New perspectives on the detection and progression of keratoconus

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Laser refractive surgery has increased markedly in recent years, making the detection of corneal abnormalities extremely relevant. For this reason, an accurate diagnosis of clinical or subclinical keratoconus is critical. Corneal topography is the primary diagnostic tool for keratoconus detection, and pachymetry data and corneal aberrations are also commonly used. Recently, tomographic measurements using optical coherence tomography and corneal biomechanical indices have been used. In incipient and subclinical keratoconus, the use of a single parameter as a diagnostic factor is not sufficiently accurate. In these cases, the use of algorithms and predictive models is necessary. In addition, determining whether the disease will progress is crucial to selecting the most appropriate treatment. Some factors, such as age, keratometric indices, corneal elevation data, and corneal thickness, seem to be useful in predicting keratoconus progression.


Keratoconus is an ectatic corneal disorder characterized by progressive corneal thinning that generates a corneal protrusion, irregular astigmatism, and decreased vision.1,2 The corneal protrusion, which has a conical shape, is generated by stromal tissue degeneration, leading to a mechanical weakening of the corneal structure.2,3 Keratoconus typically affects both eyes. Although the etiology is not fully understood, keratoconus has traditionally been considered a noninflammatory disease.1 However, recent evidence suggests that proinflammatory factors are involved in keratoconus pathogenesis, presenting some controversy about this issue.4–6

Keratoconus usually begins to develop at puberty and progresses until the third or fourth decade.7 The incidence varies depending on factors such as the ethnic group of the sample evaluated or the criteria used to establish the diagnosis. An incidence between 50 cases and 230 cases per 100 000 has been estimated in the general population,1 higher in the Asian population than the white population.8 The risk factors for keratoconus development include constant eye rubbing, the presence of some systemic diseases, floppy-eyelid syndrome, allergies, as well as a family history that predisposes to the development of the pathology.1,2

At present, the main tool used to diagnose keratoconus is corneal topography, which enables the clinician to detect the conical protrusion and the inferior–superior (I–S) asymmetry, which are typical signs of keratoconus (Figure 1).2,9,10 This tool is usually combined with biomicroscopic examination; in moderate and advanced stages, this shows the corneal protuberance, stromal thinning, the Fleischer ring, and even the Vogt striae.4 Therefore, the detection of advanced keratoconus is not difficult. However, in incipient or preclinical stage cases, the diagnosis becomes complicated. The term subclinical keratoconus refers to an incipient stage of keratoconus that can be undetected in routine clinical practice (Figure 2). The standard diagnostic criteria are shown in Figure 3.2 Subclinical keratoconus is usually asymptomatic and is considered the most significant risk factor for the development of ectasia after laser refractive surgery.11

Because laser refractive surgery has increased markedly in recent years, the diagnosis of subclinical keratoconus has become extremely relevant because an accurate diagnosis is mandatory to avoid ectasia after refractive surgery.

This review attempts to define and compile the diagnostic systems and indicators for keratoconus and subclinical keratoconus, including the latest commercially released corneal topography systems, the analysis of anatomic structures of the eye with the latest optical coherence tomography (OCT) technology, the analysis of corneal biomechanics, and the use of new predictive models.
DETECTION OF KERATOCONUS

Topographic Indices
The importance of corneal topography in the detection of keratoconus is well-known. Initially, keratometric data were used to differentiate healthy eyes from keratoconic eyes; the curvature of the cornea was significantly higher in the latter. Recent studies analyzing the diagnostic ability of mean keratometry (K) in keratoconus have shown an acceptable accuracy (sensitivities >80% and specificities >70% for cutoff points between 45.2 diopters [D] and 45.7 D). However, this parameter is poor for the detection of subclinical keratoconus, with no ability to differentiate significantly between subclinical keratoconic eyes and healthy eyes. 

Astigmatism, both anterior (3.93 D ± 2.74 [SD]) and posterior values (0.93 ± 0.64 D), has been shown to be significantly higher in keratoconus. With a topographic astigmatism of 2.5 D as a cutoff point, the ability to detect keratoconus is acceptable (sensitivity and specificity >75%) but the specificity decreases considerably in the case of subclinical keratoconus (<65%), indicating that it is not a good diagnostic parameter.

In recent years, the most studied topographic parameter as a predictor of keratoconus has been corneal elevation, especially posterior elevation, which has good diagnostic ability; sensitivities and specificities >90% have been obtained in most samples. In the detection of subclinical keratoconus, there is significant variability in the elevation data between studies. De Sanctis et al. obtained sensitivity of 73.3% and specificity of 86.5% for posterior elevation, but others obtained a more limited diagnostic accuracy.

New vector indices such as ocular residual astigmatism (ORA) and topography disparity have also been used to detect keratoconus and subclinical keratoconus; prediction accuracy for keratoconus was better with ORA (cutoff 1.255 D, sensitivity 82%, specificity 92%) and for subclinical keratoconus, with topography disparity (cutoff 0.710 D, sensitivity 73.7%, specificity 68.0%).

