Corneal Epithelial Thickness Profile in the Diagnosis of Keratoconus

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ABSTRACT

PURPOSE: To illustrate the hypothesis that epithelial thickness profile maps could be used as an adjunctive tool to improve the sensitivity and specificity of keratoconus screening by presenting a case series of examples.

METHODS: The Artemis very high-frequency digital ultrasound arc-scanner was used to obtain epithelial thickness profiles in addition to a comprehensive ophthalmic examination to screen for keratoconus. Five case examples are presented; a normal eye, an eye with advanced keratoconus, and three cases where a diagnosis of keratoconus was uncertain based only on the ophthalmic examination.

RESULTS: The epithelial thickness profile in the normal eye was slightly thinner superiorly, consistent with that previously described for a normal population. The keratoconic eye demonstrated an epithelial doughnut pattern of epithelial thinning over the cone surrounded by an annulus of epithelial thickening. In case 1, an epithelial doughnut pattern confirmed the presence of keratoconus in an eye with an abnormal front surface topography. In case 2, the absence of an epithelial doughnut pattern excluded a diagnosis of keratoconus in a patient with an abnormal front surface topography. In case 3, the presence of an epithelial doughnut pattern coincident with an eccentric posterior elevation best-fit sphere indicated a diagnosis of keratoconus. The epithelium appeared to have compensated for the stromal surface cone, resulting in an apparently normal front surface topography.

CONCLUSIONS: An epithelial doughnut pattern appears to indicate the presence of an underlying stromal cone; the lack of an epithelial doughnut pattern would indicate that an abnormal topography was not due to keratoconus. In very early keratoconus, epithelial compensation can mask the presence of an underlying cone on front surface topography, ie, a diagnosis of keratoconus might be missed. [*J Refract Surg*. 2009;25:604-610.]
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The detection of early keratoconus is one of the major safety issues faced in corneal refractive surgery, as performing LASIK on undiagnosed keratoconus has been identified as the leading cause of ectasia after laser refractive surgery.[1-5] Many methods have been suggested to discriminate between normal eyes and suspect keratoconus eyes; however, front surface corneal topography remains the current standard for keratoconus screening.[6-8]

We propose the use of epithelial thickness profile maps as a new adjunctive diagnostic tool, with the aim to provide both higher specificity and higher sensitivity to diagnose early cases of keratoconus when topography is equivocal.

The corneal epithelium has the ability to alter its thickness profile to re-establish a smooth, symmetrical optical surface and either partially or totally mask the presence of an irregular stromal surface from front surface corneal topography. Ideally, we would like a method of directly measuring stromal surface topography. Some have suggested measuring topography after epithelial removal and have shown an increase in irregularity.[9] However, this is not a clinically feasible test. Alternatively, the anterior stromal surface shape can be appreciated by an examination of its proxy—the epithelial thickness profile. Based on an understanding of the pattern of the normal epithelial thickness profile, any localized abnormal epithelial changes can be relied upon as a mirror of a relative localized stromal surface irregularity. Therefore, the epithelial thickness profile can be thought of as a form of stromal surface topography.

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Dr Reinstein has a proprietary interest in the Artemis technology (ArcScan Inc, Morrison, Colo) and is the author of patents administered by the Cornell Research Foundation, Ithaca, NY. The remaining authors have no proprietary or financial interest in the materials presented herein.

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We have previously described epithelial compensation for stromal irregularities in cases of asymmetric resection in automated lamellar keratoplasty,[10] asymmetric LASIK flaps,[10-12] microfolds,[11,12] flap malposition,[11-13] short flap,[11-13] free cap malrotation,[14] and irregular stromal surface following multiple refractive procedures.[15] We have also shown epithelial changes in response to myopic[10,16,17] and hyperopic LASIK,[10] radial keratotomy, and intracorneal ring segments.[18]

In keratoconus, the cone is often represented by a high, eccentric apex on both anterior and posterior elevation best-fit sphere (BFS).[19,20] Our hypothesis is that front and back corneal surfaces are yoked, meaning that any back surface ectatic change will therefore be accompanied by a front stromal surface ectatic change (further study is required to confirm this hypothesis). Also, the epithelium is known to be irregular in thickness[21] and clinicians have known for a long time that extreme corneal steepening can lead to epithelial breakdown. Epithelial thinning over the cone has been demonstrated histopathologically in keratoconic corneas[22] as well as in vivo using optical coherence tomography.[23] In this case, the epithelium would minimize the extent of the cone on anterior elevation BFS. In this report, we demonstrate that for small amounts of stromal front surface ectasia, epithelial changes could potentially fully compensate for the stromal surface irregularity and render a completely normal anterior elevation BFS, whereas the ectasia would still be apparent on the posterior surface elevation BFS.

