Detecting Subclinical Keratoconus

Advanced detection schemes are necessary to identify the early stages of this disorder.

BY JENS BÜHREN, MD

Corneal topography is the gold standard for the diagnosis of keratoconus (KC). It shows typical patterns associated with the advanced stages of KC that are easy for clinicians to recognize (Figure 1).[1] Detecting the subclinical stage of KC remains a challenge, because patients are typically asymptomatic until the later stages of the disorder. As a result, clinicians often miss subtleties in corneal topography patterns of eyes with subclinical KC.

"Detecting the subclinical stage of KC remains a challenge, because patients are typically asymptomatic until the later stages of the disorder."

IDENTIFYING SENSITIVE AND SPECIFIC METRICS

Since the introduction of corneal topography, numerous attempts have been made to establish automated algorithms for detecting KC. In the technology's early days, the metrics were based almost exclusively on keratometric data.[2-4] Wavefront and pachymetry have also been used to analyze KC. Although aberrometric (whole-eye wavefront) data lack the accuracy to detect early KC,[5] data from a Zernike decomposition of the anterior and posterior corneal surfaces weighted by linear discriminant analysis resulted in highly sensitive and specific metrics that distinguished between normal eyes and those with subclinical KC.[6, 7]

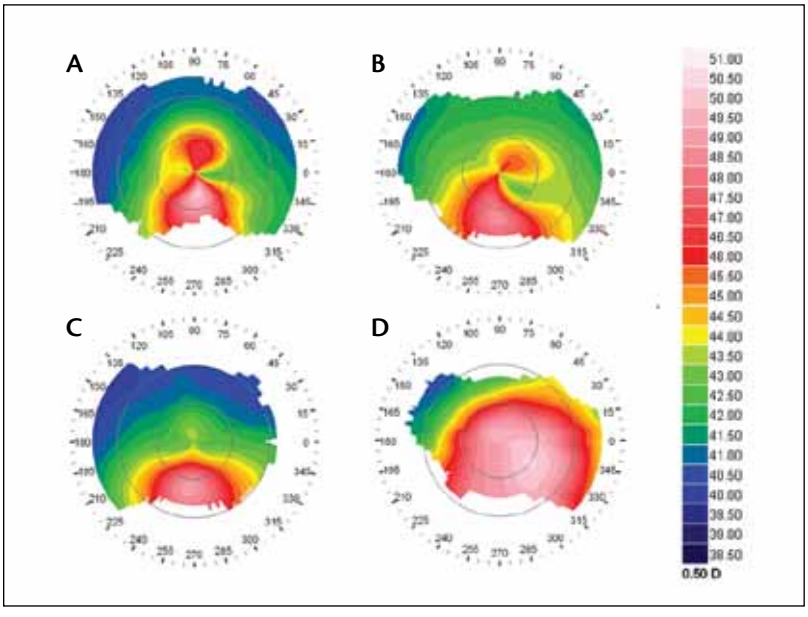

Figure 1. Typical KC in corneal topography: asymmetric centralized bowtie (A), asymmetric centralized bowtie with skewed radial axes (B), inferior steepening (C), and advanced steepening with steep radii (D).

Study Results

My colleagues and I compared the ability of conventional and wavefront-based metrics to detect subclinical KC. Our study included 16 eyes with subclinical KC (ie, the clinically normal fellow eyes of eyes with early KC) and 121 normal eyes. All patients were examined with the Orbscan IIz topography system (Bausch + Lomb). The following metrics, as introduced by Rabinowitz and Rasheed,[4] were computed based on axial-keratometric data: central keratometry (cK), astigmatism (AST), inferior-superior keratometric difference (I-S), skew of the steepest axes index (SRAX), the KISA%

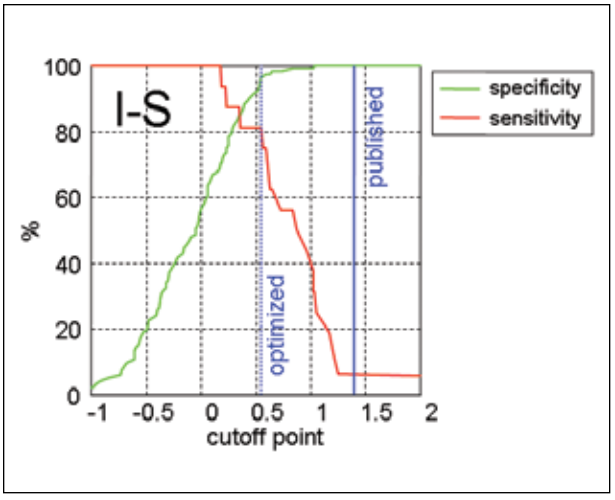

Figure 2. If the critical cut-off value were lowered from 1.40 to 0.55 D (blue lines), 81.3% of eyes with subclinical KC could be detected with a minor reduction in specificity from 100% to 96.7%.

(keratometry, I-S, SRAX, astigmatism) index, and a discriminant function from the KISA% parameters AST, cK, I-S, and SRAX (DKISA). These are referred to as "conventional" metrics hereafter.