Indices based on digital analysis of the Placido disk image were defined by Ramos-López et al., for example, PI1 (maximum distance between centers of mires), PI2 (drift of the centers of consecutive mires), and SL (alignment of the centers of mires). The ability of the indices to detect keratoconus was good for an area under the receiver operating characteristic curve of more than 0.90. The indices also have potential for detecting subclinical keratoconus.

Corneal Pachymetry
Corneal pachymetry is an important tool in the diagnosis and progression of corneal ectasias, such as keratoconus and subclinical keratoconus. The stromal thinning produced in keratoconus can be quantified by current imaging
devices based on rotating Scheimpflug imaging technology, such as the rotating Scheimpflug camera (Pentacam, Optikgeräte GmbH) and the Scheimpflug camera combined with Placido corneal topography (Sirius, Costruzione Strumenti Oftalmici). These systems measure corneal thickness data at various points of the cornea.2,23 Figure 4 shows the corneal thickness map of keratoconus (left) and subclinical keratoconus (right) obtained with the rotating Scheimpflug camera. In the keratoconus thickness map, the corneal thinning is evident in the central zone of the cone. The corneal thickness increases as a more peripheral area of the cornea is analyzed.

Corneal thickness data are especially important for subclinical keratoconus, which is not easy to detect in topographic maps or on biomicroscopic examination. The commonly used diagnostic criteria for this condition state that the central corneal thickness (CCT) should be less than 500 μm, with the presence of topographic asymmetry.2,23 Figure 4 (right) shows the thickness map of subclinical keratoconus, in which the corneal thinning is less pronounced than in clinical keratoconus. Additional diagnostic pachymetric criteria, such as minimum corneal thickness less than 461 μm or a difference between central and minimum thickness of more than 27 μm, have been related to a high probability (97.5%) of corneal ectasia.24

According to most studies, pachymetric parameters can accurately detect clinical and subclinical keratoconus. The main problem is to establish adequate cutoff points for the parameters defined in the literature, as they can vary between investigations (Table 1) depending on the characteristics of the analyzed sample and the measurement system used. Table 1 shows that pachymetric data, especially minimum corneal thickness, has an acceptable ability to detect keratoconus, making it a useful tool for this purpose. However, the variability in cutoff points between studies prevents generalization of the diagnostic criteria for any sample evaluated or any device used. Therefore, pachymetric data are helpful in clinical practice but should not be the only parameter used to detect keratoconus. For subclinical keratoconus, sensitivities and specificities of less than 70% have been reported in all studies, indicating that the diagnostic accuracy of these parameters is limited.

Moreover, current systems based on the rotating Scheimpflug camera provide a detailed corneal thickness distribution map with accuracy and repeatability within less than 3.0 mm. From these data, the corneal thickness spatial profile and percentage thickness increase graphs are calculated. These maps enable observation of the mean behavior of corneal thickness from the point of minimum corneal thickness to the corneal periphery. In Figure 5, the corneal thickness spatial profile and percentage thickness increase in a keratoconic eye are shown. The corneal thickness varies abruptly along the surface (great slope change of the red line). However, in subclinical keratoconus, although there might also be thinning in the cone zone (Figure 6), the transition between the thinner point and the rest of the cornea is less rigid than in keratoconus.

An increasing number of studies measure corneal thickness with OCT systems instead of Scheimpflug image–based devices, facilitating measurements at more points of the cornea and enabling differentiation of corneal layers, providing a measure of the thickness of each one.31-34

Aberrometric Analysis

Higher-order aberrations (HOAs) of the anterior and posterior corneal surfaces are altered in keratoconus and are therefore good indicators for diagnosing keratoconus as well as for classifying the stage of the disease.

<table>
<thead>
<tr>
<th>Main signs (must be met)</th>
<th>Keratomatric power &gt;47.0 D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-appearing cornea on slitlamp biomicroscopy</td>
<td>Oblique cylinder &gt;1.50 D</td>
</tr>
<tr>
<td>Corneal topography with abnormal localized steepening or an asymmetric bow-tie pattern</td>
<td>Central corneal thickness &lt; 500 mm</td>
</tr>
<tr>
<td>Complementary signs (at least 1 must be met)</td>
<td>Clinical keratoconus in fellow eye</td>
</tr>
</tbody>
</table>

Figure 3. Standard diagnostic criteria for subclinical keratoconus.

Figure 4. Corneal thickness map of a keratoconic (left) and subclinical keratoconic eye (right) (N = nasal; T = temporal).
The Alió-Shabayek grading system considers the root-mean-square (RMS) value for coma-like aberrations as a criterion for classifying the severity of keratoconus. Coma-like RMS values between 1.50 μm and 2.50 μm indicate keratoconus grade I; values between 2.50 μm and 3.50 μm, keratoconus grade II; values between 3.50 μm and 4.50 μm, keratoconus grade III; and values of more than 4.50 μm, keratoconus grade IV.

