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CLMI The Cone Location and Magnitude Index

Ashraf M. Mahmoud, BS^{*}, Cynthia J. Roberts, PhD^{*}, Richard G. Lembach, MD^{*}, Michael D. Twa, OD, PhD[†], Edward E. Herderick, BS^{*}, Timothy T. McMahon, OD[‡], and the CLEK Study Group

^{*} Department of Ophthalmology and Department of Biomedical Engineering, The Ohio State University, Columbus, OH

[†] College of Optometry, University of Houston, Houston, TX

[‡] Department of Ophthalmology and Visual Sciences, University of Illinois College of Medicine at Chicago, Chicago, IL

Abstract

Purpose—To develop an index for the detection of keratoconic patterns in corneal topography maps from multiple devices.

Methods—For development, an existing Keratron (EyeQuip) topographic dataset, consisting of 78 scans from the right eyes of 78 healthy subjects and 25 scans from the right eyes of 25 subjects with clinically diagnosed keratoconus, was retrospectively analyzed. The Cone Location and Magnitude Index (CLMI) was calculated on the available axial and tangential curvature data. Stepwise logistic regression analysis was performed to determine the best predictor(s) for the detection of keratoconus. A sensitivity and specificity analysis was performed by using the best predictor of keratoconus. Percent probability of keratoconus was defined as the optimal probability threshold for the detection of disease. For validation, CLMI was calculated retrospectively on a second distinct dataset, acquired on a different topographer, the TMS-1. The validation dataset consisted of 2 scans from 24 eyes of 12 healthy subjects with no ocular history and 4 scans from 21 eyes of 14 subjects with clinically diagnosed keratoconus. Probability of keratoconus was calculated for the validation set from the equation determined from the development dataset.

Results—The strongest significant sole predictor in the stepwise logistic regression was aCLMI, which is CLMI calculated from axial data. Sensitivity and specificity for aCLMI on the development dataset were 92% and 100%, respectively. A complete separation of normals and keratoconics with 100% specificity and 100% sensitivity was achieved by using the validation set.

Conclusions—CLMI provides a robust index that can detect the presence or absence of a keratoconic pattern in corneal topography maps from 2 devices.

INTRODUCTION

Keratoconus is a non inflammatory ectasia of the cornea of unknown etiology, characterized by progressive thinning and conical deformation.¹ Although this corneal degeneration may involve changes in corneal thickness and the posterior corneal surface, the debilitating optical effects are primarily related to distortions in the anterior corneal surface, such as an increase of irregular myopic astigmatism. Because of the unpredictable, progressive nature of keratoconus, refractive surgery, particularly laser in situ keratomileusis, is not recommended. Therefore, it is vital to screen candidates for keratoconus when considering a refractive laser procedure. Presently, slit-lamp biomicroscopy, retinoscopy, keratometry, and corneal topography are all used for detection. Although all of these examinations are useful in diagnosing manifest keratoconus, early detection of forme fruste keratoconus remains

problematic.^{2–7} Tracking the progression of keratoconus is also important because of the unpredictable nature of its clinical course. Currently, there are several topographic indices available, but most indicate only whether or not a keratoconic pattern is detected and not the relative size or location of the cone.^{4–10} In general, these indices are unique to specific topographic devices. In this study, we have limited the analysis to anterior corneal surface features associated with keratoconus, recognizing that most corneal topography systems measure only anterior corneal surface features. Therefore, the purpose of this study is to develop an index that can detect the presence or absence of keratoconic patterns in anterior corneal topography maps of different topographic systems, as well as determine the location and curvature magnitude of the cone, to facilitate monitoring progression of disease.

MATERIALS AND METHODS

Algorithm

The Cone Location and Magnitude Index (CLMI)¹¹ was implemented to extend the capabilities of The Ohio State University Corneal Topography Tool (OSUCTT),¹² which is a software tool for the processing and display of topographic data from multiple topographic machines.¹² The CLMI routine finds the area-corrected average steepest 2-mm-diameter circle (C1) present on the map with center P1(r,Q), by using a search region of the central 8 mm (Fig. 1) of the map, where r represents the radial distance from the center and Q represents angular position. Next, the area-corrected average of all points outside C1 is subtracted from the area-corrected average of all points inside C1, resulting in curvature difference magnitude, M1. Next, the 2-mm-diameter circle (C2) centered at P2 (r, Q + 180 degrees) is analyzed. The area-corrected average of all points outside C2 is subtracted from the area-corrected average of all points inside C2, resulting in curvature difference magnitude, M2. If P1 is outside the central 2.0-mm-diameter region of the map, $CLMI = M1 - M2$; otherwise, $CLMI = M1 - (r/3 M2)$. In simple terms, the software routine finds the steepest area on the map. It compares that area to the rest of the map to determine whether the steepest area represents a cone. The value of the CLMI index and the radial and angular position of the center of the steepest circle, P1, are reported. A schematic illustration of the routine is given in Figure 1. The magnitude of CLMI represents the relative difference of the steepest area from the rest of the map. The curvature magnitude of C1 represents the average curvature of the steepest area. The algorithm is applied to both the axial map, which represents an average or global representation of corneal curvature, and the tangential map, which represents local curvature by spatial location.

