

New corneal assessment index from the relational thickness and other OCULUS values (CAIRO Index)

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Purpose: The aim of this study was to find indices for keratoconus (KC) detection with higher sensitivity and specificity than the currently available ones with the rotating Scheimpflug imaging (Oculus I, Pentacam) software.

Patients and methods: Data of 103 normal and 73 KC eyes imaged by Oculus I, including slit-lamp examination, refraction, Scheimpflug images, and follow-up data were collected. Logistic regression was done to find new indices with higher area under receiver operating characteristic curves using the currently available ones.

Results: The Corneal Assessment Index from Relational thickness and other OCULUS Values 9 (CAIRO 9) index, deduced from the Ambrosio relational thickness-maximum and the anterior elevation at thinnest point from 9 mm best-fit sphere, and the CAIRO 8, deduced from Ambrosio relational thickness-maximum and anterior elevation at thinnest point from 8 mm best-fit sphere, have a very high area under receiver operating characteristic curves for KC detection (0.997 and 0.995, respectively).

Conclusion: New corneal assessment index is deduced with better sensitivity and specificity for KC detection.

Keywords: keratoconus, pentacam, keratoconus indices, elevation, pachymetry, keratoconus diagnosis

Introduction

The identification of apparently normal corneas that will develop ectasia after laser in situ keratomileusis (LASIK) is a challenge. The detection of the earliest form of subclinical keratoconus (KC) as a major risk factor could be done with corneal topography.¹ Although Placido disk systems are accurate in many cases of KC, there are significant limitations with the curvature map. The area of corneal coverage is limited to about 60% of the corneal surface, eliminating important data for many peripheral or paracentral pathologies. It gives no information about the posterior corneal surfaces. Moreover, the pachymetric maps representing the distribution of corneal thickness cannot be made. Additionally, there is a limitation in attempting to reconstruct the corneal surface based on curvature measurements.^{2,3}

On the other hand, the addition of elevation-based tomography offers important advantages as it can image the posterior corneal surface and produce an accurate full surface pachymetric map. Elevation maps are also more accurate in determining the cone morphology and in identifying the false positive KC suspect,⁴ as early ectatic changes could manifest earlier in the posterior surface of the cornea and therefore, necessitate accurate imaging of both surfaces.⁵

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Tomography-derived pachymetric indices are better in differentiating normal from keratoconic corneas than single-point pachymetric measurements.⁶ One of the most valuable combined indices is the tomographic relational thickness metrics; Ambrosio relational thickness (ART)⁶ which represents the ratios of thinnest point pachymetry and the pachymetry progression index (PPI) values. It had statistically better diagnostic performance than single-point values to identify KC.⁷ Another valuable combined index is the multimetric D index, which had a good specificity. It is reported to be better than other single indices in diagnosing KC and subclinical KC.⁸

It is a common practice to use combined indices to overcome the shortcomings of and get benefit of the strength of single indices. For example, KISA%,⁹ keratoconus prediction index, and keratoconus index,¹⁰ topographic keratoconus grading,¹¹ and even the ART itself.⁶ The aim of this study was to find new combined indices for early KC detection with higher sensitivity and specificity than the currently available with the rotating Scheimpflug imaging (Oculus, Pentacam) software aiming to reach the major goal of decreasing the risk factors for developing post-LASIK ectasia.

Patients and methods

A retrospective study was conducted in the time interval between June 2008 and December 2009 and the data were collected and evaluated. The patients' files were revised again in December 2015 for follow-up visits during this period to confirm the previous diagnosis made at the time of Pentacam scanning and hence to confirm the evaluated results. Patients were imaged by the Pentacam branded as Allegro Oculyzer (WaveLight, GmbH, Erlangen, Germany) with software version 1.16r12 at Al Watany Eye Hospital, Cairo, Egypt. Exclusion criteria included patients with previous ocular surgery, clinically detected corneal pathology other than KC, and contact lens wear during the last 2 weeks.

Patients were classified according to the history, clinical examination, and topographic pattern into 2 groups; Group 1: 103 normal eyes and Group 2: 73 eyes with KC. Group 2 was further divided according to the Topographic Keratoconus Classification (TKC) into 2 subgroups; Group 2a of early KC: 23 eyes (TKC <2 [1 and 1-2]) and Group 2b of established KC: 50 eyes (TKC =2-4).

