta resolução

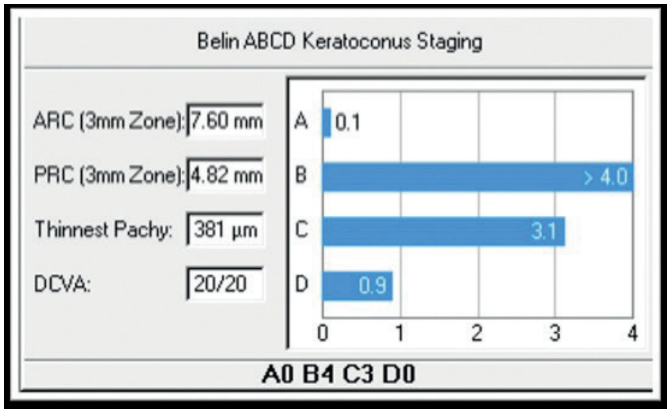

Figure 1: Biomechanical and tomographic assessment of the cornea (Corvis ST and Pentacam HR, Oculus)

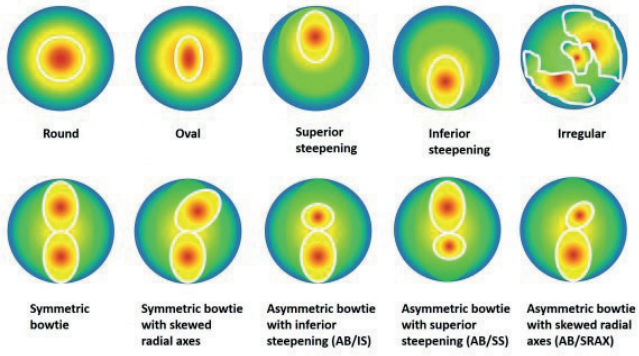

Figure 2: Topographic Patterns, Rabinowitz et al, 1996.

capturing methods used for corneal assessment over time. keratoscope, back in 1980s aimed at quantitatively assessing corneal contour in all meridians;[13] it evolved to video keratoscopy and, subsequently, to corneal topography. Rabinowitz, and collaborators, assessed regular corneas of 390 eyes in 1996 and proposed 10 different topographic patterns. It was done to create a database describing corneal patterns and quantitative indices by using video keratoscopy (Figure 2).[14]

Corneal topography based on Placido discs assesses the anterior surface of the cornea by using quantitative data to plot

Table 2
0 to IV Staging and ABCD Grading System proposed by Belin

ABCD Grading System

Criteria A and ARC (3.0mm Zone)
Anterior Radius of Curvature. Average curvature in the 3.0mm zone centered on the thinnest location of the cornea.

Criteria B and PRC (3.0mm Zone)
Posterior Radius of Curvature in the 3.0mm zone. Average curvature in the 3.0mm zone centered on the thinnest location of the cornea.

Criteria C and Thinnest Pachymetry
Thinnest pachymetry in µm

Criteria D and DCVA
"Distance Best Corrected Visual Acuity"
DCVA is not generated by the Pentacam software. It should be input manually by clicking left mouse into the corresponding field.
The input value will be saved to the examination.

Whole number stages are rounded down from the number with decimal place.

ABCD Criteria	A	B	C	D	
	ARC (3 mm Zone)	PRC (3 mm Zone)	Thinnest Pach um	BDVA	Scarring
STAGE 0	> 7.25 mm (< 46.5 D)	> 5.90 mm (< 57.25 D)	> 490 um	= 20/20 (= 1.0)	-
STAGE I	> 7.05 mm (< 48.0 D)	> 5.70 mm (< 59.25 D)	> 450 um	< 20/20 (< 1.0)	-, +, ++
STAGE II	> 6.35 mm (< 53.0 D)	> 5.15 mm (< 65.5 D)	> 400 um	< 20/40 (< 0.5)	-, +, ++
STAGE III	> 6.15 mm (< 55.0 D)	> 4.95 mm (< 68.5 D)	> 300 um	< 20/100 (< 0.2)	-, +, ++
STAGE IV	< 6.15 mm (> 55.0 D)	< 4.95 mm (> 68.5 D)	= 300 um	< 20/400 (< 0.05)	-, +, ++