Therefore, mild keratoconus might be picked up earlier on posterior surface elevation BFS than anterior surface elevation BFS; something that early adopters of Orbscan (Bausch & Lomb, Salt Like City, Utah) became convinced of in the mid to late 1990s and was first presented by our group in 2003.[24] However, this does not necessarily mean that posterior elevation BFS changes are the first anatomical morphological changes in keratoconus, just that these are the first detectable changes; further study is required to understand the sequence of anatomical morphological changes in keratoconus. Interestingly, it was not until 2008 that a paper suggesting this concept actually came to press; Schlegel et al[25] suggested that early posterior surface changes could be occurring in patients with no symptoms and with anterior surface modifications that are so small that they would not be detected. The authors concurred with our previously presented hypothesis that the corneal epithelium could remodel itself and mask or minimize some early anterior surface topographical changes. However, not all posterior elevation BFS changes will be due to keratoconus, which is why a need exists for a diagnostic tool to confirm or exclude a diagnosis of keratoconus in eyes with an eccentric posterior elevation BFS.

The key to detecting keratoconus by geometric anatomical changes appears to be the ability to examine the anterior and posterior stromal surfaces. The purpose of this article is to illustrate this hypothesis and provide descriptive examples of where the addition of epithelial thickness maps to anterior and posterior elevation BFS can increase the sensitivity and specificity of the keratoconus screening process.

ILLUSTRATION OF CONCEPT BY CLINICAL EXAMPLES

A series of eyes is presented, which illustrate the added diagnostic specificity afforded by the simultaneous consideration of the epithelial thickness map when assessing the current standard topographical screening method; correlating front surface Placido-based topography with anterior elevation BFS and posterior elevation BFS. In each case, the epithelial thickness profile appears to be able to differentiate cases where the diagnosis of keratoconus is uncertain. As we will demonstrate, the use of epithelial thickness profiles can indicate the presence of early keratoconus where only soft signs of keratoconus are evident by standard screening criteria.

Artemis Very High-frequency Digital Ultrasound Arc-scanning

The Artemis very high-frequency (VHF) digital ultrasound system (ArcScan Inc, Morrison, Colo) has been described in detail previously.[17,26,27] Artemis scanning provides very high resolution ultrasound B-scans of the cornea, showing clear delineation of the epithelial surface, Bowman's surface, and the back surface of the cornea as well as other interfaces within the cornea such as a LASIK flap. Multi-meridional scanning provides three-dimensional thickness mapping of individual corneal layers over a 10-mm corneal diameter with approximately 1-µm precision.[26]

Examples

The Figure shows the keratometry (in diopters [D]), Atlas 995 (Carl Zeiss Meditec, Jena, Germany) corneal topography map and PathFinder (Carl Zeiss Meditec) corneal analysis, Orbscan II (software version 3.00, Bausch & Lomb) anterior elevation BFS, Orbscan posterior elevation BFS, and Artemis epithelial thickness profile for a typical normal eye, a typical keratoconic eye, and three suspect keratoconus eyes (cases 1, 2, and 3). The three suspect keratoconus cases are examples where the topography and/or tomography maps were suggestive but not conclusive of keratoconus.