Gordon-Shaag et al. reported that corneal HOAs were about 38 times greater in keratoconic eyes than in healthy eyes. The most altered aberration in keratoconus was the vertical coma, which was about 78 times greater than in healthy control eyes. Other authors obtained similar results. Reddy et al. reported differences in total RMS between the keratoconus group and the healthy group, with mean values of 7.19 μm and 1.25 μm, respectively. Maeda et al. found a mean value of HOA RMS of the anterior corneal surface of 4.50 μm in keratoconic eyes and 0.52 μm in healthy eyes. For posterior HOA RMS of the posterior surface, they also found differences between keratoconic eyes and healthy eyes (1.19 μm and 0.17 μm, respectively).

Saad and Gatinel reported that anterior corneal coma RMS values of more than 0.26 μm detected keratoconus with sensitivity and specificity of 98% and 99%, respectively. To improve this precision, discriminatory functions based on coefficients and RMS of the anterior corneal wavefront (FC), coefficients and RMS of the ocular wavefront (FT), and the combination of both (FCT) have been designed, obtaining an AUC very close to the unit, with sensitivity and specificity greater than 95%.

In the case of subclinical keratoconus, coma has also been seen as the predominant aberration. However, the diagnostic capacity of coma by itself is limited. Saad and Gatinel reported that the diagnostic accuracy of coma decreased considerably (cutoff 0.157 μm, sensitivity 71%, specificity 80%), whereas Bühren et al. reported a similar accuracy in detecting subclinical keratoconus with coma RMS (cutoff 0.206 μm, sensitivity 68.8%, specificity 95.5%). An example of corneal aberrations of subclinical keratoconus is seen in Figure 8, which shows that higher-order corneal aberrations are slightly above normal. For subclinical keratoconus, the discriminatory functions FC, FT, and FCT are more important because they enable us to reach sensitivities and specificities above 80%. If the FCT is greater than 0.613 μm, subclinical keratoconus is detected with a sensitivity of 91% and specificity of 94%.

The use of other discriminatory functions, such as the function with input from anterior and posterior Zernike coefficients (DAP) or including pachymetry data (DAPT), enables a diagnostic accuracy of more than

### Table 1. Diagnostic ability of minimum corneal thickness and CCT to detect keratoconus and subclinical keratoconus.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ability to Detect Keratoconus</th>
<th>Ability to Detect Subclinical Keratoconus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff (μm)</td>
<td>AUC</td>
</tr>
<tr>
<td>Montalbán</td>
<td>525.9</td>
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</tr>
<tr>
<td>Reddy</td>
<td>500</td>
<td>0.84</td>
</tr>
<tr>
<td>CCT</td>
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<tr>
<td>Toprak</td>
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</tr>
<tr>
<td>CCT</td>
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<td>0.946</td>
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<tr>
<td>Muftuoglu</td>
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<td>0.897</td>
</tr>
<tr>
<td>CCT</td>
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<td>0.811</td>
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<tr>
<td>Uçakhan</td>
<td>493.5</td>
<td>0.896</td>
</tr>
<tr>
<td>CCT</td>
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<td>0.832</td>
</tr>
<tr>
<td>Muftuoglu</td>
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<td>0.873</td>
</tr>
<tr>
<td>CCT</td>
<td>511</td>
<td>0.832</td>
</tr>
<tr>
<td>Kovács</td>
<td>—</td>
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</tr>
<tr>
<td>Ahmadi Hosseini</td>
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<td>0.85</td>
</tr>
<tr>
<td>CCT</td>
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</tr>
<tr>
<td>Dienes</td>
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<tr>
<td>CCT</td>
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<tr>
<td>Shetty</td>
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</tr>
<tr>
<td>CCT</td>
<td>516</td>
<td>0.93</td>
</tr>
<tr>
<td>Labiris</td>
<td>522</td>
<td>0.94</td>
</tr>
<tr>
<td>CCT</td>
<td>529</td>
<td>0.90</td>
</tr>
</tbody>
</table>

AUC = area under the receiver operating characteristic curve; CCT = central corneal thickness; MCT = minimum corneal thickness; Sens = sensitivity; Spec = specificity

*First author

(Figure 7). The Alió-Shabayek grading system considers the root-mean-square (RMS) value for coma-like aberrations as a criterion for classifying the severity of keratoconus. Coma-like RMS values between 1.50 μm and 2.50 μm indicate keratoconus grade I; values between 2.50 μm and 3.50 μm, keratoconus grade II; values between 3.50 μm and 4.50 μm, keratoconus grade III; and values of more than 4.50 μm, keratoconus grade IV.