maps presenting color scales to help data interpretation.[15] There are indices to detect keratoconus, such as the Rabinowitz-Mcdonnel method: K value (central curvature) distinguishes the central cones; IS values (lower-upper dioptric asymmetry) are the difference in refractive power between the lower five points and the upper points; SRAX (relative inclination of the steepest radial axes above and below the horizontal meridian). These authors have shown K value greater than 47.20 D, IS value greater than 1.2 and SRAX index above 21° in 98% of patients with KC.[16]

The possibility of considerable variability between subjective assessment of topographic images - even performed by specialists - was questioned in 2013.[17] It has encouraged the search for more elaborated and lesser superficial diagnostic methods.

The likelihood of assessing the posterior surface of the cornea was achieved by technologies such as Scheimpflug tomography, high-frequency ultrasound and optical coherence tomography (OCT).[8] Orbscan was the first corneal tomography method (Bausch & Lomb; Rochester, EUA). Researchers found good sensitivity for diagnosing early keratoconus forms, which had not yet been detected by conventional topography.[18]

The Galilei Dual Scheimpflug Analyzer (Ziemer, Port, Switzerland) is also used to assess the posterior corneal surface; however, unlike Orbscam, it uses two Scheimplug cameras and Placid rings to form a three-dimensional image of the cornea and indices in order to distinguish patients with regular corneas from those affected by KC.[19]

Pentacam (Oculus, Wetzlar, Germany) consists of a rotating Scheimpflug camera system and a frontal lighting system, capable of performing a three-dimensional reconstruction of both the cornea and the anterior segment(Figure 3)[8] Several indices were described to diagnose KC and other ectatic diseases of the cornea.

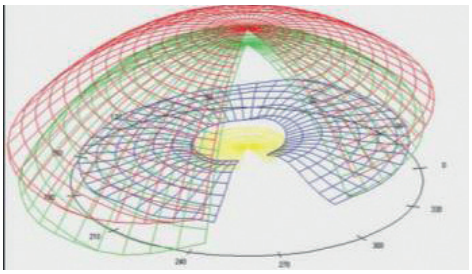

Figure 3: Three-dimensional reconstruction of the cornea and anterior chamber, Pentacam (HR, Oculus)

Belin-Ambrósio Enhanced Ectasia Display (BAD) index uses elevation maps based on a Best-Fit Sphere (BFS) and on enhanced BFS based on pachymetric assessment performed by the device.[20] BFS-based elevation maps are calculated based on the central 8mm of the cornea, whereas the enhanced BFS excludes the 3.5mm area centered at the thinnest point. This technique used to calculate elevation barely changes the maps found in healthy corneas but makes it possible changing the most evident ectatic corneas.[21] A "D" value is calculated based on linear regression analysis by using several parameters, such as anterior and posterior elevation at the thinnest point, changes in anterior and posterior elevation based on BFS, pachymetric distribution, relative thickness and maximum corneal curvature (Kmax) .[22] The BAD-D cut-off found in a study comparing 47 corneas with very asymmetric ectasia (VAE) to one eye randomly selected from 331 patients with healthy corneas reached 1.22 (93.62% sensitivity and 94.56% specificity).[23]

The Pentacam Random Forest Index (PRFI) was developed by using patterns from Pentacam and artificial intelligence to diagnose keratoconus, subclinical KC, eyes with normal topography and very asymmetric ectasia.