Development Dataset

For development purposes, an existing Keratron topographic dataset, consisting of 78 scans from the right eyes of 78 healthy subjects with no history of ocular disease and 25 scans from the right eyes of 25 subjects with clinically diagnosed keratoconus, by using slit-lamp findings, collected by 1 investigator (M.D.T.), was retrospectively analyzed. The keratoconus subjects were identified by first locating records with an ICD-9 diagnosis for keratoconus. To ensure correct selection of patients to the keratoconus category, we elected to include eyes that were clinically diagnosed with the disease by factors other than videokeratography (eg, reduced corneal thickness and biomicroscopic signs such as Fleischer rings and Vogt striae). The scans were exported from the Keratron and processed through the OSUCTT to generate CLMIs on both the axial and tangential curvature maps. The goal was to determine a threshold for separating a keratoconic pattern from a normal one. Examples of the calculation of CLMI, along with the corresponding Keratron map, are given in Figure 2.

Validation Dataset

To validate the threshold values determined with the development dataset, we calculated CLMI retrospectively on a second distinct dataset that was acquired on a different topographer (TMS-1; Tomey Technology, Nagoya, Japan). The validation dataset consisted of 2 scans from 24 eyes of 12 healthy subjects and 4 scans from 21 eyes of 14 subjects with clinically diagnosed keratoconus. The keratoconus subjects were identified from the clinical practice of 1 of the authors (R.G.L.). The validation set represents all available keratoconic data from an archival topographic database acquired by 1 investigator (R.G.L.) on the TMS-1 platform. A clinical diagnosis of keratoconus was established by this investigator by using a combination of corneal thickness and slit-lamp findings (eg, Vogt striae, Fleischer rings, and optical distortions such as distorted ophthalmoscopic and retinoscopic reflexes). Healthy subjects had no history of ocular disease. All data generated by the TMS-1 were exported and processed through the OSUCTT to calculate the CLMI. Multiple scans from the same subject and eye were averaged before analysis, resulting in one mean record for each eye in the sample. We did so to reduce variability and increase reliability of the measurements. For comparison, the Keratoconus Prediction Index (KPI)⁷ was also recorded for each map directly from the TMS-1. KPI is a composite index made up of 8 separate indices that capture patterns of corneal curvature often associated with keratoconus, such as steep central curvature and asymmetric toricity.⁷ The range of possible KPI values is between 0% and 100%. Two maps were excluded because of an error by the TMS-1 that reported KPI values of 235% and 250% for an eye diagnosed as keratoconic. Examples of the calculation of CLMI, along with the corresponding TMS-1 map, are given in Figure 3.

Data Analysis

Stepwise logistic regression analysis was performed on the development dataset to determine the best predictors for the detection of keratoconus. Analysis was done by using SAS (v9.1; SAS Institute, Cary, NC). The following parameters were included in the model: CLMI calculated by using axial data (aCLMI), the radial distance of the center point P1 on the axial map from the map center (a_rad), CLMI calculated by using tangential data (tCLMI), and the radial distance of the center point P1 on the tangential map from the map center (t_rad) (Fig. 1). The entrance and exit criteria were set at $P = 0.05$ for the stepwise logistic regression. A sensitivity and specificity analysis was performed on the development dataset by using the equation generated by the parameter that was the single best predictor of keratoconus. The percent probability of keratoconus (PPK) was defined as the optimal probability threshold for the detection of disease. The PPK was calculated for the validation set from the equation determined from the development dataset. Sensitivity and specificity for CLMI were calculated, as well as the sensitivity and specificity for KPI, both by using the validation dataset.

Disease Severity

Two terms were added as a measure of disease severity, a_C1 and t_C1, which represent the average dioptric value inside the circle, C1, on the axial map and tangential map, respectively. In other words, these terms are an indication of the average curvature of the cone itself, or the curvature magnitude of the cone. They were not used as a part of the initial analysis but were evaluated for possible use as indicators for severity. A stepwise logistic regression was performed on the development dataset to determine which of the disease severity terms was the best predictor of keratoconus: cone curvature magnitude on the axial curvature map or cone curvature magnitude on the tangential curvature maps.