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90%. This precision can be increased by certain models, such as the one developed by Smadja et al., which integrates curvature, elevation, and pachymetric and aberrometric data, leading to higher levels of precision (sensitivity 93.6%, specificity 97.2%).

**Corneal Biomechanics**

Topographic and aberrometric alterations in keratoconic eyes appear as a consequence of the structural changes occurring in the keratoconic cornea. Therefore, it is assumed that parameters commonly used to characterize corneal biomechanics in clinical practice, such as corneal hysteresis (CH) and the corneal resistance factor (CRF), are altered in keratoconus. The main problem has been the lack of reliable devices that have the ability to adequately characterize corneal biomechanical properties. However, several clinical devices that offer this possibility are currently available, although their validity for keratoconus detection is questionable.

**Dynamic Bidirectional Applanation Device** The Ocular Response Analyzer (Reichert Technologies) analyzes the corneal reaction during a bidirectional applanation process. It delivers an air pulse to the eye that causes the cornea to move inward, registering the moment of maximum applanation (P1). After milliseconds, the pressure decreases and the cornea passes through a second applanated state (P2) while recovering its normal curvature. The initial version provided only 2 values: CH and CRF. Corneal hysteresis was defined as the difference between the 2 pressures (P1 – P2), whereas the CRF was calculated using a proprietary algorithm and theoretically provided information focused on the elastic properties of the cornea. These measures have been shown to be repeatable in healthy and keratoconic eyes.

Many studies have also shown that both CH and the CRF are decreased in keratoconic eyes. Shah et al. reported a mean CH of 10.7 mm Hg in healthy eyes and 9.6 mm Hg in keratoconic eyes. Ortiz et al. reported a more significant difference in CH between healthy eyes and keratoconic eyes (10.8 mm Hg versus 7.5 mm Hg). This study also showed that larger differences between healthy eyes and keratoconic eyes were present in the CRF than in CH (11.0 mm Hg versus 6.2 mm Hg). Galletti et al. proposed a correction factor for the biomechanical waveform analyzer parameters to consider CCT, obtaining an acceptable keratoconus diagnostic capacity for the CRF (sensitivity 83% to 94%, specificity 69% to 83%). In summary, CH and the CRF can be used for an accurate detection of moderate and advanced keratoconus, but their diagnostic ability is limited for incipient keratoconus.

Recently, other biomechanical variables have been incorporated that are derived from the analysis of the response curve, such as the hysteresis loop area, which is the area enclosed by pressure versus applanation function or concavity\textsubscript{min} that is the minimum applanation intensity between A1 and A2; concavity\textsubscript{min} has shown a diagnostic accuracy of 93.2% for a cutoff point of 50.37 (sensitivity 94.9%, specificity 91.7%). In the same study, the low predictive capacity of CH was confirmed, providing a sensitivity of...
only 52.0%. Another study suggests that the p2area and p1area are better parameters to diagnose keratoconus than the standard biomechanical waveform analyzer parameters, providing sensitivities of 80.5% and 82.9%, respectively, and specificities of 96.4% and 89.3%, respectively. For incipient keratoconus, the new parameters incorporated by the biomechanical waveform analyzer (p1area, p2area) have shown greater diagnostic precision than CH and the CRF, with ROC curves with AUCs around 0.900 and increasing to 0.987 when all the parameters are combined in a predictive model. Other new indices such as the keratoconus match index or keratoconus match probability also seem to be good tools for detecting advanced stages of keratoconus, with sensitivities and specificities above 90%, but research on incipient keratoconus is lacking.

Because the diagnosis of subclinical keratoconus is complex and depends on many factors, 1 biomechanical parameter by itself is not a good predictor of the condition, but reliable predictive models can be obtained in combination with other indicators, as shown in the study by Zhang et al. The authors combined several biomechanical parameters obtained with the second-generation dynamic bidirectional applanation device system and obtained a model providing an AUC of 0.904 for the detection of subclinical keratoconus.

