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Detection of Keratoconus in Clinically and Algorithmically Topographically Normal Fellow Eyes Using Epithelial Thickness Analysis

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Abstract

PURPOSE—To assess the effectiveness of a keratoconus-detection algorithm derived from Artemis very high-frequency (VHF) digital ultrasound (ArcScan Inc., Morrison, CO) epithelial thickness maps in the fellow eye from a series of patients with unilateral keratoconus.

METHODS—The study included 10 patients with moderate to advanced keratoconus in one eye but a clinically and algorithmically topographically normal fellow eye. VHF digital ultrasound epithelial thickness data were acquired and a previously developed classification model was applied for identification of keratoconus to the clinically normal fellow eyes. Pentacam (Oculus Optikgeräte, Wetzlar, Germany) Belin-Ambrósio Display (BAD) data (5 of 10 eyes), and Orbscan (Bausch & Lomb, Rochester, NY) SCORE data (9 of 10 eyes) were also evaluated.

RESULTS—Five of the 10 fellow eyes were classified as keratoconic by the VHF digital ultrasound epithelium model. Five of 9 fellow eyes were classified as keratoconic by the SCORE model. For the 5 fellow eyes with Pentacam and VHF digital ultrasound data, one was classified as keratoconic by the VHF digital ultrasound model, one (different) eye by a combined VHF digital ultrasound and Pentacam model, and none by BAD-D alone.

CONCLUSIONS—Under the assumption that keratoconus is a bilateral but asymmetric disease, half of the 'normal' fellow eyes could be found to have keratoconus using epithelial thickness

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AUTHOR CONTRIBUTIONS

Study concept and design (TJA, MG, DZR, RHS); data collection (TJA, MG, DRZ); analysis and interpretation of data (TJA, MG, AR, DZR, RU); writing the manuscript (TJA, AR, DZR, RHS); critical revision of the manuscript (MG, AR, RU); statistical expertise (TJA, AR, DZR, RHS)

Drs. Silverman and Reinstein have a proprietary interest in the Artemis technology (ArcScan Inc., Morrison, CO) and are the authors of patents related to VHF digital ultrasound administered by the Cornell Center for Technology Enterprise and Commercialization (CCTEC), Ithaca, NY. Dr. Reinstein is also a consultant for Carl Zeiss Meditec, Jena, Germany. The remaining authors have no proprietary or financial interest in the materials presented herein.

maps. The Orbscan SCORE or the combination of topographic BAD criteria with epithelial maps did not perform better.

The early detection of keratoconus has become a vital part of clinical practice in corneal refractive surgery to avoid possibly accelerating keratectasia, but also perhaps because of the possibility of halting the progression of loss in visual quality by corneal cross-linking.¹ Advances in topographic algorithms^{2–7} and then tomographic algorithms^{8–15} have greatly improved the ability to detect keratoconus at earlier and earlier stages.

The latest modality to have been added to the anatomical screening for keratoconus is examination of the epithelial thickness profile. Using Artemis very high-frequency (VHF) digital ultrasound (ArcScan Inc., Morrison, CO), Reinstein et al. described how the epithelium remodels to maintain a smooth corneal surface in response to underlying stromal irregularities¹⁶; specifically, in keratoconus, the epithelium compensates for the subsurface cone by thinning over the cone and thickening around the cone.¹⁷ Recent optical coherence tomography (OCT)-based studies of the epithelial thickness distribution have described similar epithelial thickness patterns in keratoconus.^{18–20} Therefore, based on these findings Reinstein et al.²¹ proposed and demonstrated that epithelial thickness mapping could be used for earlier keratoconus detection than topography and tomography given that epithelial remodeling may be sufficient in early keratoconus to fully mask a subsurface stromal cone so that front surface corneal topography appears normal. Based on this concept, Silverman et al.²² developed an automated multivariate classifier from VHF digital ultrasound-derived epithelial and stromal map analysis and reported full separation of normal from clinical keratoconus using this automatic classifier.²³

Keratoconus is generally regarded as a bilateral progressive disease, although it is often asymmetric and, on rare occasions, unilateral. In studies based solely on clinical signs, approximately 15% of patients with keratoconus have been reported to be unilateral.^{23,24} However, a much lower frequency of 2% to 4% is reported in studies using topography-based methods.^{3,25–27}