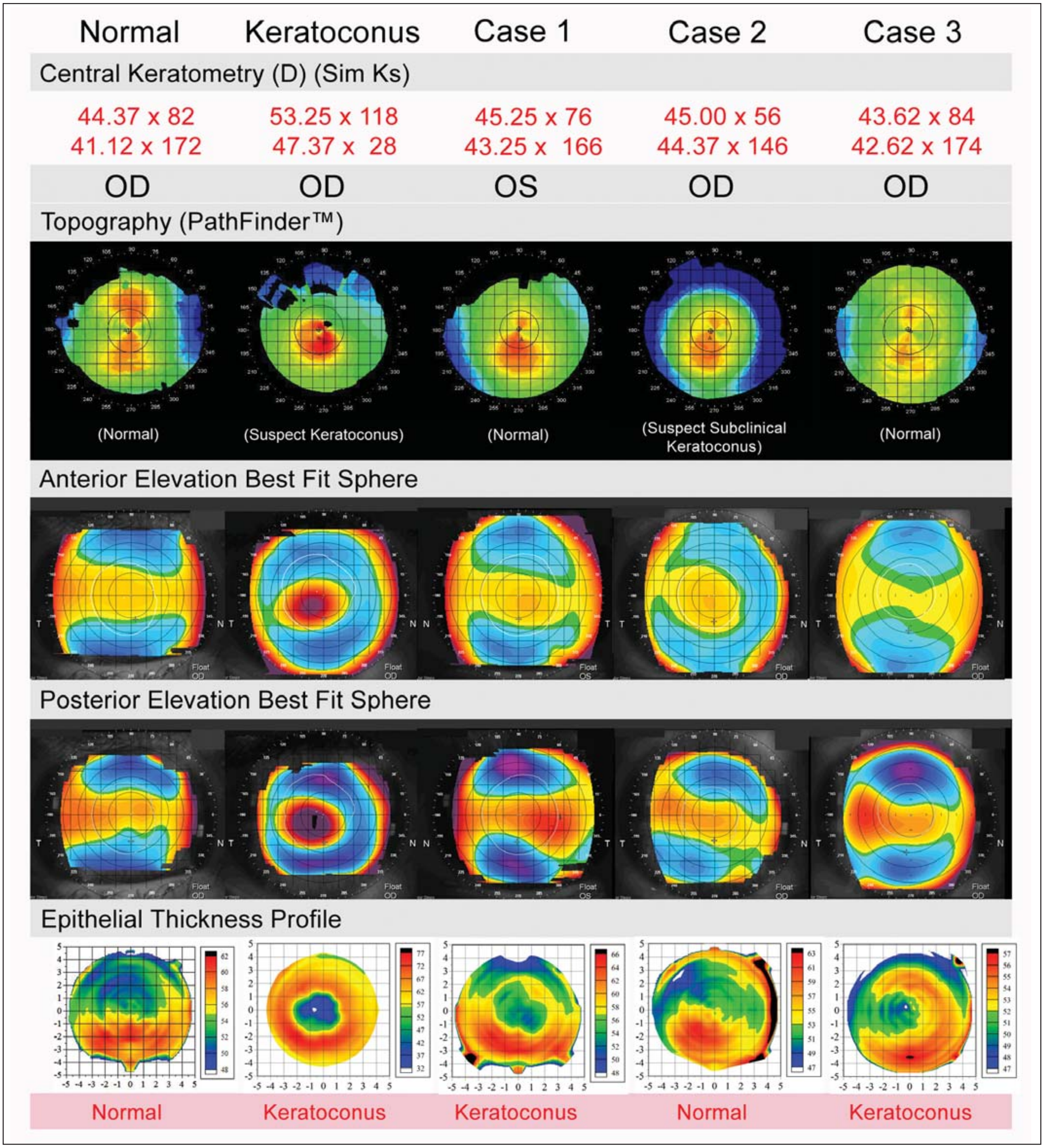

Figure. Central keratometry, Atlas corneal topography and PathFinder corneal analysis (Carl Zeiss Meditec) (indicated below the topography map), Orbscan anterior and posterior elevation BFS (Bausch & Lomb), and Artemis (ArcScan Inc) epithelial thickness profile for one normal eye, one keratoconic eye, and three example eyes where the diagnosis of keratoconus might be misleading from topography. The final diagnosis based on the epithelial thickness profile is shown at the bottom of each example. OD = right eye, OS = left eye