The association between corneal mechanical features and corneal ectasias pathophysiology is well described in the literature.[11,24] The Ocular Response Analyzer (ORA – Reichert Ophthalmic Instruments, Depew, NY) was the first device commercially available for corneal biomechanical evaluation.[25] It works as a non-contact tonometer that provides air pulse and evaluates two parameters: corneal hysteresis (CH) and corneal resistance factor (CRF). Significant result overlap was found when corneas of healthy patients and of patients with keratoconus were compared, despite the statistical significance.[26]

Corvis ST (OCULUS Optikgerate GmbH; Wetzlar, Germany) works as non-contact tonometer with ultra-speed Scheimpflug camera for biomechanical assessment. Although there is significant overlap when parameters of this device are used, it is possible increasing diagnostic accuracy with the aid of artificial intelligence.[27,28]

Vinciguerra, and collaborators, described the Corneal Biomechanical Index (CBI) by combining deformation parameters to corneal horizontal thickness. This index has 0.5 cut-off with 100% sensitivity and 94.1% specificity.[29]

The Tomographic Biomechanical Index (TBI) proposed by Ambrósio, and collaborators, integrates the group of tomographies based on Scheimpflug (Pentacam) with biomechanical data (Corvis ST).[30] This parameter can detect patients with unchanged topographies and VAE, and report better diagnoses for patients susceptible to keratoconus than any other isolated index.[28,30] Specificity of 96% and sensitivity of 90.4% were achieved in keratoconus diagnoses by using 0.29 cut-off - results were validated in other studies.[28,30]

Ocular aberrometry based on wavefront examination is described as a useful tool to diagnose suspected keratoconus cases. Trefoil and vertical coma increased in patients described with subclinical keratoconus were some high-order aberrations.[31] In addition, manifest refraction aided by wavefront analysis can increase the efficiency of refractive methods in patients with keratoconus.[8]

Confocal microscopy shows diverse cell changes in all corneal layers of patients with keratoconus.[32] Some examples of it are increased pleomorphism, decreased keratocytes in the superficial and deep stroma, thinning of the basal layer and thickening of the subbasal nerves.

The study of other features of the anterior segment, such as anterior chamber depth (ACD), is allowed by Scheimpflug tomography. Cornea evaluation and assessment is often the main focus in patients with keratoconus. However, a Chinese study found ACD increase in patients with advanced KC in comparison to lesser affected eyes.[33] Such finding is presumably accompanied by increased prolate aspect of the cornea. However, another study carried out with an Australian sample showed difference in ACD measurements in comparison to patients with subclinical keratoconus and the ones with unchanged eyes.[34]

Corneal Tomography with High Frequency Ultrasound is used to individually assess corneal layers. Reinstein, and collaborators, related epithelial thickness to the diagnosis of initial keratoconus cases.[35]

It is important highlight the correlation between environmental exposure (scratching the eyes) and genes related to keratoconus. It is estimated that more than 700 genetic mutations are associated with KC diagnosis, 8% as direct ectasia cause and 92% due to environmental factors.[36]

Clinical Example 1:

Men, aged 13 years, diagnosed with "unilateral keratoconus" one month before. Chronic eye allergy. Reported RE visual acuity (VA) 20/20 (plane/-1.00x60) and LE 20/40 (plane/-4.50x130). RE corneal topography without characteristic changes related to keratoconus, IS 0.8D, Kmax 44.7D, negative Topographic Keratoconus Classification (TKC), and changes in BAD-D, PRFI, CBI, and TBI indices (Figure 4a). Moderate keratoconus on LE, with Kmax 55.4D, TKC featuring grade 2 keratoconus and changes in the BAD-D, PRFI, CBI, and TBI indices (Figure 4b). Very asymmetric ectasia (VAE) case, with subclinical keratoconus form (FFKC) in the RE and moderate keratoconus in the LE.

Clinical Example 2:

Men, aged 52 years, father of patient 1, 20/20 correction VA in both eyes and biomicroscopy without changes. The patient denies having clinical history of ocular pruritus, unlike the son - who presents chronic ocular allergy. Topographic examination without changes; however, changes were evidenced in tomography and biomechanics integrated assessment (TBI). The case suggests susceptibility to bilateral ectasia (Figuras 4c e 4d).

Normal topography does not exclude KC diagnosis at subclinical form in the referred cases,[37] and it reinforces the need of tomographic and biomechanical approach for ectasia screening.