Every eye was scanned at least thrice by the Allegro Oculyzer. Each scan included 25 Scheimpflug images. Data were collected from the most reliable scan as stated by the "QS" pop-up box (ie, largest analyzed area, valid data percent, and

good alignment). The data were collected from the automatically displayed indices with the default reference surface and on choosing different reference surfaces shape (ie, best-fit toric ellipsoid [BFTE]) and different calculation areas (7, 8, or 9 mm). Elevation values at thinnest point were displayed on mouse click at this point (Figure 1).

Only 1 eye from each patient was selected based on the more reliable scan, as previously described.

Logistic regression was done using the 10 indices with highest area under receiver operating characteristic curves (AUROC) from our previous work¹² to find new indices with higher AUROC. The 10 indices included:

1. Elevation indices:
 1. Elevation of the thinnest point from the 7 mm posterior (PE) best-fit sphere (BFS) (in μm).
 2. Elevation of the thinnest point from the 8 and 9 mm anterior (AE) and posterior (PE) BFS (in μm).
 3. Elevation of the thinnest point from the 7, 8, and 9 mm posterior (PE) BFTE (in μm).
2. Pachymetry indices:
 1. PPI-average and PPI-maximum
 2. ART-average (ART-Avg), and maximum (ART-Max).

The study adhered to the Tenets of the Declaration of Helsinki and was approved by the ethical committee of Watany Research and Development Center, Cairo, Egypt. Patient consent to review their medical records was not required by the ethical committee as this investigation was

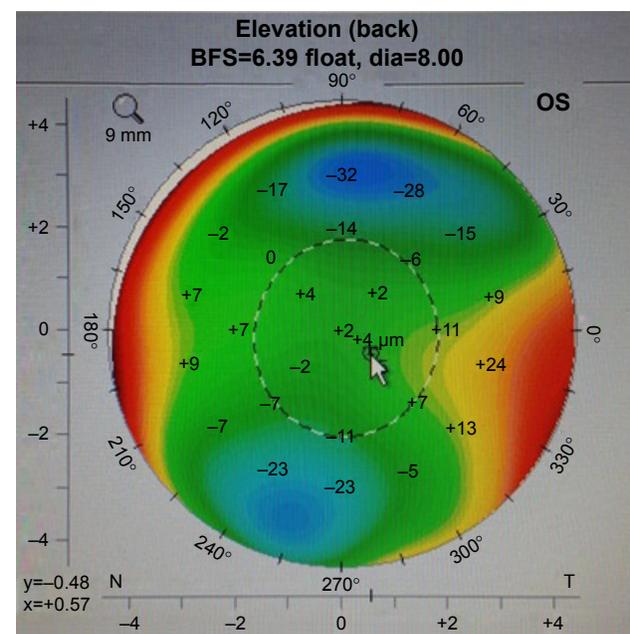


Figure 1 Getting the elevation of the thinnest point on mouse click at this exact point. **Abbreviation:** BFS, best-fit sphere.

part of their routine preoperative evaluation with respect to the patient data confidentiality.

Statistical analysis

Compound indices were calculated using Microsoft Excel 2010 (Redmond, WA, USA). Statistical analyses were done using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium) and IBM SPSS Statistics version 23 (Armonk, NY, USA).

The tests were performed as follows: calculation of the mean, SD, unpaired *t*-test, chi-squared test, sensitivity, and specificity at different cutoff values, and AUROC. Logistic regression was done using the aforementioned 10 indices to find new indices with higher AUROC. Their AUROCs were compared with others using the DeLong et al method.

Results

The patients' average age was 29.2 ± 8.8 (range 17.4–53.2) and 27.8 ± 7.3 years (range 14–44.4) in normal and KC groups, respectively. There was no statistically significant difference between the 2 groups ($P=0.253$). The ratios between right and left eyes were 53:50 and 40:33 in normal and KC groups, respectively ($P=0.777$).

On revising the files in December 2015, no patient's diagnosis was changed. All eyes diagnosed as normal underwent laser refractive surgery and remained with stable postoperative

refraction with no ectatic symptoms or signs. On the other hand, cases diagnosed as KC showed progression unless crosslinked.

Logistic regression using the 10 indices with highest AUROC from our published work¹² resulted in 2 new indices with high AUROC at BFS of 8 and 9 mm diameters; Corneal Assessment Index from Relational thickness and other OCULUS values (CAIRO):

$$\text{CAIRO 8 Index} = 5.0549 + 0.6392 (\text{AE at 8 mm}) - 0.02251 (\text{ART-Max})$$

$$\text{CAIRO 9 Index} = 2.6835 + 0.6492 (\text{AE at 9 mm}) - 0.02134 (\text{ART-Max})$$

CAIRO indices included 1 of the elevation indices, which is AE, and 1 of the pachymetry indices which is ART-Max.

