Enhanced Diagnostics for Corneal Ectatic Diseases

Subjects: Ophthalmology

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There are different fundamental diagnostic strategies for patients with ectatic corneal diseases (ECDs): screening, confirmation of the diagnosis, classification of the type of ECD, severity staging, prognostic assessment, and clinical follow-up. The conscious application of such strategies enables individualized treatments. The need for improved diagnostics of ECD is related to the advent of therapeutic refractive procedures that are considered prior to keratoplasty.

keratoconus corneal ectasia multimodal corneal imaging

1. Introduction

Keratoconus (KC) is the most common ectatic corneal disease (ECD), which comprises a class of disorders characterized by progressive thinning and subsequent bulging of the cornea, causing irregular astigmatism [1][2]. When evaluating patients with ectatic disorders of the cornea, the clinician must consider the different fundamental diagnostic strategies (**Table 1**): screening, confirmation of the diagnosis, classification of the type of ectasia, staging severity, prognostic evaluation, and clinical follow-up for individualized treatments. Refractive surgery boosted extensive developments in diagnostic and therapeutic technologies for ECD [3][4][5][6]. Therapeutic refractive procedures are less invasive alternatives to keratoplasty. Corneal crosslinking, customized ablations, and intracorneal ring segments (ICRSs) can be indicated for such patients. Introducing such options for managing ECD determined the need for an improved disease evaluation.

Table 1. Diagnostic strategies in keratoconus.

Diagnostic Strategies	What Is?	How?
Screening	Detect mild forms of KC, and ectasia susceptibility, considering the refractive treatment and the impact on the cornea.	Placido-disk corneal topography, Scheimpflug tomography, OCT (or VHF US) segmental tomography, and biomechanical assessments.
Diagnostic confirmation	Paradigm shift related to the management of ECD and access ectasia risk and progression to improve treatment.	Comprehensive clinical evaluation with multimodal imaging.

Diagnostic Strategies	What Is?	How?
Classification of ectasia	Group of disorders characterized by progressive thinning and following protruding of the corneal structure.	Integration of tomographic and biomechanical data with AI, genetics, and molecular biology.
Staging	To prevent visual loss before it even occurs, with new treatment modalities.	ABCD + E ectasia/KC staging.
Prognostic	Management of KC varies depending on the severity of the disease	Biomechanical parameters (SPA-1) and patient compliance.

of ECD is relevant for identifying patients at higher risk for progressive iatrogenic ectasia after laser vision correction (LVC). The current concept for assessing ectasia risk before LVC combines the characterization of corneal properties, related to the inherent susceptibility for ectasia progression, and the impact of the LVC procedure on the corneal structure. External mechanical factors, such as eye rubbing and pressurizing the eyes during sleep, also play a significant role. This concept contemplates the two-hit hypothesis for the pathogenesis of ECD [7].

Multimodal refractive imaging involves different technologies, including Placido-disk corneal topography, Scheimpflug 3-D tomography, segmental or layered tomography with layered epithelial thickness using OCT (optical coherence tomography), digital very high-frequency ultrasound (VHF-US), and ocular wavefront. Corneal biomechanical assessments were translated from mathematical models. In vitro laboratory destructive tests to clinically measure beyond shape analysis have been promising as a crucial tool for enhancing the accuracy of identifying mild forms of ECD and the capacity to characterize ectasia susceptibility [7][8].

Artificial intelligence (AI) has proven its relevance in integrating the overabundance of data generated for facilitating clinical decisions. Genetic and molecular biology tests are promising to further enhance diagnostic accuracy for allowing personalized treatments. Moreover, the hypothesis that mild or fruste keratoconus is a risk factor for a mother delivering a baby with Down's syndrome opened a new horizon for the relevance of the diagnostics of ECD [9].

2. Multimodal Imaging

The concept of multimodal corneal imaging was announced to integrate several diagnostic tools offered for corneal and anterior segment imaging (**Table 2**) [5]. Placido disk-based corneal topography improved the ability to detect abnormalities in mild corneal ectasia, even in patients with normal distance-corrected visual acuity and slit-lamp examinations within normality [4][10][11].

Table 2. Exams for multimodal propaedeutics in keratoconus.

Imaging Tests	Characterization
Corneal Topography	Analysis of the front surface of the cornea using Placido-disk-based reflection.

Imaging Tests	Characterization
Corneal Tomography	Three dimensional reconstruction of the cornea enables the calculation of elevation maps of the front and back surfaces, along with a pachymetric map, typically with rotating Scheimpflug imaging.
Segmental Corneal Tomography	Tomographic evaluation of segments of the cornea, including epithelium, Bowman's layer, and Descemet's membrane.
Corvis ST	Non-contact tonometer system that uses an ultra-high-speed Scheimpflug camera to monitor the corneal deformation response over a 5–6 mm area during a constant application of an air pulse, allowing for a more detailed assessment of the deformation process.