It is thus generally believed that such normal-appearing eyes of cases with unilateral keratoconus represent a latent form of keratoconus and, as such, a gold standard for studies aimed at early keratoconus detection. Several reports have evaluated the fellow eye in unilateral keratoconus as a test bed for assessment of methods for early diagnosis of occult keratoconus using topography, tomography, and biomechanical indicators.^{7,10–13,24}

In this report, we set out to evaluate the ability of our previously developed epithelial and stromal thickness multivariate classifier^{22,23} to detect subclinical keratoconus by analyzing a population of clinically and algorithmically topographically normal-appearing fellow eyes of patients with unilateral keratoconus.

PATIENTS AND METHODS

Patients

Participants were recruited from a population of candidates presenting for corneal refractive surgery to the London Vision Clinic. The study included 10 clinically and algorithmically

topographically normal fellow eyes of 10 patients with unilateral moderate to advanced keratoconus. The research followed the tenets of the Declaration of Helsinki. Informed consent for research, analysis, and publication of data was obtained from patients. The research was conducted under protocols approved by the Western Institutional Review Board and the Institutional Review Board of the Columbia University Medical Center.

Preoperative assessment included manifest refraction, logMAR corrected distance visual acuity (CDVA) (CSV-1000; Vector Vision Inc., Greenville, OH), and cycloplegic refraction using one drop of tropicamide 1% (Alcon Laboratories UK Ltd., Hemel Hempstead, United Kingdom). Topography and simulated keratometry were assessed using the ATLAS 995 or ATLAS 9000 corneal topography system (Carl Zeiss Meditec AG, Jena, Germany). Tomography was assessed using the Orbscan II (Bausch & Lomb, Rochester, NY) and/or Pentacam HD (Oculus Optikgeräte, Wetzlar, Germany). Dynamic pupillometry was performed using the P2000 pupillometer (Procyon, Manchester, United Kingdom). Wavefront assessment was performed using the WASCA aberrometer (Carl Zeiss Meditec AG). Single-point pachymetry was performed with the Corneo-Gage Plus (50 MHz) hand-held ultrasound pachymeter (Sonogage, Cleveland, OH) by choosing the minimum of 10 consecutive central corneal measurements.

Keratoconus diagnosis was confirmed by clinical signs such as microscopic signs at the slit lamp, corneal topographic and tomographic changes, high refractive astigmatism, reduced CDVA and contrast sensitivity, and significant level of higher-order aberrations, in particular coma. According to Krumeich classification criteria, the population included 4 eyes classified as grade I and 7 eyes classified as grade II keratoconus. Patients with clear topographically defined pellucid marginal degeneration and eyes with pathology other than keratoconic ectatic degeneration were excluded. Fellow eyes were deemed to be of normal appearance if they lacked clinical signs of keratoconus and the ATLAS Pathfinder keratoconus screening index classified the front corneal surface topography as normal.

All patients were scanned with the Artemis-1 VHF digital ultrasound system as described in detail previously.^{17,21–23,25–27} VHF digital ultrasound scans were acquired with the patient in a sitting position gazing at a fixation light and with optical monitoring of eye centration. Scans consisted of 128 vectors over an arc encompassing an approximate width of 10 mm in the focal plane. Each scan plane takes approximately 1 second to acquire. The scan series comprised 4 scans, or 8 hemi-meridians, spaced radially at 45° intervals. Art-Pro software was used to determine epithelial and stromal thickness at each vector position within the central 7-mm diameter zone to generate pachymetric maps and to produce 10 × 10 mm Cartesian representations of layer thickness at 0.1-mm intervals. Custom MatLab software (The MathWorks, Inc., Natick, MA) was then used to extract variables characterizing the epithelial, stromal, and full corneal thickness distributions.

Classification

Our previously described multivariate linear discriminant model to separate clinical keratoconus from normal corneas was employed for analysis.^{22,23} Briefly, the reference database used for this classification model consisted of 130 normal corneas and 74 corneas with clinically evident keratoconus as previously described.^{17,18} The model consisted of six

parameters related to the position of the thinnest point in the cornea and the epithelial thickness distribution around that point. The six variables related to the epithelial thickness distribution, including the gradient about the thinnest point. The classification function derived from these data was applied to the population of 10 normal fellow eyes of patients with unilateral keratoconus to test whether these eyes would be classified as keratoconic.