Normal Eye. In the Figure, column 1 shows an example of a normal eye. This is the right eye of a 21-year-old woman, with a manifest refraction of −3.00 −3.50 × 171 and a best spectacle-corrected visual acuity (BSCVA) of 20/32. The patient was amblyopic in both eyes most likely due to uncorrected astigmatism during childhood. The corneas were both completely normal. Atlas corneal topography demonstrated regular with-the-rule astigmatism. The keratometry was 44.37/41.12 D × 82, and PathFinder corneal analysis classified the topography as normal. Orbscan anterior and posterior elevation BFS maps were symmetrical and well centered. Corneal pachymetry minimum by Artemis was 562 µm. Vertical coma measured with WASCA aberrometry (Carl Zeiss Meditec) was low: −0.05 µm (Optical Society of America [OSA] notation). Corneal hysteresis was 13.9 mmHg and corneal resistance factor was 13.6 mmHg measured with the Ocular Response Analyzer (Reichert, Depew, NY). Artemis epithelial thickness profile showed a pattern of thinner epithelium superiorly than inferiorly, which was consistent with that previously published for a population of normal eyes.[27] There was no suggestion of keratoconus by any of the parameters measured.

Keratoconic Eye. In the Figure, column 2 shows an example of a typical keratoconic eye. This is the right eye of a 20-year-old woman, with a manifest refraction of −1.50 −3.75 × 45 and BSCVA of 20/40. As expected, the Atlas corneal topography showed inferotemporal steepening with steep keratometry (53.25/47.37 D × 118) and high astigmatism; PathFinder corneal analysis classified the topography as suspect keratoconus. Orbscan anterior and posterior elevation BFS maps demonstrated that the apex of the cone was located inferotemporally. Corneal pachymetry minimum by handheld ultrasound (Corneo-Gage Plus; Sonogage, Cleveland, Ohio) was 421 µm. Corneal hysteresis was 8.2 mmHg and corneal resistance factor was 6.1 mmHg, which were low. The epithelial thickness profile showed epithelial thinning at the apex of the cone surrounded by an annulus of thicker epithelium (epithelial doughnut pattern). The large difference in thickness between the apex of the cone (32 µm) and the surrounding annulus (76 µm) demonstrated that the epithelial thickness profile was different than the normal average profile[27] (see Fig, column 1). The apex of the anterior and posterior elevation BFS coincided with the location of the epithelial thinning at the center of the epithelial doughnut pattern. All parameters measured confirmed the diagnosis of keratoconus.

Diagnosing Early Keratoconus Using Epithelial Thickness Profile. These examples demonstrate that the epithelial thickness profile of the normal cornea has a significantly distinct pattern from that of a keratoconic eye. The epithelium in the normal eye was thicker inferiorly than superiorly and slightly thicker nasally than temporally, although there was little variation in epithelial thickness within both the inferior hemi-cornea and the superior hemi-cornea. In contrast, in the keratoconic eye, there was localized epithelial thinning inferotemporally surrounded by an annulus of thicker epithelium (epithelial doughnut pattern). The epithelial thickness profile demonstrated a much greater within-eye range of thickness in the keratoconic eye, than in the normal eye.

In early keratoconus, we would expect to see a similar epithelial doughnut pattern with the thinnest epithelium coincident with a suspected cone on posterior elevation BFS surrounded by an annulus of thicker epithelium. Therefore, epithelial thickness profiles might be used to confirm or exclude a diagnosis of keratoconus in eyes suggestive but not conclusive of a diagnosis of keratoconus on topography. The coincidence of an epithelial doughnut pattern together with posterior elevation BFS apex eccentricity may reveal whether or not to ascribe significance to an eccentric posterior elevation BFS apex concurrent with normal front surface topography. In other words, in the presence of normal front surface topography, an epithelial doughnut pattern coincident with the location of the posterior elevation BFS apex would represent total masking or compensation for a sub-surface stromal cone and herald back surface changes, which present keratoconus. Conversely, the lack of an epithelial doughnut pattern over an area of topographic steepening or an eccentric posterior elevation BFS apex would imply that the steepening is not due to a keratoconic sub-surface stromal cone.

Examples of Suspect Keratoconus Eyes (Cases 1, 2 and 3). In the Figure, columns 3, 4, and 5 show three selected examples where epithelial thickness profiles helped interpret and diagnose anterior and posterior elevation BFS abnormalities.