They indicate normal cornea if the value is <0.5 and KC for values ≥ 0.5 . The mean CAIRO 9 was -3.70 ± 2.63 in normal corneas, 6.47 ± 3.92 in early KC, and 29.33 ± 13.3 in established KC. The mean CAIRO 8 was -4.93 ± 2.35 in normal corneas, 4.28 ± 3.72 in early KC, and 23.5 ± 11.34 in established KC. Table 1 presents the AUROC of the new CAIRO indices compared with the 10 indices with highest AUROC published in our previous study.¹²

CAIRO 8 and 9 indices had high sensitivity and specificity. Their AUROCs are statistically superior to most of

Table 1 The indices with highest AUROC

Indices	AUROC	95% CI	Criterion	Sensitivity	Specificity	AUROC compared with that of CAIRO 9 (P)	AUROC compared with that of CAIRO 8 (P)
CAIRO using 9 mm BFS	0.997	0.973–1.0	≥ 0.5	95.89	97.09		0.268
CAIRO using 8 mm BFS	0.995	0.970–1.0	≥ 0.5	93.15	98.06	0.268	
ART-Max	0.987	0.957–0.998	≤ 412	97.26	93.2	0.046	0.087
PPI-Max	0.987	0.958–0.998	> 1.4	91.78	98.06	0.033	0.074
Elevation of the thinnest point from the 9 mm anterior BFS	0.979	0.945–0.995	> 7	95.89	92.23	0.108	0.138
Elevation of the thinnest point from the 8 mm posterior BFS	0.979	0.945–0.995	> 20	86.3	100	0.017	0.024
PPI-Avg	0.978	0.944–0.994	> 1.1	87.67	98.06	0.038	0.049
Elevation of the thinnest point from the 9 mm posterior BFS	0.977	0.942–0.994	> 22	89.04	96.12	0.027	0.04
ART-Avg	0.976	0.942–0.993	≤ 496	94.52	94.17	0.028	0.035
Elevation of the thinnest point from the 7 mm posterior BFS	0.971	0.934–0.990	> 10	87.67	100	0.049	0.061
Elevation of the thinnest point from the 8 mm anterior BFS	0.968	0.930–0.989	> 5	91.78	96.12	0.096	0.099
Elevation of the thinnest point from the 7 mm posterior BFTE	0.953	0.910–0.979	> 10	87.67	99.03	< 0.001	< 0.001

Abbreviations: 95% CI, 95% confidence interval of the AUROC; ART-Avg, Ambrosio's relational thickness average; ART-Max, Ambrosio's relational thickness maximum; AUROC, area under the receiver operating characteristic curve; BFS, best-fit sphere; BFTE, best-fit toric ellipsoid; CAIRO, Corneal Assessment Index from the Relational thickness and other Oculus values using 9 mm BFS (CAIRO 9) and 8 mm BFS (CAIRO 8); P from CAIRO indices, probability of chance that the AUROC of the index is less than that of CAIRO 9 or CAIRO 8 indices; PPI-Avg, pachymetric progression index average; PPI-Max, pachymetric progression index maximum.

Table 2 Fallacies of each index included in the CAIRO indices

	PPI-Max	ART-Max	Elevation of the thinnest point from the 8 mm anterior BFS	Elevation of the thinnest point from the 9 mm anterior BFS	CAIRO 8	CAIRO 9
False diagnosis rate	4.55%	5.11%	6.25%	6.82%	3.98%	3.41%

Abbreviations: ART-Max, Ambrosio relational thickness in maximum meridian; BFS, best-fit sphere; CAIRO, Corneal Assessment Index from Relational thickness and other OCULUS values using 8 mm BFS (CAIRO 8) and 9 mm BFS (CAIRO 9).

the other indices and have the least rate of false diagnosis compared with each index included in the new formulae (Table 2; Figure 2).

The CAIRO indices were obviously statistically superior to some commonly used indices, that is, ART-Avg and posterior elevation of the thinnest point from BFS at 8 mm when trying to differentiate early KC (TKC <2, n=23) from normal corneas (n=103) (Figure 3). However, there was no such significance between their high AUROC when used to differentiate established KC (TKC =2–4, n=50) from normal corneas (Table 3).