Dynamic Scheimpflug Analyzer The Corvis ST (Oculus Optikgeräte GmbH) is a noncontact tonometer that emits an air pulse that applanates and indents the cornea. It differs from the biomechanical waveform analyzer system in the use of an ultra-high-speed Scheimpflug camera (4330 frames/second) to record in vivo cross-sectional images of the cornea during and after application of the air pulse. The device facilitates obtaining a variety of parameters: time, length, and speed of applanation 1 states (A1T, A1L, and A1V, respectively) and applanation 2 states (A2T, A2L, and A2V, respectively); deformation amplitude (DA), which is the corneal displacement at highest concavity; and the radius of curvature at highest concavity and peak distance, which is the distance between the corneal peaks at maximal concavity (Figure 9). All these parameters have been shown to be repeatable in healthy and keratoconic eyes. In addition, the diagnostic ability of these parameters to detect keratoconus has been analyzed, DA being the parameter with the best diagnostic accuracy, with an AUC of 0.77 (cutoff 1.18 mm, sensitivity 82.4%, specificity 61.1%). Although DA is the best parameter for this purpose, it has poor specificity, which suggests that the central sensitivity threshold would not be useful for detecting incipient keratoconus. Tian et al. reported higher sensitivity and specificity of DA for the detection of keratoconus (81.7% and 83.3%, respectively) for the same cutoff point, whereas Wie et al. obtained even better results for DA, A1V, and A2V, with ROC curves with AUCs of more than 0.9. In addition, it has been shown that the combination of several of these parameters in a predictive model using logistic regression increases
the keratoconus diagnostic accuracy. One recent example of a model that combines these biomechanical parameters is the Corvis biomechanical index, which offers an accuracy of 98.3%. It is a normalized index from 0 (normal) to 1 (abnormal) combining the following parameters: deformation amplitude ratio at 1.0 and 2.0 mm, applanation 1 velocity, standard deviation of deformation amplitude at highest concavity, Ambrósio relational thickness to the horizontal profile, and a novel stiffness parameter. In the case of subclinical keratoconus, significant differences between healthy eyes and keratoconic eyes have been found in many parameters and a predictive model based on DA, A1T, and CCT was found to be acceptable, achieving a precision of 0.894 (sensitivity 85.7%, specificity 82.0%).

Due to the relatively recent appearance of devices to measure corneal biomechanical properties in clinical practice, a few studies have compared healthy eyes and keratoconic cases. Substantially, the deviations in corneal biomechanical properties in keratoconic cases were found to be significantly different from healthy eyes. These differences were observed in various parameters such as deformation amplitude ratio, applanation velocity, and corneal thickness.

Figure 7. Corneal aberrometric maps of a keratoconic eye provided by the Scheimpflug camera combined with Placido corneal topography system for a 6.0 mm pupil. The first map (upper left) includes both low and high corneal aberrations. The second map (upper center) shows the HOAs of the cornea, whereas the coefficients of corneal aberrations are shown in the upper right of the Figure. The bottom maps represent the astigmatism, coma, spherical aberration, and residual aberrations, respectively.

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eyes and there is controversy between some studies due to the sample selection of the sample. However, it seems that some parameters evaluating corneal biomechanics can be useful for diagnosing keratoconus, especially if they are combined in predictive models. It is a relatively recent discipline, and more investigation of this issue is needed.

**Tomographic Measures Using Optical Coherence Tomography**

Pachymetric measurements obtained with OCT are comparable to those obtained with Scheimpflug image–based systems. Therefore, minimum corneal thickness and CCT values provided by both devices are equally useful for detecting subclinical and clinical keratoconus. Optical coherence tomography can obtain other pachymetric data, such as the difference between the thickness of the upper and lower area of the cornea and between the superonasal and inferotemporal cornea, as well as the vertical location of the thinnest point of the cornea. The ability of these parameters to detect keratoconus is acceptable but not excellent. However, regression models that combine all these parameters provide high keratoconus diagnostic precision (95% sensitivity, specificity 90.9%).

The pachymetric pattern standard deviation (PSD) has shown high diagnostic ability in the detection of clinical and subclinical keratoconus. In the study by Li et al., the epithelial PSD was the best predictive parameter in the detection of subclinical keratoconus, with an AUC of 0.98 and sensitivity and specificity of 96% and 100%, respectively. For the total pachymetric PSD, the AUC was slightly lower (0.941); it was the lowest value obtained for the stromal PSD (0.924). Other studies have confirmed higher precision of epithelial thickness for keratoconus detection than of total pachymetry because differences between keratoconic eyes and healthy eyes are more relevant. Some studies have evaluated changes in epithelial thickness in different areas of the cornea, concluding that epithelial thinning is more significant in the inferotemporal zone of the keratoconic eye. Measurement of Bowman membrane thickness in the lower corneal hemidivision has also been shown to be a good predictor of keratoconus. Algorithms derived from the thickness of this membrane have been designed for different sections of the cornea, such as the Bowman ectasia index, which offers 100% accuracy in the detection of keratoconus. Reinstein et al. performed 3-dimensional thickness mapping and characterization of the epithelial, stromal, and total corneal thickness profiles in keratoconus and found that this type of analysis might help in the early diagnosis of keratoconus. They found that the average epithelial thickness profile in keratoconus showed an epithelial doughnut pattern characterized by localized central thinning surrounded by an annulus of thick epithelium. Similarly, the position of the thinnest point was displaced on average by 0.48 ± 0.66 mm temporally and 0.32 ± 0.67 mm inferiorly in the epithelium and by 0.31 ± 0.45 mm and 0.54 ± 0.37 mm inferiorly in the stroma.

