New Diagnostics in Corneal Ectatic Disease

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Background

Keratoconus was first described in detail in 1854 as a chronic, noninflammatory ectasia of the cornea.1 Although it is the most common primary ectasia, keratoconus is relatively rare with a reported annual incidence of around 2 per 100,000 and prevalence of 54.5 per 100,000, though rates vary geographically.2–4 Keratoconus is characterized by corneal steepening, visual distortion, apical corneal thinning, and central corneal scarring. The corneal thinning induces irregular astigmatism and myopia, leading to mild or marked visual impairment.1 The disease is typically bilateral, although only 1 eye may be affected at the onset, and it can be highly asymmetric.5,6 Early in the disease, and in subclinical or forme fruste keratoconus, there may be minimal or no symptoms, whereas in advanced disease there can be profound visual loss.

The detection of subclinical or forme fruste keratoconus is one of the most important steps in the preoperative evaluation of a refractive surgery candidate. Postoperative iatrogenic keratectasia is a rare but dreaded complication following excimer laser corneal refractive surgery. It most commonly occurs after laser in situ keratomileusis (LASIK), but has been reported following photorefractive keratectomy and small incision lenticule extraction as well.7–9 It typically occurs after surgery in eyes with undetected forme fruste keratoconus or, much less frequently, pellucid marginal degeneration. Other risk factors include preoperative topographic abnormalities, low postoperative residual stromal bed thickness, younger patient age, low central corneal thickness, and percent tissue altered (PTA).6 Postoperative keratectasia induces similar clinical features to those seen in keratoconus, and can be equally, if not more debilitating.
A major challenge for any corneal or refractive surgeon is the detection of keratoconus at its earliest stages. Many studies have been performed and screening tools have been developed to help clinicians more accurately identify the earliest forms of this disease in hopes of preventing or lessening the risk of postoperative keratectasia. However, a major limitation of many of these studies is that they are designed to diagnosis frank keratoconus, rather than screen for forme fruste disease. In addition, different definitions of forme fruste keratoconus exist in the literature and there is no real consensus on which is best, creating further challenges when screening these patients.

Placido topography, scanning-slit tomography, Scheimpflug tomography, optical coherence tomography (OCT), and direct biomechanical testing have been utilized, alone or in combination, in an attempt to identify patients at risk for postoperative ectasia. However, no system is able to detect all cases and predict unequivocally the risk of developing keratectasia after LASIK. Combining data from newer technologies may aid in identifying patients at risk of developing postoperative ectasia.

Screening for Ectasia

Topographic Screening

Placido-based topography, using corneal data taken only from the anterior surface, remains the mainstay of preoperative refractive screening. Numerous topographic keratoconus screening tests and indices have been described, documented, and validated to help identify the earliest forms of this disease. Although advanced forms of keratoconus generally do not raise any diagnostic difficulties, no single method of topographic mapping can reliably screen for or exclude the presence of early keratoconus.

Topographic indices permit quantitative analysis of topographic data and are designed to help distinguish the corneas presenting with subclinical keratoconus from normal ones (Fig. 1). Mean simulated keratometry (Sim K) is a topographic index which gives an estimation of the average apical keratometric power. This parameter can indicate the presence of keratoconus when it exceeds certain cutoff values, such as 50 to 55 D. However, the use of a low Sim K cutoff for the detection of early keratoconus can result in over diagnosis of this disease and still miss cases of early keratoconus.

Maximum anterior sagittal curvature ($K_{\text{max}}$) is a commonly used parameter to detect ectatic disease or follow progression, and is regularly used as an indicator for the efficiency of corneal crosslinking. $K_{\text{max}}$, however, has been acknowledged as a poor parameter to follow, as it represents the steepest anterior corneal curvature taken from a small area. $K_{\text{max}}$ fails to reflect the degree of ectasia, ignores the contribution of the posterior cornea, and can be low even in marked ectatic disease.
The inferior-superior (I-S) value is another topographic index, which was designed by Rabinowitz and McDonnell to compare the amount of inferior corneal steepening to that of the superior cornea. Rabinowitz initially proposed a cutoff value of 1.2 D to suggest the possible presence of subclinical keratoconus, but a cutoff value of 1.4 D was later adopted to more specifically distinguish between normal physiological asymmetry and the presence of subclinical keratoconus. Skewed radial axes (SRAX) is an index that corresponds to the angular difference between the steepest semimeridians situated above and below the horizontal meridian. According to Rabinowitz, a SRAX value >21 eliminates the presence of early keratoconus. The KISA\% index was developed by Rabinowitz et al. It incorporates multiple indices, including SRAX, maximum keratometry, keratometric astigmatism, and I-S. According to the authors, a KISA\% between 60 and 100 represents early keratoconus, even in the absence of clinically evident signs. Several other topographic indices such as Differential Sector Index, opposite Sector Index, Surface Regularity Index, and Surface Asymmetry Index have been described, but their discriminative ability is limited, and the utility of these in the screening for patients at risk for postrefractive ectasia is unknown.