Eyes with regular topography in patients with VAE - clinical ectasia was detected in only one eye - are often examined to detect susceptibility to ectasia. These patients often have one eye with evident clinical ectatic disease and contralateral eye with regular topography. It can be a mild case, or even subclinical form or uni-

lateral ectasia - only one eye was affected by the environmental factor due to eye scratching .[30]

The subclinical condition can occur in both eyes, as reported in a study with identical twins carried out by Guerra et al.37 Twin 1 had clinical keratoconus in one eye and subclinical condition in the contralateral eye, whereas twin 2 had subclinical condition reported by tomography and biomechanics (Figure 5). It is important highlighting that twin 1 admitted to intensely scratch the RE, whereas twin 2 denied such a habit.

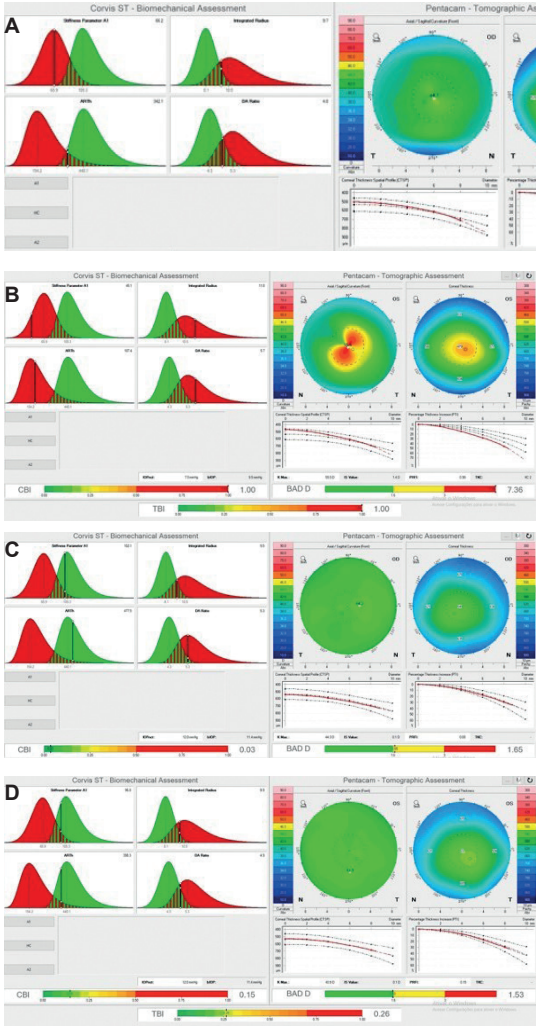

Figure 4 : Two patients (father and son) subjected to Pentacam AXL and Corvis ST exams.

Conclusion

Assessing ectatic diseases of the cornea (together) and keratoconus (KC) is a practice that has been gaining relevance due to the increased number of refractive surgeries and to improved diagnostic methods. It is important investigating this pathology by using a multimodal approach, which is challenging, given the the several resources available.

New studies carried out with patients with VAE are increasingly valuable since keratoconus is known to be a disease with bilateral involvement, although it is commonly asymmetric. its morbidity rate is high when it is not treated; therefore, it is important diagnosing initial cases that often have unchanged topography.

Possible future integration among diagnostic indices, artificial intelligence, genetic research and molecular biology has great potential for improving sensitivity to and specificity for keratoconus detection.

References

1. Gokul A, Patel DV, McGhee CN. Dr John Nottingham's 1854 Landmark Treatise on Conical Cornea Considered in the Context of the Current Knowledge of Keratoconus. Cornea. 2016;35(5):673–8.
2. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK, Binder PS, et al.; United States Crosslinking Study Group. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. Ophthalmology. 2017;124(9):1259–70.
3. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42(4):297–319.
4. Espandar L, Meyer J. Keratoconus: overview and update on treatment. Middle East Afr J Ophthalmol. 2010;17(1):15–20.
5. Jhanji V, Sharma N, Vajpayee RB. Management of keratoconus: current scenario. Br J Ophthalmol. 2011;95(8):1044–50.
6. Sugar J, Macsai MS; J. S. What causes keratoconus? Cornea. 2012;31(6):716–9.