The birefringence of corneal stromal fibers measured using polarization-sensitive OCT has been compared in keratoconic eyes and healthy eyes. Phase retardation of the posterior surface of the cornea increased in the keratoconic eyes because of changes in the lamellar structure of collagen fibers. Therefore, phase retardation is accurate (accuracy close to 100%) in discriminating between keratoconus-suspect eyes and control eyes and might be useful for detecting very early or even subclinical keratoconus.

Optical coherence tomography has been used to analyze other ocular structures for the detection of keratoconus. The measurements of thickness and area of the iris showed acceptable diagnostic ability (sensitivity 80%, specificity 85%) but lower than those obtained for corneal parameters.

In addition to use as a detection system, OCT provides an accurate assessment of structural changes occurring in keratoconic eyes (Figure 10). These changes enable the clinician to grade the keratoconus based on the visualization of various signs: grade I, slight thinning of the epithelial
and stromal levels; grade II, hyperreflective anomalies at the Bowman layer level; grade III, posterior displacement of the hyperreflective structures at the Bowman layer level and increased epithelial thickening and stromal thinning; grade IV, pan-stromal scar; and grade V, hydrops.74

**Algorithms and Predictive Models**

Along with the parameters that have been mentioned, there are specific indices for the detection of corneal ectasia. The first and 1 of the most common is the I–S index, which represents the amount of steepening of the inferior cornea compared with that of the superior cornea. Values between 1.4 D and 1.9 D are consistent with subclinical keratoconus, whereas larger values are consistent with clinical keratoconus.75 The main disadvantage of this index is that it is dependent on the position of the cone. Although the cone is located in the lower area of the cornea in most keratoconus cases, central keratoconus is possible and such cases could be undetected by this index. Other indices calculated from keratometric data useful in differentiating between keratoconic eyes and healthy eyes are the SAI, surface asymmetry index; SRI, surface regularity index; CIM, corneal irregularity measurement; MTK, mean toric keratometry; SRAX, skew of steepest radial axis; CSI, center surrounding index; DSI, different sector index; and OSI, opposite sector index.10

A later development, the keratoconus prediction index, is derived from a series of video keratographic indices (previously described). This index enables the clinician to classify subjects according to the shape of the anterior cornea surface, with accuracy close to 90%.2,76 Other predictive indices derived from topography with similar diagnostic ability are the keratoconus severity index and the keratoconus index.10

The keratoconus percentage index (KISA%) value is calculated from a combination of 4 videokeratographic parameters: the central keratometric power, the I–S index, corneal simulated astigmatism, and the SRAX index. The SRAX index reaches a value of 100 in keratoconus and has an accuracy of 99.6% in detecting keratoconus.76 In addition, we suggest the KISA% index in subclinical keratoconus ranges from 60% to 100%. Recently, this index has been correlated with tomographic parameters, including minimum corneal thickness, corneal elevation data, and other predictive indices based on pachymetry, such as the Belin-Ambrósio display or Ambrósio relational thickness, obtaining very high determination coefficients and confirming the effectiveness of the KISA% in detecting clinical and subclinical keratoconus.77 Another index obtained from topographic analysis is the cone location and magnitude index, which has a keratoconus detection accuracy of 92%.78 Recently, the calculation algorithm of this index has been modified to improve its detection accuracy, reaching almost 100% (sensitivity 99.4%, specificity 99.6%).79

Tummanapalli et al.80 found that the anterior–posterior apex ratio on the tangential map was associated with the highest diagnostic precision (AUC 0.992, cutoff −6.97, sensitivity 98.6%, specificity 98.7%) followed by the posterior irregularity index in the 5.0 mm zone (AUC 0.938, cutoff 0.4, sensitivity 98.6%, specificity 84.2%) of all parameters provided by the scanning-slit topography system (Orbscan IIz, Bausch & Lomb GmbH) for differentiating between subclinical keratoconic eyes and healthy eyes.

In addition to indices and detection models generated from tomographic data, there are indices based on pachymetric data, such as the Ambrósio relational thickness (mentioned above). This index is calculated by the following formulas: average Ambrósio relational thickness = minimum corneal thickness/average pachymetric progression index; Ambrósio relational thickness = minimum corneal thickness/minimum pachymetric progression index; and Ambrósio relational thickness maximum = minimum corneal thickness/maximum pachymetric progression index.81 Its application for the detection of keratoconus has been widely studied. Table 2 shows the ability of maximum and average Ambrósio relational thickness to detect subclinical keratoconus and keratoconus in various studies.14,25,26,81–85

The table shows that maximum Ambrósio relational thickness offers greater diagnostic ability than average Ambrósio relational thickness.14,25,26,81–85 Although there is some variability between studies, a value between 300 μm and 400 μm can generally be considered the threshold for determining the presence of keratoconus with high precision. In contrast, in subclinical keratoconus, the threshold is around 400 μm but with significantly lower associated diagnostic accuracy.