Figure 1. Placido-based corneal topographic image display seen on the Tomey Corneal Topographer (Tomey). This older modality images only the anterior corneal surface. The Placido ring image (upper left) shows no significant gross abnormalities, whereas the anterior map (lower left) shows significant inferior corneal steepening. The Klyce/Maeda and the Smolek/Klyce Keratoconus screening tools available on this device can be seen (right). In the setting of preoperative refractive screening, this would be concerning for frank ectatic disease and require further evaluation.
**Tomographic Screening**

Tomographic-based data have added significantly more information to the screening of corneal ectasia. In addition to anterior corneal analysis, tomography also provides information about the posterior cornea and the pachymetric distribution, which can increase our ability to identify early and subtle corneal changes. Several studies have emphasized the clinical relevance of posterior corneal curvature, pachymetric data, and even epithelial thickness in the early diagnosis of ectatic disease.21

The Cone Location and Magnitude Index (CLMI), originally described by Mahmoud and colleagues, compares the steepest area of the anterior corneal surface to the corresponding area 180 degrees away in an attempt to identify eyes with keratoconus. CLMI was later expanded to CLMI-X to include analysis of the posterior surface and corneal thickness, as well as 10 additional parameters.22 CLMI-X showed improved accuracy in keratoconus diagnosis.22 This index represents not only the percent probability of keratoconus (PPK), but also defines the cone with more descriptive parameters, such as its location and its average magnitude of curvature. A PPK cutoff value of 25% was offered to discriminate healthy corneas from keratoconus-suspect corneas. PPK values >45% signify the presence of advanced keratoconus.23 One additional benefit of CLMI is that it is not solely based on a single platform, whereas most other keratoconus topography indices are unique to specific topography devices. The CLMI-X system was constructed with its development data set and then tested with 2 separate validation data sets, potentially increasing its reliability. Although all tomographic indices require a development data set, most are not published with independent validation sets, which may explain, in part, the potential variability in their clinical utility. One limitation of CLMI-X is that it was originally developed to distinguish keratoconus from normal eyes and not to identify forme fruste keratoconic corneas.

Scheimpflug imaging is considered among the most prevalent modalities in the screening, diagnosis, staging, and follow-up of patients with keratoectasia. It is based on a rotating camera and a monochromatic slit-light source, which rotate together. In addition to pachymetry and topographic imaging, Scheimpflug devices provide elevation maps of the anterior and the posterior corneal surfaces.8,24,25 Each device utilizes slightly different technology and contains proprietary software to aid in corneal mapping and screening for ectatic disease. The main Scheimpflug devices utilized are Pentacam (Oculus, Wetzlar, Germany), and the Galilei Dual-Scheimpflug Analyzer (Ziemer Ophthalmic Systems AG, Port, Switzerland). The Pentacam using a single rotating Scheimpflug camera, where the Galilei uses a dual-Scheimpflug camera with Placido disc technology incorporated to improve curvature information on the central cornea. This is in contrast to the Orbscan IIz (Bausch & Lomb,
Role of Posterior Corneal Elevation in Screening for Keratoectasia

Although anterior corneal imaging and various topographic indices have been used in an attempt to screen for subclinical keratoconus, recent studies suggest that the posterior elevation map may also be very useful in the diagnosis of early ectatic disease. Others have proposed that posterior elevation is more sensitive than anterior elevation for identifying ectasia-susceptible corneas. De Sanctis et al found a high area under the curve (AUC) of 0.99 and 0.93 for posterior elevation in the diagnosis of keratoconus and subclinical keratoconus, respectively. Similarly, Ucakhan et al found an AUC 0.94 when using posterior elevation to discriminate keratoconus eyes from normal eyes; however, they found a relatively lower AUC value of 0.78 in their subclinical keratoconus and normal eye comparison. Other studies have found the use of posterior corneal elevation to be less reliable when attempting to distinguish forme fruste keratoconus from normal eyes.

Best Fit Sphere (BFS) Versus Best Fit Toric Asphere (BFTA)

Evaluation of corneal shape is an important component of the preoperative assessment of refractive surgery candidates. The most common method to assess corneal shape with a tomographer is by comparing the measured elevation data to a reference sphere or asphere.