Pentacam HD data were available for 5 of the 10 patients. We previously described a classification function that combined VHF digital ultrasound epithelial and stromal thickness data with parameters obtained from the Pentacam HD tomography.²³ This classification function was applied to this subgroup of 5 eyes with Pentacam HD data. Finally, the Belin-Ambrósio Enhanced Ectasia Display (BAD) was also evaluated to test whether the fellow eyes would be classified as keratoconic according to the BAD-D and Ambrósio Relational Thickness maximum (ART-Max) values.^{8,9} A BAD-D value of 1.45 was used as the cut-off to diagnose keratoconus, and a cut-off value of 339 μm was used for the ART-Max, with the Pentacam HD running software version 6.07r12.

Orbscan data were available for 9 of the 10 patients. The SCORE value was generated, which uses discriminant functions based on linear regression analyses of selected Orbscan parameters and indices.^{13,15} A positive SCORE value was used to classify keratoconus.

RESULTS

The ATLAS front surface corneal topography, VHF digital ultrasound epithelial thickness profile, and either Orbscan II posterior elevation best-fit sphere (BFS) or Pentacam HD BAD are shown for all 10 patients in Figures 1–5 and Figures A–E (available in the online version of this article). Table 1 summarizes the diagnosis derived for the fellow eyes using the classification function based only on epithelial thickness parameters, the classification function combining VHF digital ultrasound (epithelial and stromal thickness) and Pentacam HD parameters, the BAD-D and ART-Max values, and the Orbscan SCORE value. The last column of Table 1 indicates whether the topographic map displayed suspicious features of keratoconus such as inferior steepening and asymmetric bow-tie. Table 1 also shows the percentage of eyes that were classified as keratoconic by each method.

DISCUSSION

Li et al. reported that 35% of asymptomatic fellow eyes developed clinical findings of keratoconus within 6 years and 50% in approximately 16 years, supporting the supposition that keratoconus is a bilateral disease but that its expression may be asymmetric. We know that in a significant proportion of cases, epithelial remodeling manifests prior to changes in anterior corneal surface topography, therefore masking early diagnosis. In this report, we demonstrated that 50% of topographically ‘normal’ fellow eyes could be found to have keratoconus by using an automated algorithm based on VHF digital ultrasound maps of epithelial thickness alone. In the future, OCT mapping of curvature, epithelium, and stroma could play an important role. Furthermore, improved metrics relating to the epithelial thickness distribution may yield better sensitivity.

In this report we evaluated keratoconus-detection algorithms based on VHF digital ultrasound-derived epithelial thickness maps and where data were available on Pentacam parameters including Belin-Ambrósio indices and the SCORE algorithm derived from Orbscan data. An important consideration in assessing the significance of comparative results is the specificity of each algorithm, because low specificity could result in cases being classified as keratoconus by chance. We have reported greater than 99% specificity on the VHF digital ultrasound multivariate model.²² Saad and Gatinel reported 96% specificity for the SCORE algorithm, although this was for retrospective classification; no cross-validation was performed.¹⁵ The BAD-D is reported to have a specificity of 98.5%.²⁸

In the subset of 9 eyes where Orbscan data were also available, 5 eyes (55%) were classified as keratoconic by both the epithelium classification function and the SCORE algorithm. Interestingly, there were 2 eyes (cases 1 and 3 [Figures A and C]) classified as keratoconic by epithelium that were classified as normal by SCORE, and 2 eyes where the classification was reversed (cases 4 and 8 [Figures 1 and 3]).