Other indices combining topographic and pachymetric information, such as the multimetric D index, which is derived from keratometric, pachymetric, and back elevation data, have been described. Muftuoglu et al.25 found that the best cutoff for the D index was 2.1, with 100% sensitivity and 100% specificity. This result suggests that the new D index can be a sole parameter in diagnosing keratoconus. In differentiating eyes with subclinical keratoconus from healthy eyes, the best cutoff was 1.3, but with a sensitivity of 60% and specificity of 90%, suggesting good specificity but limited sensitivity.25

The maximum K7/thinnest pachymetry algorithm developed by Toprak et al.13 was also able to detect keratoconus.
with high accuracy (sensitivity 99.5%, specificity 95.7%). This algorithm was also good in identifying incipient keratoconus (grades I and II), with sensitivity values higher than 99% and specificity values of more than 94%.13

Recently, a new index for use with the Sirius system was developed using a support vector machine (Figure 11). The index is calculated using the symmetry index of front and back corneal curvatures, the best-fit radius of the front corneal surface, the Baiocchi-Calossi-Versaci front and back indices,86 the RMS of corneal HOAs, and the minimum corneal thickness. It is able to classify subclinical and clinical keratoconus with 92% accuracy.

The scanning-slit topography system has specialized software, the SCORE analyzer (Bausch & Lomb GmbH), which integrates all the data obtained with the topography system to predict the presence of subclinical or clinical keratoconus. If the value of the index provided by this software is greater than 0, the cornea evaluated can be considered abnormal. The sensitivity and specificity of this index are 92% and 96%, respectively.87

Another predictive model for keratoconus, based on curvature, elevation, pachymetric, and wavefront data, was created by Smadja et al.41 This model detects keratoconus with 100% sensitivity and 99.5% specificity and subclinical keratoconus with 93.6% sensitivity and 97.2% specificity.

Algorithms of keratoconus detection combining various parameters have been developed for the rotating Scheimpflug camera.88,89 One is the keratoconus assistant, which uses 22 parameters for classification using a support vector machine algorithm developed in Waikato Environment for Knowledge Analysis, a machine-learning computer software.4 This system provides sensitivity and specificity of 99.1% and 98.5%, respectively, for keratoconus detection and 79.1% and 97.9%, respectively, for forme fruste keratoconus detection. Belin et al.90 developed a keratoconus grading system (ABCD) incorporating posterior curvature, thinnest pachymetric values, and distance visual acuity in addition to the standard anterior curvature and consisting of stages 0 to IV (5 stages).

As well as the creation of models that integrate all the information provided by a specific device, general models have been developed. One example is the pachymetry/asymmetry/asymmetry/I–S index that combines data obtained with videokeratography and OCT. This model is excellent in detecting keratoconus and very useful in detecting subclinical keratoconus (accuracy between 87.5% and 100%).91 Another index that combines information from various devices is DAPT (anterior and posterior Zernike coefficients and pachymetry data), which combines aberrometric and pachymetric data to detect subclinical keratoconus with an accuracy between 82.3% and 90.7%.38

Analysis of the Corneal Microstructure

The corneal epithelium, subepithelial nerve plexus, stroma, stromal nerves, and endothelium can be observed by confocal microscopy. This system has shown that both corneal nerve fiber density and corneal nerve fiber length are reduced in keratoconus.92 The keratocyte density is also lower in keratoconic eyes.93 At the same time, corneal stromal nerve thickness has been shown to be greater in keratoconic eyes (mean 7.2 μm) than in healthy eyes (mean 5.7 μm).94 Confocal microscopy is therefore useful to observe these changes.

**Table 2. Diagnostic ability of maximum Ambrósio relational thickness and average Ambrósio relational thickness to detect keratoconus and subclinical keratoconus.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Ability to Detect Keratoconus</th>
<th>Ability to Detect Subclinical Keratoconus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff (μm)</td>
<td>AUC</td>
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<tr>
<td>Muftuoglu14</td>
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</tr>
<tr>
<td></td>
<td>avART</td>
<td>407</td>
</tr>
<tr>
<td>Muftuoglu25</td>
<td>maxART</td>
<td>313</td>
</tr>
<tr>
<td></td>
<td>avART</td>
<td>392</td>
</tr>
<tr>
<td>Kovács86</td>
<td>maxART</td>
<td>—</td>
</tr>
<tr>
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<td>339</td>
</tr>
<tr>
<td></td>
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</tr>
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<td>Ruíserior Vázquez85</td>
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</tr>
<tr>
<td>Orucoglu85</td>
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<td>311</td>
</tr>
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</table>

AUC = area under the curve; AvART = average Ambrósio relational thickness; maxART = maximum Ambrósio relational thickness; Sens = sensitivity; Spec = specificity
*First author
for detecting structural changes occurring in incipient keratoconus, although there are no studies analyzing the diagnostic ability of these structural measures.