One example of a BFS model is seen in the Belin-Ambrosio Enhanced Ectasia Display, available on the Pentacam (Fig. 2). It utilizes both anterior and posterior elevation data and pachymetric data to screen for ectatic change. It displays the elevation data against a BFS within the central 8.0-mm zone. It also uses an “Enhanced reference surface,” designed to resemble the patient’s more normal peripheral cornea. A small diameter optical zone centered on the thinnest portion of the cornea is excluded from the standard BFS reference shape calculation. The new “enhanced BFS” utilizes all the valid elevation data from within the 8.0 mm central cornea and outside the exclusion zone, which is typically 3.0 mm in keratoconic corneas. The enhanced reference surface works because the exclusion zone centered on the thinnest point incorporates the major ectatic region. Excluding this zone from the standard BFS results in a reference surface that closely mimics the more normal portions of the cornea. A back difference elevation >20 μm is suggestive of ectatic disease and a change between 10 to 20 μm is suspect for early ectasia. Using the Pentacam, Muftuoglu et al found a cutoff level of 13.2 μm to discriminate between forme fruste keratoconus eyes and normal eyes. Use of the elevation function on the Galilei topographer, and a 6 mm zone, a cutoff of 21.5 μm was defined.

Rochester, NY), which is based on a slit-scanning beam projected on the cornea. It is an older modality and derives its posterior corneal map mathematically, possibly leading to an overestimation of posterior elevation.
for the maximum elevation difference to differentiate normal cornea from those with forme fruste keratoconus.\textsuperscript{29,31}

Others have proposed that a reference surface that is both toric and aspheric may better fit the corneal shape and therefore might be more sensitive in highlighting local changes and underlying abnormalities.\textsuperscript{32} Smadja and colleagues looked at 309 eyes of 208 patients and acknowledged that the use of the BFTA surface is better than the BFS for discriminating between normal and keratoconus and between normal and forme fruste keratoconus. When using a cutoff value of 16 µm for the maximum posterior elevation above a BFTA reference surface to differentiate between normal and keratoconic corneas, they found a sensitivity of 99% and a specificity of 99%. In a similar analysis, a cutoff value of 13 µm had a sensitivity of 82% and specificity of 80% when attempting to discriminate between normal and forme fruste keratoconus, which serves to illustrate the increased difficulty in separating these populations. Kovacs et al\textsuperscript{24} reported that the use of a toric and ellipsoid reference surface (best fit toric ellipsoid)
enabled better discrimination between normal and keratoconus with a cutoff value of 9.5 μm with an AUC of 0.99.

**Role of Pachymetric and Epithelial Thickness Evaluation in Screening for Keratoectasia**

Refractive surgeons routinely use corneal thickness or pachymetry in screening, surgical planning, and monitoring. Using corneal cross-section analysis, a full pachymetric map of the cornea can be generated. As keratoconus is characterized by focal thinning, a full pachymetric map may be able to identify keratoconus cases with normal or borderline topographies. Previous studies have shown success in using pachymetry for keratoconus screening. Scanning-slit imaging, Scheimpflug imaging, and OCT can all generate pachymetric maps. Ambrosio et al looked at several tomographic-derived pachymetric parameters and were better able to differentiate normal and keratoconic corneas, as compared with single-point pachymetric measurements. They found the best parameters, named Ambrosio’s relational thickness (ART), were ART-Ave and ART-Max. The best cutoffs were 424 and 339 μm for ART-Ave and ART-Max, with AUC of 0.987 and 0.983, respectively. However, further studies would need to determine and validate if this can be used to diagnose early forms of ectasia or screen for ectasia risk among refractive candidates.

Of note, pachymetric measurements acquired with OCT were more repeatable than those obtained with Scheimpflug imaging in keratoconic eyes in 1 study. Spectral domain OCT has been shown to accurately map the corneal thickness of normal and keratoconic eyes (Fig. 3). Li and colleagues used 5 OCT pachymetric-derived indices (minimum-median, I-S, inferotemporal-superonasal, minimum, and vertical location of the minimum) and determined a diagnostic cutoff for each value (Table 1). They concluded that any one of the OCT pachymetric parameter which was below the cutoff was diagnostic for keratoconus and yielded an AUC of 0.99. In addition, OCT pachymetry-based imaging has been used to evaluate early epithelial changes seen in keratoconus in an attempt to screen for those at risk for postrefractive ectasia. Temstet and colleagues studied 145 eyes and determined that forme fruste keratoconic corneas had less epithelial thickness in the thinnest corneal zone than normal corneas, and greater epithelial thickness in the thinnest corneal zone than keratoconic corneas. The thinnest corneal zone was located inferiorly and corresponded to the zone of minimal epithelial thickness and maximal posterior corneal elevation. They determined a threshold value of 52 μm to distinguish between forme fruste keratoconic corneas and normal corneas. Li and colleagues also used OCT to evaluate epithelial thickness–based variables for keratoconus detection. They found the epithelial changes seen in keratoconic eyes compared with the normal epithelial pattern could be detected with very high accuracy using...
the pattern standard deviation (PSD). In fact, using a PSD cutoff value of 0.057 alone gave 100% specificity and 100% sensitivity. The PSD was calculated from the pattern deviation map, but hopefully will be available as a part of the typical display in the future.