Discussion

Elevation-based tomography became the invaluable tool for screening refractive surgery candidates for any risk of developing post-LASIK ectasia. It provides many KC indices with different sensitivity and specificity. Combined indices are sometimes more accurate than simple indices.⁶⁻⁸

In a previous study, we evaluated the diagnostic accuracy (including both sensitivity and specificity) of KC indices with the use of different reference surfaces, at different diameters.¹² The 10 indices with highest AUROC for diagnosing KC included the PPI-Max at a cutoff value of >1.4 and the combined index ART-Max at a cutoff value of ≤412 (0.987 for both). These results were comparable with those of Ambrósio et al⁶ who reported that the most sensitive parameters were the combined indices ART-Avg and ART-Max (AUROC =0.987 and 0.983, respectively). The AUROC of these 10 indices were statistically non-inferior to each other (P>0.05). Meanwhile, all other indices were statistically inferior to at least 1 of these 10 indices. All the 10 indices were pachymetry and elevation indices, with no curvature indices. This matches the results of the previous studies.^{7,13,14}

In the current study, we adopted a subgrouping of the KC group into 2 subgroups, instead of 3 in our previous published

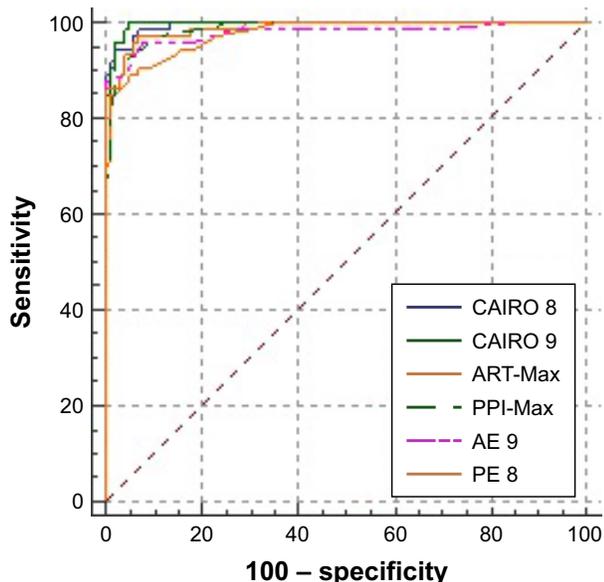


Figure 2 AUROC of CAIRO indices compared with the 4 indices of highest AUROC throughout all cases.

Abbreviations: ART-Max, Ambrosio’s relational thickness maximum; CAIRO, Corneal Assessment Index from the Relational thickness and other Oculus values using 9 mm BFS (CAIRO 9) and 8 mm BFS (CAIRO 8); PPI-max, pachymetric progression index maximum; AE, anterior elevation from 9 mm BFS (AE 9) and 8 mm BFS (AE 8).

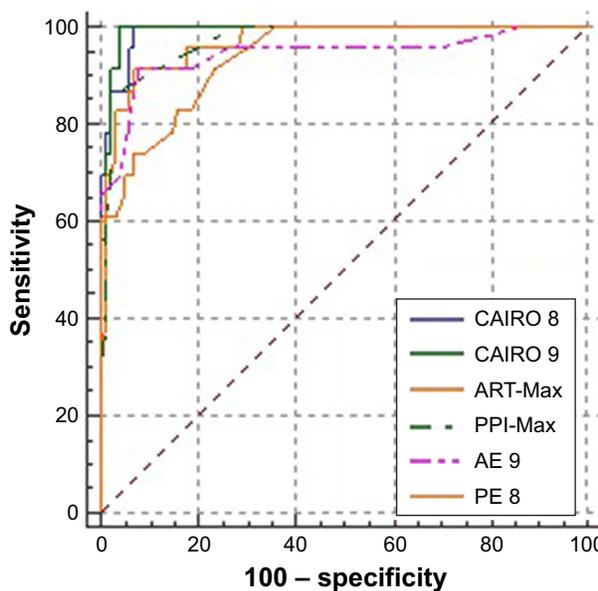


Figure 3 AUROC of CAIRO indices compared with the 4 indices of highest AUROC in differentiating early KC from normal corneas.

Abbreviations: ART-Max, Ambrosio’s relational thickness maximum; AUROC, Area Under Receiver Operating Characteristic curves; CAIRO, Corneal Assessment Index from the Relational thickness and other Oculus values using 9 mm BFS (CAIRO 9) and 8 mm BFS (CAIRO 8); PPI-max, pachymetric progression index maximum; KC, keratoconus; AE, anterior elevation from 9 mm BFS (AE 9) and 8 mm BFS (AE 8).