RESULTS

The means, SDs, and 95% confidence limits of the CLMI parameters calculated for both the normal eyes and eyes with keratoconus in the development dataset are given in Tables 1 and 2. The strongest parameter selected as a significant predictor in the stepwise logistic regression was aCLMI. From this analysis, the following equation to calculate the probability level for the presence of a keratoconic pattern (PPK) resulted:

$$PPK = (e^{(-6.4483 + 2.1319 \times aCLMI)}) / (1 + e^{(-6.4483 + 2.1319 \times aCLMI)})$$

The threshold for determining the presence of a keratoconic pattern was chosen to be 0.45 to maximize specificity with high sensitivity, as shown in Table 3. Keratoconus detection is not easily defined as a binary classification task. As a result, the threshold for determining a disease “suspect” was chosen to be PPK=0.20. This suspect range includes PPK values between the lower limit of maximum sensitivity and greater than the value associated with maximum specificity. Two keratoconic subjects were incorrectly classified on the basis of these thresholds: one as normal and one as suspect. These 2 maps are shown in Figure 4. The first incorrectly classified map was due to the uncharacteristic nature of the map pattern, with symmetric circumferential steepening. The second incorrectly classified map represents a suspicious pattern that passed the threshold for “suspect,” but not keratoconus. However, the suspect label would alert the clinician to perform a careful clinical examination. In addition, 3 normals were classified as “suspect.” These 3 maps are shown in Figure 5, demonstrating that all 3 subjects had asymmetric inferior steepening, indicating a suspect.

By using the probability threshold of 45% that was set for keratoconus in the development dataset, we achieved a complete separation of normals and keratoconics with 100% specificity and 100% sensitivity by using the validation set. By using a threshold of 30%, as reported in the literature, KPI had 100% specificity and 85% sensitivity for the validation dataset. Tables 4 and 5 give the means and SDs of aCLMI, a_rad, a_C1, tCLMI, t_rad, and t_C1.

Severity of disease as represented by cone curvature magnitude on the tangential map, t_C1, was found to be a better predictor than a_C1 on the axial map. Therefore, we defined the severity index as the curvature magnitude of the cone on the tangential map, t_C1. Figures 6 and 7 plot the severity term, t_C1, against the screening term, aCLMI, and include the thresholds determined for t_C1 and PPK. When the disease severity term, t_C1, is used in combination with the screening term, aCLMI, the 2 misclassified keratoconic maps from the development dataset are correctly classified as keratoconus, because they are both above the t_C1 threshold for keratoconus.

DISCUSSION

Early in the development of laser-based refractive surgery, there was a recognized need for a sensitive method to detect early or subclinical forme fruste keratoconus. Two reasons are mostly commonly noted. First, tissue removal resulting in thinning of the cornea through a refractive procedure would probably lead to poor outcome because of irregular astigmatism and potentially further thinning, which might lead to progressive ectasia if performed on an unstable surface. Second, it would seem that patients with undiagnosed, as well as those with diagnosed, keratoconus seek out refractive surgery as a means to improve their vision.¹³ Therefore, this need drove the development of videokeratography more than any other single need for the instrumentation. Color-coded maps enable clinicians to absorb a great deal of data in a short time and provide a more sensitive means to identify keratoconus.

Nevertheless, correct interpretation of more subtle cases remains problematic. Clinicians in general, and refractive surgeons in particular, want objective evidence that a topographic map indicates the presence of keratoconus to avoid the rare but serious complication of iatrogenic ectasia. To address this issue, others have developed many detection schemes by using indices calculated from topographic data.^{7,9,13–17} These include relatively simple composite indices from multiple individual indices,⁹ binary decision trees from multiple individual indices,¹⁸ Fourier analyses,¹⁷ and complex neural networks.¹⁴ In general, these techniques are specific to certain topographic platforms and/or only report the presence or absence of a keratoconic pattern. However, a neural network–based approach has recently been reported that allows specific indices to be mapped from 1 topographer to another, as well as classifying other pathologies such as pellucid marginal degeneration.¹⁹

Several attempts have been made to use indices to track disease progression, with varied results. Monitoring disease progression and severity by videokeratography has been studied by several investigators.^{1–20} Maeda et al⁷ have used a composite index to characterize keratoconus into mild, moderate, and severe stages. In addition, Rabinowitz and Rasheed²⁰ have developed a summed composite of 4 indices that rapidly increases in value as disease severity worsens. Both of these are linked to proprietary topography instruments and thus are available only to those who have these specific instruments. Nevertheless, quantitative methods for detecting changes in corneal shape over time is an active area of current research.²¹