In the subset of 5 eyes where Pentacam HD data were also available, only one eye (20%) was classified as keratoconic by the epithelium classification function. When Pentacam HD data were included in the classification function alongside the VHF digital ultrasound epithelial and stromal thickness data, the keratoconus classification percentage remained the same (1 of 5 eyes, 20%). One eye (case 8 [Figure 3]) that was classified as normal by epithelium alone was reclassified as keratoconic by inclusion of Pentacam HD data, which represented an improvement; however, the classification changed in the opposite direction for another eye (case 9 [Figure 4]). This showed that the addition of Pentacam HD with epithelial data can help in some cases but hinder in others. Using the Pentacam HD BAD-D value, none of the 5 eyes were classified as keratoconic, although the BAD-D value was 1.35 in one of these eyes, which was close to the threshold of 1.45. Similarly, none of the 5 eyes were classified as keratoconic according to the ART-Max. The disagreement between methods suggests that further work is needed to determine the optimal combination of epithelial and tomographic data.

The sensitivity of the BAD-D and ART-Max values for the cases in our study was worse than for Pentacam HD variables previously reported in other populations of unilateral keratoconus. For example, Muftuoglu et al.¹² reported approximately 70% sensitivity for a range of different parameters between normal and fellow eyes of patients with keratoconus. However, the results of the current study were in agreement with those reported by Bae et al.,¹¹ who found no difference in the BAD-D or ART-Max values between normal and topographically normal fellow eyes of patients with keratoconus. The differences between studies are most likely due to the different inclusion criteria used to classify unilateral keratoconus. In the current study, as in the study by Bae et al.,¹¹ fellow eyes were included only if the front surface topography was normal, whereas many other unilateral keratoconus studies exclude these cases (ie, only include cases with suspicious front surface topography).

Indeed, 3 of 5 eyes (60%, cases 6, 7, and 10 [Figures E, 2, and 5]) were classified as normal by corneal topography, epithelial thickness profile, BAD-D, and ART-Max, whereas cases 7 and 10 (Figures 2 and 5) were also classified as normal by SCORE (data were not available

for case 6 [Figure E]). It seems possible that these eyes were truly monocularly keratoconic (and possibly also case 4 [Figure 1], although Pentacam HD data were not available). Alternatively, it may be that the phenotypically unexpressed form of keratoconus might actually be undetectable by current strategies of anatomical analysis. This would imply that there will be some cases where no amount of anatomical corneal measurements (ie, topography, tomography, pachymetry, epithelial thickness, wavefront, etc.) will be able to detect keratoconus. However, this would explain the rare but described cases of iatrogenic keratectasia after LASIK “without a cause.”^{29,30}

It is important to note that objective Atlas algorithmic classification may significantly differ from expert clinician subjective classification of suspicious topography. For example, eyes 3, 5, and 8 showed asymmetric bow-tie with inferior steepening that an expert clinician may have classified as suspicious. However, for these cases, there was no agreement between the four objective classification methods tested; case 3 (Figure C) was classified as certain keratoconus (94% probability) by VHF digital ultrasound but as normal by Orb-scan II (SCORE -0.3). Case 5 (Figure D) was classified as highly probable keratoconus (85% probability) by VHF digital ultrasound and Orbscan II (SCORE 5.6). Case 8 (Figure 3) was classified as normal by VHF digital ultrasound alone (8% probability), as near normal by Pentacam HD (BAD = 1.35, ART-Max = 380) alone, as certain keratoconus by combined VHF digital ultrasound and Pentacam HD (95%), and as keratoconus by Orbscan (SCORE = 0.6). Therefore, it is clear that there is poor correlation in fellow eyes between objective and subjective assessment.

As with any measurement in early keratoconus, there are often only small changes in epithelial thickness compared to normal, which makes confident diagnosis difficult. For example, case 4 (Figure 1) was classified as normal, but the epithelial thickness profile could be interpreted by an experienced observer as suggestive of keratoconus given the localized region of thinner epithelium, which was also coincident with the apex of the posterior surface elevation BFS. It is possible that this case would have been classified as keratoconus using the combined classification function had Pentacam HD tomography data also been available (we have not developed a function to incorporate Orbscan II data). However, the fact that the classification function using epithelium alone did not pick this up suggests that there may be ways that it could be improved. One possibility is to consider the epithelial thickness relative to the normal epithelial thickness profile,²⁶ rather than using direct epithelial thickness values. Furthermore, the detection algorithm currently does not relate the spatial distribution of epithelial thickness to spatially co-localized topography and curvature enhancements that we plan to implement. We have previously described how the epithelial thickness profile in a population of normal eyes was asymmetric with the superior epithelium being 5.7 μm thinner than inferiorly at the 3-mm radius,²⁶ and a similar result has been found with OCT.^{18,31} We have suggested that this asymmetry was due to the force applied during blinking with greater force superiorly from the greater influence of the upper eyelid.^{26,27} In eyes with early keratoconus, the epithelial thickness changes are on the order of only a few microns, in which case the asymmetry inherent in the normal epithelial thickness profile may be sufficient to hide the classic epithelial donut shape found in keratoconus.¹⁷ We intend to evaluate this in a future study by plotting a map of the standard