Table 3 AUROC of CAIRO indices and some of the conventional indices in both normal and each subdivision of KC groups

Indices	TKC <2 (n=23) vs normal (n=103)			TKC 2–4 (n=50) vs normal (n=103)		
	AUROC	P-value when compared with CAIRO 8	P-value when compared with CAIRO 9	AUROC	P-value when compared with CAIRO 8	P-value when compared with CAIRO 9
CAIRO 8	0.989		0.533	0.997		0.341
CAIRO 9	0.992	0.533	–	0.999	0.341	
ART-Avg	0.934	0.028	0.033	0.996	0.651	0.135
ART-Max	0.968	0.072	0.083	0.996	0.609	0.127
Elevation of the thinnest point from the 8 mm anterior BFS	0.937	0.191	0.182	0.982	0.318	0.318
Elevation of the thinnest point from the 8 mm posterior BFS	0.938	0.011	0.012	0.998	0.612	0.359

Abbreviations: ART-Avg, Ambrosio relational thickness average; ART-Max, Ambrosio relational thickness maximum; AUROC, area under the receiver operating characteristic curve; CAIRO, Corneal Assessment Index from the Relational thickness and other Oculus values; TKC, Topographic Keratoconus Classification.

paper,¹² as we found from our previous study that there were limited significant variations in the indices accuracy in already established KC starting from TKC grade 2.

Although single-point values could differentiate between normal and keratoconic corneas, they suffer significant overlap.^{6,9} Many authors tried to overcome the shortcomings of these single-point values through complex systems. Maeda et al¹⁵ presented a classification that detects KC based on the analysis of 8 numerical topographic indices derived from the Placido-based topography. Smolek and Klyce¹⁰ designed a neural network approach that distinguishes KC suspect. Rabinowitz system uses 4 indices⁹ to distinguish normal from KC and provide a range for KC suspect. All these systems were based on complex indices in order to have both good sensitivity and specificity at the same time. However, these systems are solely confined to anterior surface topography, which has many confounding conditions. Recently, few tomographic-combined indices were suggested to overcome these confounding conditions like ART values⁶ and multimetric D values.⁸

This study calculated a new combined index “Corneal Assessment Index from the Relational thickness and other OCULUS values (CAIRO)” at BFS of different diameters (8 and 9 mm) through a regression analysis. This formula combined the index of high sensitivity, ART-Max, with the anterior elevation. The advantages of the new indices are getting highest AUROC (CAIRO 9=0.997 and CAIRO 8=0.995) (Table 1) with least false diagnosis rate 3.41% and 3.98% for CAIRO 9 and CAIRO 8, respectively (Table 2). It combines both pachymetric and elevation parameters and this could be the cause of its higher sensitivity and specificity.

The regression analysis lead to an accurate combined index that included the anterior elevation with the ART-max,

but didn't incorporate the posterior elevation in its formula. This combination has its own specific advantage, as a previous study reported that posterior elevation could be variable with hyperopic individuals and nowadays there is an increasing percentage of hyperopic people asking for refractive surgery.¹⁶

When differentiating between normal and early KC (TKC <2), CAIRO indices were statistically superior to some of the conventional indices as ART-Avg and posterior elevation of the thinnest point from BFS at 8 mm, both are considered of the gold standard indices in screening the refractive surgery candidates.^{6,17} On the other hand, there was no statistical significance in established KC (TKC =2–4).

Limitations of the current study are that it was done only with basic Pentacam model (Allegro Oculyzer I), which is still being used in many centers. Further studies on Pentacam HR are recommended and the validation of these indices on Pentacam HR is ongoing based on Randleman et al¹⁸ report that, for refractive surgical screening, regular and high-resolution Scheimpflug imaging devices generated different objective values and the 2 devices are not interchangeable. It is recommended also to compare the accuracy of CAIRO indices to the new combined biomechanical index, which is based on deformation parameters and corneal thickness profile as it showed high accuracy in differentiating between normal and KC corneas.¹⁹

CAIRO indices will be beneficial in clinical use when the usual indices, including the ART-Max or the D indices, are suspicious or give conflicting results.

Conclusion

Proposed new corneal assessment indices (CASIRO 8 and CAIRO 9) have better sensitivity and specificity for KC

detection than many other gold standard indices, especially in early KC.

Disclosure

The authors report no conflicts of interest in this work.

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