The objective of this study was to develop a method for detecting anterior corneal features of keratoconus that quantifies cone location, and curvature magnitude, recognizing that the steepest area may not necessarily be the area of greatest protrusion. To ensure correct assignment of patients to the keratoconus category, we elected to include eyes that were clinically diagnosed with the disease by factors other than videokeratography (eg, reduced corneal thickness and biomicroscopic signs such as Fleischer rings and Vogt striae). Although these criteria help ensure correct classification of disease, it will also bias our sample toward the more advanced spectrum of disease. Future studies are needed to characterize how CLMI performs for other patient categories, such as keratoconus suspects, contact lens warpage, and refractive surgery, as well as other platforms. Nevertheless, we strongly caution against the exclusive use of anterior shape measurements as a diagnostic standard for keratoconus. Rather, this information should be used as 1 of several tools for the possible detection and monitoring of disease, along with clinical judgment.

Although the spatial location of corneal ectasia in keratoconus is often symmetric between fellow eyes, disease severity is usually not.²² Although we do not report any summary statistics of cone location for this sample, using both eyes of the same subject would bias any composite estimate of cone location. Nevertheless, the asymmetric nature of disease severity reduces any correlation in our data with respect to combined sample estimates of the curvature magnitude component from the CLMI index.

By reporting the location of the cone on the tangential map, in addition to other CLMI values, we provide corneal shape information regarding both absolute and relative curvature magnitude. By design, calculation of the CLMI index provides information regarding the relative difference between the “bump,” or region of greatest curvature magnitude, and the surrounding corneal surface. The t_C1 value provides some additional information by reporting the absolute value of curvature magnitude within the steepest zone of the tangential map. The value of t_C1 is a product of both the global corneal curvature and the local regional features identified by C1. Abnormally high corneal curvature is a hallmark of keratoconus and is therefore worth reporting separately.

CLMI provides a robust index that can detect the presence or absence of a keratoconic pattern in anterior corneal topography maps and is independent of a specific platform, because of the nature of the index. In addition, CLMI finds the location and curvature magnitude of the cone present in corneal topographic maps in patients with keratoconus. Therefore, CLMI has the potential to track progression of the disease through the curvature magnitude of the cone.

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Depiction of CLMI – Axial Map

FIGURE 1.

A schematic depiction of CLMI. C1, 2-mm-diameter circle encompassing the steepest region on the map; P1, center of circle C1; r, radial distance of P1 from the center of the map; P2, point 180 degrees from P1; C2, 2-mm-diameter circle centered at P2.

FIGURE 2.

For these topographic maps, the images in the left column are the output display from OSUCTT, with CLMI indicated. The images in the right column are the corresponding output from the Keratron. Top, A normal astigmatic map with the center of the steepest area outside the central 2.00-mm diameter threshold region. Therefore, 2 areas, C1 and C2, are analyzed to calculate CLMI. Bottom, A keratoconic cornea with the cone located centrally. Only the steepest area, C1, is shown because its center is within the central 2.0-mm-diameter threshold region.

FIGURE 3.

FIGURE 2.

For these topographic maps, the images in the left column are the output display from OSUCTT, with CLMI indicated. The images in the right column are the corresponding output from the TMS-1. A, Only the steepest area, C1, is shown because its center is within the central 2.0-mm-diameter threshold region. B, An astigmatic map with the center of the steepest area outside the central 2.00-mm diameter threshold region. Therefore, 2 complete areas, C1 and C2, are analyzed to calculate CLMI. C, A keratoconic cornea with the cone located centrally. D, A keratoconic cornea with the cone located peripherally.

FIGURE 4.

Axial maps for the 2 keratoconic subjects in the development set that were incorrectly classified by CLMI. The steepest areas found by the CLMI routine are shown by the small circles. PPKs were 0% (left) and 23% (right). These subjects were correctly classified with the disease severity index.

FIGURE 5. Axial maps for the 3 healthy subjects in the development set that were classified as “suspect” by CLMI. The steep areas identified by CLMI are shown by the small circles in each map. PPKs were 23% (left), 33% (center), and 42% (right).

FIGURE 6.

The disease severity term, t_C1 , which represents the curvature magnitude of the cone on the tangential map, versus the screening term, $aCLMI$, of the development set. The 3 vertical lines indicate values of PPK calculated from the corresponding $aCLMI$. Values of PPK between 0.2 and 0.45 are defined as the suspect range for keratoconus. Values of PPK .0.45 indicate that a keratoconic pattern is detected. The horizontal line represents the threshold for t_C1 , above which keratoconus is indicated. Two keratoconic subjects were misclassified as normal by $aCLMI$ alone but were detected by the disease severity index.