PTA and the Effect on Ectasia Development

Despite rigorous screening regimens, postrefractive ectasia can still be seen in patients with normal preoperative topography and tomography.

Table 1.

<table>
<thead>
<tr>
<th>Units (µm)</th>
<th>Minimum</th>
<th>Minimum-Median</th>
<th>I-S</th>
<th>IT-SN</th>
<th>Vertical Location of Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff value</td>
<td>491.6</td>
<td>−62.6</td>
<td>−31.3</td>
<td>−48.2</td>
<td>−716</td>
</tr>
</tbody>
</table>

Adapted from Li et al. Five OCT pachymetric-derived indices (minimum-median, I-S, inferotemporal-superonasal, minimum, and vertical location of the minimum) and the diagnostic cutoff for each value. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

I-S indicates inferior-superior; IT-SN, inferotemporal-superonasal.
Postoperative ectasia is theorized to result from a reduction in biomechanical integrity below the threshold required to maintain corneal shape and curvature. There is an association between preoperative corneal thickness, ablation depth, and flap thickness in determining the relative amount of biomechanical change that has occurred after a LASIK procedure. The PTA describes this relationship, where PTA is equal to the sum of the flap thickness plus the ablation depth, divided by the central corneal thickness. This metric may more accurately represent the risk of ectasia than each measure individually. In fact, a PTA >40% was the most prevalent factor for post-LASIK ectasia in 1 study with 97% sensitivity and 89% specificity, and in eyes with more signs of topographic abnormalities, even less tissue alteration, or a lower PTA values may induce ectasia.

**Scoring Systems Used for Ectasia Screening**

Another method used in preoperative screening has been the use of risk scales or scoring systems. Among the most commonly used is the Randleman Ectasia Risk Score System. On the basis of a large series of cases reported in the literature, Randleman and colleagues proposed a score that can be used to predict the risk of ectasia (Ectasia Risk Score) to prevent the development of post-LASIK corneal ectasia. This score takes into account the preoperative topographic appearance, the preoperative central corneal thickness, the residual stromal bed, the patient’s age, and the planned correction. This scoring system assigns points, 0 to 4, to each parameter. The sum of the these 5 parameters equals the patient’s relative risk of ectasia as defined by the authors, where 0 to 2 points is low risk, 3 points represents moderate risk, and ≥4 points is high risk. The authors recommend caution with LASIK at 3 points and recommend against LASIK with ≥4 points with a sensitivity 96% and specificity 91%. Qin and colleagues later described an OCT-based scoring system that utilizes the previously mentioned pachymetric variables (minimum, minimum-median, S-I, superonasal-inferotemporal), and the vertical location of the thinnest cornea (Ymin) to create a risk assessment scoring system for screening for ectasia. In this system, 0 to 3 points are assigned to each variable and the keratoconus risk score in each eye is the summation of all single variable scores, where 0 to 3 is low risk, and ≥4 is high risk for developing ectasia. This risk scoring system provided high accuracy in keratoconus detection and may be useful in keratoconus screening with area under the receiver operating characteristic of 0.975.

The use of new technologies in the preoperative evaluation of laser refractive surgery candidates has increased the accuracy and effectiveness of the screening process for ectasia risk detection, however no system is...
perfect. Currently, Placido topography, scanning-slit tomography, Scheimpflug tomography, and OCT are being utilized, alone or in combination, in an attempt to identify patients at risk for this dreaded complication. Despite rigorous screening, keratectasia may still develop in the absence of any topographic or tomographic abnormalities. It has been theorized that this may occur because of biomechanical instability for which no preoperative abnormalities were detectable with the existing technology. Using metrics such as corneal hysteresis, resistance, or elasticity, future technology may be able to identify the inherent biomechanical changes of these corneas preoperatively and further reduce the incidence of ectasia after refractive surgery.

The authors declare that they have no conflicts of interest to disclose.

References