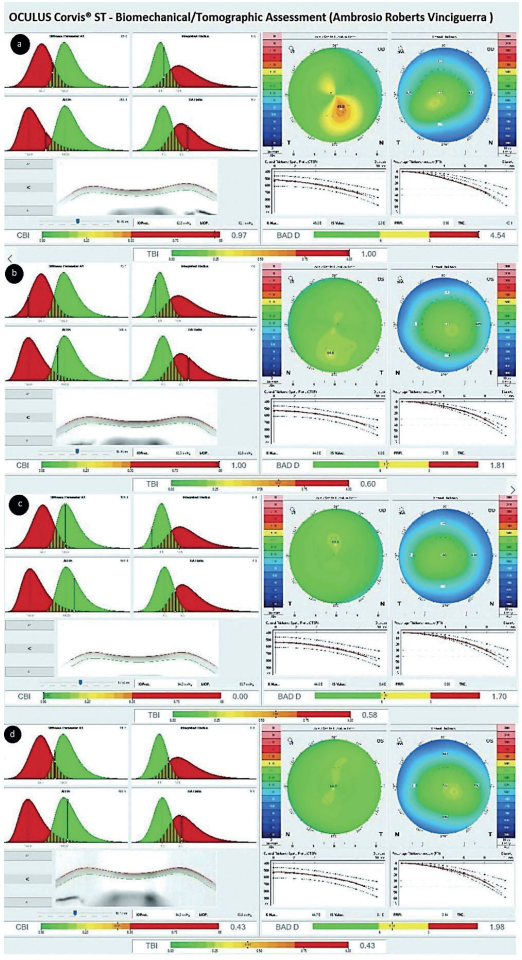

Figure 5: Two twin patients subjected to Pentacam AXL and Corvis ST exams.