Case 1 is the left eye of a 25-year-old man, with a manifest refraction of −1.00 −0.50 × 150 and BSCVA of 20/16. Atlas corneal topography demonstrated inferior steepening, which would traditionally indicate possible keratoconus. The keratometry was 45.25/43.25 D × 76, and PathFinder corneal analysis classified the topography as normal. Orbscan posterior elevation BFS showed that the posterior elevation BFS apex was decentered inferotemporally. Corneal pachymetry minimum by handheld ultrasound was 479 µm. Contrast sensitivity was slightly below normal range using the CSV-1000 (Vector Vision Inc, Greenville, Ohio). There was −0.30 µm (OSA notation) of vertical coma on WASCA aberrometry. Corneal hysteresis was 7.5 mmHg and corneal resistance factor was 7.1 mmHg, which were low. The combination of inferior steepening, an eccentric posterior elevation BFS apex, and a low to normal corneal thickness raised the suspicion of keratoconus although there was no suggestion of keratoconus by refraction, keratometry, or PathFinder corneal analysis. Artemis epithelial thickness profile showed an epithelial doughnut pattern typical of keratoconus displaced inferotemporally coincident with the eccentric posterior elevation BFS apex, which confirmed the diagnosis of early keratoconus.

Case 2 is the right eye of a 31-year-old woman, with a manifest refraction of −2.25 −0.50 × 88 and BSCVA of 20/16. Atlas corneal topography demonstrated a similar pattern to case 3 of inferior steepening, therefore also suggesting possible keratoconus. The keratometry was 44.12/44.75 D × 148, and PathFinder corneal analysis classified the topography as suspect subclinical keratoconus. Orbscan posterior elevation BFS showed that the posterior elevation BFS apex was slightly decentered nasally. Corneal pachymetry minimum by handheld ultrasound was 538 µm. Contrast sensitivity was in the normal range. There was −0.38 µm (OSA notation) of vertical coma on WASCA aberrometry. Corneal hysteresis was 10.1 mmHg and corneal resistance factor was 9.8 mmHg, which were well within normal range. The combination of inferior steepening, against-the-rule astigmatism, and high degree of vertical coma raised the suspicion of keratoconus, which was also noted by PathFinder corneal analysis. Artemis epithelial thickness profile showed a typical normal pattern with thicker epithelium inferiorly and thinner epithelium superiorly. The lack of an epithelial doughnut pattern over the suspected cone (inferior steepening on topography) was inconsistent with an underlying stromal surface cone, and therefore the diagnosis of keratoconus was excluded. This patient would have been rejected for surgery given a documented PathFinder corneal analysis warning of suspect subclinical keratoconus, but given the epithelial thickness profile, this patient was deemed a suitable candidate for LASIK.

The anterior corneal topography in case 3 (right eye) bears no features related to keratoconus. The patient is a 35-year-old woman with a manifest refraction of −4.25 −0.50 × 4 and BSCVA of 20/16. The refraction had been stable for at least 10 years and the contrast sensitivity was within normal limits. The keratometry was 43.62/42.62 D × 74 and PathFinder analysis classified the topography as normal. Orbscan posterior elevation BFS showed that the posterior elevation BFS apex was slightly decentered inferotemporally, but the anterior elevation BFS apex was well centered. Corneal pachymetry minimum by handheld ultrasound was 484 µm. Pentacam (Oculus Optikgeräte, Wetzlar, Germany) keratoconus screening indices were normal. WASCA ocular higher order aberrations were low (root-mean-square=0.19 µm) as well as the level of vertical coma (coma=0.066 µm). Corneal hysteresis was 8.9 mmHg and corneal resistance factor was 8.8 mmHg, both within normal limits. In this case, only the slightly eccentric posterior elevation BFS apex and the low–normal corneal thickness were suspicious for keratoconus, whereas all other screening methods gave no indication of keratoconus. However, the epithelial thickness profile showed an epithelial doughnut pattern coincident with the eccentric posterior elevation BFS apex, indicating the probable presence of keratoconus. In this case, it seems that the epithelium had fully compensated for the stromal surface irregularity so that the anterior surface topography of the cornea appeared perfectly regular. Given the regularity of the front surface topography and the normality of nearly all other screening parameters, it is feasible that this patient could have been deemed suitable for corneal refractive surgery and subsequently developed ectasia. As we were able to also consider the epithelial thickness profile, this patient was rejected for corneal refractive surgery. This type of case may explain cases of ectasia "without a cause."