Anterior segment tomography with 3D reconstruction of the cornea offered more detail about corneal architecture with a range of quantitative indices derived from the front and back elevation along with pachymetric maps [5][12][13][14]. Different studies involving eyes with typically "innocent" topography, from patients with clinical ectasia identified in the fellow eye, confirmed the capacity of corneal tomography to improve the accuracy of detecting mild or subclinical ectatic disease [4][15][16][17][18][19][20]. Corneal tomographic parameters revealed an excellent ability to identify susceptibility to developing ectasia after LASIK (Laser-Assisted in Situ Keratomileusis) in retrospective studies involving patients with such complications [13][21][22]. The need to go beyond corneal shape evaluation for describing ectasia risk within the biomechanical domain was supported and promoted [23][24].

3. Screening for Ectasia Risk before Laser Vision Correction

The key to refractive surgery screening is to identify cases with mild ectasia and cases of high susceptibility or predisposition for biomechanical failure and ectasia after LVC [25][26]. Corneal ectasia has been a severe complication of LASIK surgery since the first report by Seiler in 1998 [27]. Clinical risk factors associated with ectasia include preoperative ectactic corneal disease, young age, and low preoperative pachymetry [21][28][29][30].

Corneal ectasia is the consequence of a biomechanical decompensation of the stroma. This could be related to either the impact of the procedure on the corneal structure or the preoperative individual biomechanical properties. The present understanding is that a combination of these factors determines stability or progression of ectasia after LVC [7][8][31]. However, some cases with low preoperative risk factors can develop ectasia, whereas others with high probabilities of developing ectasia continue to be stable [7]. Long-term stability after LVC is determined by the preoperative biomechanical strength of the patient's corneal stroma, the amount of biomechanical alteration caused by the surgery, and the postoperative stress load on the cornea [31].

3.1. Corneal Topography

Placido disk-based corneal topography projects a sequence of concentric rings onto the anterior corneal surface and uses quantitative data to generate color-coded maps [32][33]. For the diagnosis of KC, one of the most commonly used indices is Rabinowitz and McDonnell's [34]. Corneal topography epitomizes a revolution in corneal imaging. It has the sensitivity to detect ectatic disease before any loss of best-corrected visual acuity, and any

significant slit-lamp examination findings acquired [10][11]. Consequently, corneal topography is considered an essential examination when screening refractive surgery candidates [35]. Randleman and co-workers developed the Ectasia Risk Scoring System with corneal topography, pachymetric measurements, and clinical variables [29][36].

However, limitations of topography examination were documented after literature presented patients who developed post-LVC ectasia, despite normal preoperative anterior surface maps [7][28][37] and patients with renowned risk factors and abnormal topographic maps who stayed stable years after LVC [38]. Therefore, there is a need for a complete characterization of the cornea to improve screening for ectasia susceptibility of refractive candidates.

3.2. Corneal Tomography

The Pentacam (Oculus, Wetzlar, Germany) uses a rotating Scheimpflug camera and a frontal view illumination system to reconstruct topographic images of the cornea and anterior segment, and diverse indices have been proposed to increase the diagnosis of KC.

The Pentacam Belin–Ambrósio Enhanced Ectasia Display (BAD) was designed as a clinical tool to assist clinical diagnosis of KC and ECD [15][16][17][19][39]. Tomographic parameters are displayed as the standard deviation from normality to disease (d values), including front and back elevation at the thinnest point, change in anterior and posterior elevation of the standard and enhanced best-fit sphere (BFS), the thinnest value and its vertical location, pachymetric progression index, Ambrósio's relational thickness, and maximal curvature (KMax). A final 'D' value is calculated based on linear regression analysis, which weights each parameter differently [8][14][15].

Lopes and collaborators proposed using random forest (RF) to enhance pattern recognition [40]. The Pentacam Random Forest Index (PRFI) was developed to detect ectatic corneal disease among the following groups, performing with better accuracy than any individual tomographic parameter: normal eyes (stable LASIK cases), clinical KC, normal topographic eyes with very asymmetric ectasia (VAE-NT), and eyes with higher ectasia susceptibility (preoperative data of post LASIK ectasia). Compared with the BAD-D, which correctly classified only 55.3% of the post-LASIK ectasia, the PRFI correctly detected 80%. Considering the recognition of the VAE-NT, the PRFI presented a sensitivity of 85.2% and specificity of 96.6% in the independent test set [40].

3.3. Segmental Corneal Tomography

Corneal epithelial indices for identifying KC were developed with this technology, and studies proposed this approach as a valuable instrument in identifying milder forms of the disease [41][42]. Working with optical coherence tomography (OCT) technology, Huang and collaborators developed a similar approach with an extended epithelial thickness map and different indices to detect KC in its initial stages [43][44]. Sinha-Roy and coauthors also investigated the irregularity of the Bowman's layer in normal and ectatic corneas and proposed a new Bowman's roughness index. This index had a good performance in detecting KC and, when combined with the BAD-D and epithelial thickness data, improved the sensitivity for detecting mild forms of ectasia [45].

Studies also demonstrated the use of this technology to investigate flap thickness reproducibility, to understand corneal refractive surgery complications, and to measure epithelial changes after refractive surgery [46].

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