7. Daxer A, Fratzl P. Collagen fibril orientation in the human corneal stroma and its implication in keratoconus. Invest Ophthalmol Vis Sci. 1997;38(1):121–9.
8. 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.
9. McMahon TT, Edrington TB, Szczotka-Flynn L, Olafsson HE, Davis LJ, Schechtman KB; CLEK Study Group. Longitudinal changes in corneal curvature in keratoconus. Cornea. 2006;25(3):296–305.
10. Ambrosio R Jr. Simplifying Ectasia Screening with Pentacam corneal tomography. Highlights Ophthalmol. 2010;38(3):12-20.
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. Duncan JK, Belin MW, Borgstrom M. Assessing progression of keratoconus: novel tomographic determinants. Eye Vis (Lond). 2016;3(1):6.
13. Rowsey JJ, Reynolds AE, Brown R. Corneal topography: Corneascope. Arch Ophthalmol. 1981;99(6):1093–100.
14. Rabinowitz YS, Yang H, Brickman Y, Akkina J, Riley C, Rotter JI, Elashoff J. Videokeratography database of normal human corneas. Br J Ophthalmol. 1996;80(7):610-6.
15. Wilson SE, Ambrosio R Jr. Computerized corneal topography and its importance to wavefront technology. Cornea. 2001;20(5):441–54.
16. Cavas-Martínez F, De la Cruz Sánchez E, Nieto Martínez J, Fernández Cañavate FJ, Fernández-Pacheco DG. Corneal topography in keratoconus: state of the art. Eye Vis (Lond). 2016;3(1):5.
17. Ahmed D, Stattin M, Glittenberg C, Krebs I, Ansari-Shahrezaei S. Stellate nonhereditary idiopathic foveomacular retinoschisis accompanied by contralateral peripheral retinoschisis. Retin Cases Brief Rep. 2019;13(2):135–40.
18. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. Invest Ophthalmol Vis Sci. 2010;51(11):5546–55.
19. Demir S, Sönmez B, Yeter V, Ortak H. Comparison of normal and keratoconic corneas by Galilei Dual-Scheimpflug Analyzer. Cont Lens Anterior Eye. 2013;36(5):219–25.
20. Belin MW, Ambrósio R. Scheimpflug imaging for keratoconus and ectatic disease. Indian J Ophthalmol. 2013;61(8):401–6.
21. Belin MW, Khachikian SS. An introduction to understanding elevation-based topography: how elevation data are displayed - a review. Clin Exp Ophthalmol. 2009;37(1):14–29.
22. Lopes BT, Ramos IC, Dawson DG, Belin MW, Ambrósio R Jr. Detection of ectatic corneal diseases based on pentacam. Z Med Phys. 2016;26(2):136–42.
23. Ambrósio R Jr, Valbon BF, Faria-Correia F, Ramos I, Luz A. Scheimpflug imaging for laser refractive surgery. Curr Opin Ophthalmol. 2013;24(4):310–20.
24. Ambrósio R Jr, Correia FF, Lopes B, Salomão MQ, Luz A, Dawson DG, et al. Corneal Biomechanics in Ectatic Diseases: Refractive Surgery Implications. Open Ophthalmol J. 2017;11(1):176–93.
25. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg. 2005;31(1):156–62.
26. Fontes BM, Ambrósio Junior R, Jardim D, Velarde GC, Nosé W. Ability of corneal biomechanical metrics and anterior segment data in the differentiation of keratoconus and healthy corneas. Arq Bras Oftalmol. 2010;73(4):333–7.
27. Ali NQ, Patel DV, McGhee CN. Biomechanical responses of healthy and keratoconic corneas measured using a noncontact scheimpflug-based tonometer. Invest Ophthalmol Vis Sci. 2014;55(6):3651–9.
28. Sedaghat MR, Momeni-Moghaddam H, Ambrósio R Jr, Heidari HR, Maddah N, Danesh Z, et al. Diagnostic Ability of Corneal Shape and Biomechanical Parameters for Detecting Frank Keratoconus. Cornea. 2018;37(8):1025–34.
29. Vinciguerra R, Ambrósio R Jr, Elsheikh A, Roberts CJ, Lopes B, Morenghi E, et al. Detection of keratoconus with a new biomechanical index. J Refract Surg. 2016;32(12):803–10.
30. 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.
31. Saad A, Gatinel D. Evaluation of total and corneal wavefront high order aberrations for the detection of forme fruste keratoconus. Invest Ophthalmol Vis Sci. 2012;53(6):2978–92.
32. Ghosh S, Mutalib HA, Kaur S, Ghoshal R, Retnasabapathy S. Corneal cell morphology in keratoconus: A confocal microscopic observation. Malays J Med Sci. 2017;24(2):44–54.
33. Jian W, Shen Y, Chen Y, Tian M, Zhou X. Ocular dimensions of the Chinese adolescents with keratoconus. BMC Ophthalmol. 2018;18(1):43.
34. Article O. Assessment of Anterior Segment Parameters of. 2014;91(7):803–9.
35. Silverman RH, Urs R, RoyChoudhury A, Archer TJ, Gobbe M, Reinstein DZ. Combined tomography and epithelial thickness mapping for diagnosis of keratoconus. Eur J Ophthalmol. 2017;27(2):129–34.
36. Michael A, Hauser JW. The Genetics of Keratoconus: A Review. Reprod Syst Sex Disord. 2012;01(02):1–8.
37. Ramos I, Guerra G, de Oliveira VB, Ferreira I. Subclinical Keratoconus Detection in Identical Twins. Int J Keratoconus Ectatic Corneal Dis. 2016;5(1):35–9.

Autor correspondente:
Renato Ambrósio Jr.
Departamento de Oftalmologia da Universidade Federal do Estado do Rio de Janeiro; Grupo de Estudos de Tomografia e Biomecânica da Córnea do Rio de Janeiro, Rj, Brasil
E-Mail: dr.renatoambrosio@gmail.com