DISCUSSION

Mapping of the epithelial thickness profile may increase sensitivity and specificity of screening for keratoconus compared to current conventional corneal topographic screening alone and may be useful in clinical practice.

In the general population, the consequences of missing a diagnosis of keratoconus are small, in that the disease typically progresses and a definitive diagnosis will eventually be evident. In ordinary clinical practice, patients with mild keratoconus will have spectacles or contact lenses prescribed and corneal topography probably would not have been performed.

Conversely, a missed diagnosis of keratoconus in a candidate for refractive surgery can have dire consequences in a matter of months. It is for this reason that detection of keratoconus in refractive surgery candidates is crucial. Epithelial thickness profile mapping could be valuable for preoperative assessment in refractive surgery in two important ways.

First, epithelial thickness mapping appears to be able to exclude the appropriate patients by detecting keratoconus earlier or confirming keratoconus in cases where front surface topographic changes may be clinically judged as being "within normal limits." Epithelial information may allow an earlier diagnosis of keratoconus, as epithelial changes will precede changes on the front surface of the cornea; Artemis epithelial thickness changes can be detected to within 1 µm of change. An epithelial doughnut pattern, characterized by epithelial thinning surrounded by an annulus of thicker epithelium, coincident with an eccentric posterior elevation BFS apex, is consistent with keratoconus.

Second, epithelial thickness profiles may be useful in excluding a diagnosis of keratoconus despite suspect topography. Epithelial thickening over an area of topographic steepening implies that the steepening is not due to an underlying ectatic surface. In such cases, excluding keratoconus using epithelial thickness profiles appears capable of allowing patients to be deemed suitable for corneal refractive surgery who otherwise would have been denied treatment due to suspect keratoconus.

Pellucid marginal degeneration is often considered alongside keratoconus. Clinically, there is some overlap between keratoconus and pellucid marginal degeneration, however, anatomically they are distinct entities. Pellucid marginal degeneration is characterized by a zone of inferior mid-peripheral flattening and far-peripheral steepening on front surface topography. Because of the lack of a protruding cone, epithelial thickness profiles will not demonstrate the epithelial doughnut pattern as seen in keratoconus. We believe that hemi-meridian examination of stromal thickness profiles will be more useful for detecting pellucid marginal degeneration and that epithelial thickness profiles should be used only for suspect keratoconus.

We are currently carrying out further work on using epithelial thickness profiles as a new adjunctive diagnostic tool to screen for keratoconus. We have already characterized the corneal epithelial[27] and corneal stromal thickness profiles[28] in the normal population. We have also determined the average epithelial, stromal, and corneal thickness profiles in a population of advanced keratoconic eyes to characterize the layered thickness changes and geometry associated with keratoconus.[29] This paper also discusses our hypotheses on the cause of the epithelial changes seen in keratoconus of apical epithelial thinning and surrounding annulus of epithelial thickening.[29] Next, we aim to identify and parameterize several features of the epithelial thickness profile that might help discriminate between normal and suspect keratoconus eyes. We are currently developing an automated scoring system based on these features to quantify the deviation from the normal epithelial thickness profile. We intend to apply the automated scoring system to a large population of eyes being screened for corneal refractive surgery and test the sensitivity and specificity of using epithelial thickness profiles as a keratoconus screening tool. Finally, we are assessing the long-term refractive stability and safety of LASIK in eyes with suspect keratoconus where the diagnosis of keratoconus was excluded by epithelial thickness mapping.[30]

AUTHOR CONTRIBUTIONS

Study concept and design (D.Z.R., T.J.A., M.G.); data collection (D.Z.R., T.J.A., M.G.); interpretation and analysis of data (D.Z.R., T.J.A., M.G.); drafting of the manuscript (D.Z.R., T.J.A., M.G.); critical revision of the manuscript (D.Z.R., T.J.A., M.G.)

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