FIGURE 7.

The disease severity term, t_C1 , which represents the curvature magnitude of the cone on the tangential map, versus the screening term, $aCLMI$, of the validation set. The 3 vertical lines indicate values of PPK, calculated from the corresponding $aCLMI$. Values of PPK between 0.2 and 0.45 are defined as the suspect range for keratoconus. Values of PPK .0.45 indicate that a keratoconic pattern is detected. The horizontal line represents the threshold for t_C1 , above which keratoconus is indicated. $aCLMI$ alone produced 100% sensitivity and 100% specificity on this validation dataset.

TABLE 1

Development Set

Keratoconus				
Variable	Mean	SD	Lower 95% CL	Upper 95% CL
aCLMI	8.66	5.02	6.60	10.74
a_rad	2.09	0.60	1.84	2.33
a_C1	53.73	5.97	51.27	56.20
tCLMI	13.11	7.04	10.20	16.01
t_rad	1.55	0.65	1.28	2.33
t_C1	55.68	6.92	52.83	58.54

The means, SDs, and CLs for the keratoconus subset of the development set. aCLMI, a_rad, and a_C1 are CLMI parameters that were calculated by using axial curvature data. tCLMI, t_rad, and t_C1 are CLMI parameters that were calculated by using tangential curvature data. CL, confidence limit.

TABLE 2

Development Set

Normal				
Variable	Mean	SD	Lower 95% CL	Upper 95% CL
aCLMI	0.95	0.72	0.78	1.11
a_rad	1.77	0.59	1.63	1.90
a_C1	44.76	1.61	44.40	45.12
tCLMI	2.00	1.30	1.71	2.29
t_rad	1.53	0.73	1.37	1.70
t_C1	44.89	1.77	44.49	45.29

The means, SDs, and CLs for the normal subset of the development set. aCLMI, a_rad, and a_C1 are CLMI parameters that were calculated by using axial curvature data. tCLMI, t_rad, and t_C1 are CLMI parameters that were calculated by using tangential curvature data. CL, confidence limit.

TABLE 3

Probability Level of Development Set

Probability Level	Sensitivity	Specificity
0.05	96.00	82.05
0.10	96.00	87.18
0.15	96.00	92.31
0.20	96.00	96.15
0.25	92.00	97.44
0.30	92.00	97.44
0.35	92.00	98.72
0.40	92.00	98.72
0.45	92.00	100.00
0.50	92.00	100.00
0.55	88.00	100.00
0.60	88.00	100.00
0.65	84.00	100.00
0.70	84.00	100.00
0.75	84.00	100.00
0.80	80.00	100.00
0.85	80.00	100.00
0.90	76.00	100.00
0.95	72.00	100.00

Sensitivity/specificity results for the development dataset as a function of probability level threshold. The numbers in bold represent the “suspect” range limits $0.20 < \text{PPK} < 0.45$. The range limits are at maximum sensitivity/high specificity to maximum specificity/high sensitivity.

TABLE 4

Validation Set

Variable	Mean	SD	Keratoconus	
			Lower 95% CL	Upper 95% CL
aCLMI	9.39	3.85	7.64	11.15
a_rad	1.71	0.60	1.44	1.99
a_C1	53.31	3.42	51.75	54.87
tCLMI	13.11	5.23	10.74	15.50
t_rad	1.39	0.76	1.05	1.74
t_C1	54.97	4.71	52.83	57.12

The means, SDs, and CLs for the keratoconus subset of the validation set. aCLMI, a_rad, and a_C1 are CLMI parameters that were calculated by using axial curvature data. tCLMI, t_rad, and t_C1 are CLMI parameters that were calculated by using tangential curvature data. CL, confidence limit.

TABLE 5

Validation Set

Variable	Mean	SD	Normals	
			Lower 95% CL	Upper 95% CL
aCLMI	1.04	0.67	0.76	1.32
a_rad	1.87	0.67	1.66	2.08
a_C1	44.74	1.14	44.39	45.09
tCLMI	2.68	1.48	2.06	3.30
t_rad	1.24	0.81	1.00	1.49
t_C1	44.97	1.50	44.51	45.43

The means, SDs, and CLs for the normal subset of the validation set. aCLMI, a_rad, and a_C1 are CLMI parameters that were calculated by using axial curvature data. tCLMI, t_rad, and t_C1 are CLMI parameters that were calculated by using tangential curvature data. CL, confidence limit.