deviation from the mean normal epithelial thickness profile,²⁶ hence accounting for the superior-inferior asymmetry in epithelial thickness.

Epithelial thickness measurement adds useful information for keratoconus screening. The current version of our classification function appears to need some improvement, one possibility being the inclusion of parameters based on the standard deviation from the mean normal epithelial thickness profile, because this would adjust for the asymmetric epithelial thickness profile that can occur naturally due to eyelid forces. The relatively high number of cases that appeared normal by all methods applied in the study implies that this population included patients who were truly monocularly keratoconic, these patients were asymmetric eye rubbers, or there may be cases that are undetectable by anatomical analysis, meaning that complete sensitivity for detecting keratoconus might not be possible without also adding biomechanical and/or genetic screening methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The ATLAS corneal topography (Carl Zeiss Meditec AG, Jena, Germany), VHF digital ultrasound epithelial thickness profile, and Orbscan II tomography (Bausch & Lomb, Rochester, NY) all clearly show keratoconus in the left eye (bottom row). In the fellow eye, the ATLAS corneal topography was completely normal, but there was a slightly elevated and eccentric apex on the posterior elevation best-fit sphere (BFS) and the SCORE value of 0.2 indicated keratoconus. The epithelial thickness profile showed a region of thinner epithelium temporally, coincident with the posterior surface apex, which suggested a diagnosis of keratoconus, but the epithelium classification function did not classify this as keratoconus.

Figure 2.

The ATLAS corneal topography (Carl Zeiss Meditec AG, Jena, Germany), VHF digital ultrasound epithelial thickness profile, Pentacam HD tomography (Oculus Optikgeräte, Wetzlar, Germany), and Orbscan tomography (Bausch & Lomb, Rochester, NY) all clearly show keratoconus in the right eye (bottom row). In the fellow eye, the ATLAS corneal topography was completely normal, as was the Pentacam HD (Belin-Ambrósio Display value was 0.83) and Orbscan (SCORE value was -0.2). The epithelial thickness and standard deviation from normal epithelium maps also showed no indication of keratoconus. This case appears to be a true case of unilateral keratoconus, or the keratoconus was unexpressed in the fellow eye leaving no anatomical differences from a normal eye. This kind of case may explain the reports of ectasia “without a cause.”

Figure 3.

The ATLAS corneal topography (Carl Zeiss Meditec AG, Jena, Germany), VHF digital ultrasound epithelial thickness profile, Pentacam HD tomography (Oculus Optikgeräte, Wetzlar, Germany), and Orbscan tomography (Bausch & Lomb, Rochester, NY) all clearly show keratoconus in the left eye (bottom row). In the fellow eye, the ATLAS corneal topography showed a small degree of inferior steepening, but was classified as normal by the Pathfinder algorithm. There was a small degree of eccentric elevation on the posterior elevation best-fit sphere, which was classified as keratoconus by SCORE (0.6), but, the Belin-Ambrósio Display value of 1.35 indicated that this was not abnormal. The epithelial thickness profile appeared normal with thinner epithelium superiorly than inferiorly, although the thin region was extending into the inferior half of the cornea. This case was not classified as keratoconus by the epithelium classification function.

Figure 4.