**PROGRESSION OF KERATOCONUS**

Determining whether keratoconus will progress is a critical issue because it should influence the mode of action and treatment in each case. However, there is no consistent or clear definition of ectasia progression because all the factors affecting keratoconus progression have not been identified. Despite this, some factors seem to be correlated with keratoconus progression. Age is a primary risk factor; young age at diagnosis and development are risk factors for progression.95,96 Choi and Kim95 classified the degree of progression according to the annual keratometric development, considering a keratometric increase of 1.50 D or greater per year as progressive and an increase of less than 1.50 D per year as nonprogressive. They reported that the mean age of patients showing progressive keratoconus (21.5 years) was younger than the mean age of patients with nonprogressive keratoconus (25.8 years). Ahn et al.96 classified keratoconic eyes as progressive or nonprogressive based on the topographic progression. They found a lower mean age in the groups of eyes with progressive keratoconus (22.2 years) than in the groups with nonprogressive keratoconus (24.7 years). In pediatric cases, the keratoconus progression seems to be faster than in adult cases. A previous study97 suggests that the percentage of progressive keratoconus cases in children is 88%. In pediatric keratoconus cases, the risk for progression was greater if the minimum corneal thickness was less than 450 μm, the mean K reading was greater than 50 D, or the posterior elevation was greater than 50 μm.98

The use of topographic systems is common in the study of keratoconus progression.95,96,99–103 One study100 suggests an annual increase in the maximum K greater than 1.0 D or 1.5 D is indicative of keratoconus progression. Specific topographic indices, such as the index of surface variance or the index of height asymmetry, have been found to predict keratoconus progression with acceptable sensitivity and specificity.100 The I–S index is valid for assessing whether a keratoconus case is progressing, with an associated odds ratio of 5.465. Therefore, an elevated I–S index is related to an increased risk for progressive keratoconus.102

From corneal elevation data, the anterior best-fit sphere appears to be a good index to predict the progression of keratoconus; elevation changes greater than 0.04 mm predict keratoconus progression with an accuracy of 81.4%.95 Other corneal elevation parameters such as the Bellin-Ambrósio display or the enhanced reference surface can also help in assessing keratoconus progression.100

Concerning pachymetry, it has been shown that corneal thickness values lower than 350 μm are associated with an increased risk for keratoconus progression (3.32 more risk).95 Moreover, an annual CCT decrease of 2% represents an advance of the pathology.100 Other parameters such as the regularity index, spherical equivalent, and irregular astigmatism also appear to be useful in predicting keratoconus progression.95,96,100,104

Piñero et al.99 evaluated refractive, keratometric, pachymetric, and aberrometric changes in untreated keratoconus during a 3-year follow-up. They suggest that the change in corneal astigmatism calculated by vector analysis might be one of the most important factors in predicting keratoconus progression. The change in corneal astigmatism was found to correlate with the refractive value of the sphere and with...
lymphocyte ratio has been analyzed to differentiate between healthy eyes and keratoconic eyes because it allows an accurate pachymetric characterization. Recently introduced systems, such as the Ocular Response Analyzer and Corvis systems, analyze in clinical practice the biomechanical properties of the cornea, providing good results in terms of keratoconus detection.

The detection of moderate and advanced keratoconus using all technologies mentioned above is not a difficult task. However, when the pathology is in an incipient or subclinical stage, the use of a single parameter as a diagnostic factor is not accurate enough. In such cases, the use of algorithms and predictive models that combine data from different systems and analyses is mandatory to obtain an acceptable diagnostic accuracy.

As the use of larger samples of keratoconus cases that have not had any intervention. This is becoming state of the art. Eye Vis 2016; 3:5. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3029330/pdf/pone.0016437.pdf. Accessed July 9, 2017


CONCLUSION

In conclusion, the primary diagnostic tool for keratoconus detection is corneal topography because the indices and maps have been found to be useful for diagnosis. However, corneal topography is not an infallible method and therefore complementary techniques should be used; these include corneal pachymetry to characterize the corneal thinning and aberrometry to characterize degradation of the corneal optics. Systems based on the rotating Scheimpflug camera, such as Pentacam, Galilei, or Sirius systems, offer the possibility of obtaining topographic, pachymetric, and aberrometric information simultaneously as their use is very adequate for the detection of keratoconus. Tomographic measurements using OCT technology are also currently being used to differentiate between healthy eyes and keratoconic eyes because it allows an accurate pachymetric characterization. Recently introduced systems, such as the Ocular Response Analyzer and Corvis systems, analyze in clinical practice the biomechanical properties of the cornea, providing good results in terms of keratoconus detection.

The detection of moderate and advanced keratoconus using all technologies mentioned above is not a difficult task. However, when the pathology is in an incipient or subclinical stage, the use of a single parameter as a diagnostic factor is not accurate enough. In such cases, the use of algorithms and predictive models that combine data from different systems and analyses is mandatory to obtain an acceptable diagnostic accuracy.


**OTHER CITED MATERIAL**


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