The ATLAS corneal topography (Carl Zeiss Meditec AG, Jena, Germany), VHF digital ultrasound epithelial thickness profile, Pentacam HD tomography (Oculus Optikgeräte, Wetzlar, Germany), and Orbscan tomography (Bausch & Lomb, Rochester, NY) all clearly show keratoconus in the right eye (bottom row). In the fellow eye, the ATLAS corneal topography was normal. There was a slight elevation on the posterior elevation best-fit sphere, which was classified as keratoconus by SCORE (1.5), but the Belin-Ambrósio Display value of 1.03 indicated that this was not abnormal. The epithelial thickness profile showed a central zone of thinner epithelium, coincident with the posterior surface apex, which confirmed a diagnosis of keratoconus. This case was correctly classified as keratoconus by the epithelium classification function.

Figure 5.

The ATLAS corneal topography (Carl Zeiss Meditec AG, Jena, Germany), VHF digital ultrasound epithelial thickness profile, Pentacam HD tomography (Oculus Optikgeräte, Wetzlar, Germany), and Orbscan tomography (Bausch & Lomb, Rochester, NY) all clearly show keratoconus in the right eye (bottom row). In the fellow eye, the ATLAS corneal topography was completely normal, as was the Pentacam HD (Belin-Ambrósio Display value was 0.07), and Orbscan (SCORE value was -2.2). The epithelial thickness profile appeared relatively normal with thinner epithelium superiorly than inferiorly, although the thin region was extending into the inferior half of the cornea. This case was not classified as keratoconus by the epithelium classification function.

Keratoconus Classification by Four Methods^a for 10 Fellow Eyes Classified as Normal by Topographic Algorithm of Patients With Clinically Evident Unilateral Keratoconus

TABLE 1

Classification Function VHF Digital Only			Pentacam HD			Classification Function VHF Digital Ultrasound+Pentacam HD			Orbiscan II		Suspicious Atlas Topographic Features
Case	KC Probability	Diagnosis	BAD-D	Diagnosis	ART-Max	Diagnosis	KC Probability	Diagnosis	SCORE	Diagnosis	
1	69%	KC	-	-	-	-1.1	-	-	Normal	-	-
2	86%	KC	-	-	-	0.8	-	-	KC	-	-
3	94%	KC	-	-	-	-0.3	-	-	Normal	Skewed bow-tie; low astigmatism	-
4	4%	Normal	-	-	-	0.2	-	-	KC	-	-
5	83%	KC	-	-	-	5.6	-	-	KC	Asymmetric bow-tie; inferior steepening	-
6	< 1%	Normal	-0.39	Normal	576	Normal	< 1%	Normal	-	-	Small central bow-tie
7	< 1%	Normal	0.83	Normal	454	Normal	< 1%	Normal	-0.2	Normal	-
8	8%	Normal	1.35	Normal	380	Normal	95%	KC	0.6	KC	Asymmetric bow-tie; inferior steepening
9	76%	KC	1.03	Normal	446	Normal	12%	Normal	1.5	KC	-
10	< 1%	Normal	0.07	Normal	524	Normal	< 1%	Normal	-2.2	Normal	-
KC%	-	5/10 (50%)	-	-	-	-	-	-	-	4/9 (55%)	-
KC%	-	1/5 (20%)	-	0/5 (0%)	-	0/5 (0%)	-	1/5 (20%)	-	2/5 (40%)	-

KC = keratoconus; BAD-D = Belin-Ambrósio Enhanced Ectasia Display "D" score; ART = Ambrósio Relational Thickness maximum

^aFirst, predicted keratoconus probability and diagnostic category (classified as keratoconus is probability was > 50%) using the automated algorithm based on epithelial thickness data alone. Second, predicted keratoconus probability and diagnostic category (classified as keratoconus is probability was > 50%) using the automated algorithm based on epithelial thickness and corneal tomography data. Third, the BAD-D value taken from corneal tomography and the diagnostic category using a cut-off value of 1.45 to represent keratoconus. Fourth, the ART-Max value taken from corneal tomography and the diagnostic category using a cut-off value of 339 μ m to represent keratoconus. Fifth, the SCORE algorithm value and the diagnostic category classified as keratoconus if > 0.

The Pentacam HD is manufactured by Oculus Optikgeräte, Wetzlar, Germany; the Orbiscan II is manufactured by Bausch & Lomb, Rochester, NY; the ATLAS 995 or ATLAS 9000 corneal topography system is manufactured by Carl Zeiss Meditec AG, Jena, Germany.