We performed a Zernike decomposition of corneal first-surface wavefront (1st-7th order, 6-mm pupillary diameter) and computed corneal vertical coma (C_3^{-1}) and a discriminant function from corneal Zernike coefficients (wavefront metrics). We assessed the ability of the metrics to discriminate between eyes with subclinical KC and normal eyes using receiver operating characteristic (ROC) curves. For conventional metrics, both published and optimized critical (cut-off) values were tested. The optimized value equaled the cut-off value that yielded maximum accuracy for discrimination between the groups.

When we applied the Rabinowitz-McDonnell test (cK > 47.00 D and I-S > 1.40 D), I-S alone (> 1.40 D) and KISA% (logKISA > 1.78) lacked sensitivity. Adjusting critical values using ROC curve analysis improved discriminative ability. When the critical value for I-S was lowered to 0.55 D, sensitivity was 81.3% at a specificity of 96.7% (A_zROC = 0.947; Figure 2). Even after adjustment, cK alone failed to reasonably classify the two groups of eyes (A_zROC = 0.716). The KISA% index had an area under the ROC curve of 0.737, indicating a rather mediocre discriminative ability.

At a critical value of more than 0.84 log units, 87.5% of eyes with subclinical KC were diagnosed correctly, but specificity was only 60.3%. Weighting the KISA% components by discriminant analysis (DKISA) significantly improved discriminative ability (A_zROC = 0.957; sensitivity, 99.2%; specificity, 81.3%). C_3^{-1} was the single metric with the highest discriminative ability (A_zROC = 0.98; sensitivity, 94.1%; specificity, 96.7%). In a recent validation study,[8] we confirmed the critical value of less than -0.2 µm (6-mm pupillary diameter, wavefront mode) obtained from training datasets (A_zROC = 0.87; sensitivity, 68.8%; specificity, 95.6%).

Our results suggest that the construction of discriminant functions allows the combination of different characteristics of corneal shape (as represented by Zernike polynomials and their correspondent coefficients) in a single metric to differentiate between normal eyes and those with subclinical KC. The discriminant function based on corneal first-surface Zernike coefficients showed the highest discriminative ability of all metrics (A_zROC = 0.993) and correctly recognized all eyes with KC (specificity, 93.4%). Sensitivity and specificity of the different metrics compared in the study are displayed in Figure 3. If threshold values such as I-S and KISA% are lowered, for example, the results show that conventional keratometry-based metrics are capable of detecting subclinical KC.

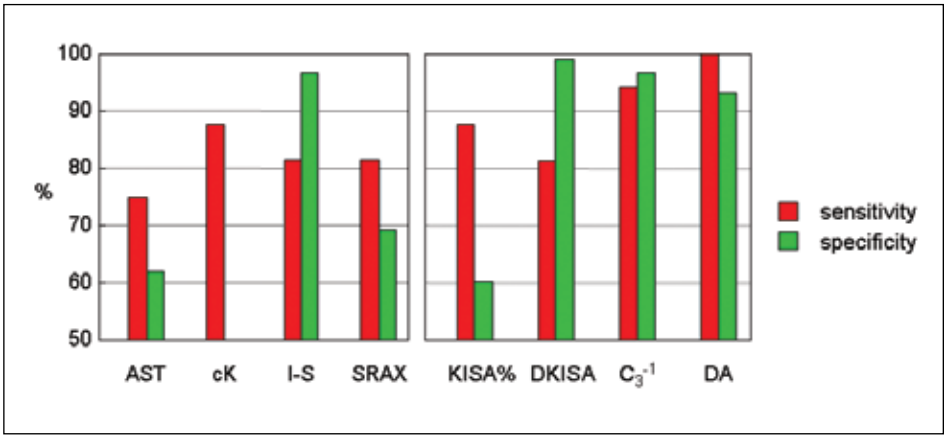

Figure 3. A comparison of optimum sensitivity and specificity of different conventional and wavefront-based metrics for the detection of subclinical KC.

Scheimpflug-based corneal tomography illustrates information about the cornea's anterior and posterior surfaces (topography) and spatially resolved pachymetry data. Numerous studies have shown that these parameters provide valuable information for the detection of early and subclinical KC.[7, 8-10] A discriminant function that was based

TABLE. METRICS FOR DETECTING SUBCLINICAL KERATOCONUS

Metric	A_zROC	Cutoff Value (Keratoconus if …)	Sensitivity (%)	Specificity (%)
I-S value	0.871	> 0.55 D	81.3	96.7
KISA% index	0.870	> 0.84 log units	87.5	60.3
C_3^{-1} (anterior, 6-mm pupillary diameter, wavefront mode)	0.980	≤ -0.2	94.1	96.7

Abbreviations: A_zROC, area under the receiver operating characteristic curve; I-S value, inferior-superior keratometric difference; KISA% index, compound index from central keratometry, I-S value, skew of the steepest radial axes index and keratometric astigmatism; C_3^{-1}, corneal vertical coma.

> "Flexible classification schemes are needed to build an algorithm that detects eyes with subclinical KC and eyes that are at risk for ectasia."

on anterior, posterior, and pachymetry data had the highest discriminative ability of all metrics tested (A_zROC = 1).[7] In a new validation dataset (J.B., unpublished data, 2013), A_zROC was lower with 0.857 (sensitivity, 83.6%; specificity, 92.2%), but still outperformed other metrics.

Advanced Classification Methods Are Needed

On the other hand, the risk of post-LASIK keratectasia cannot be detected by simply applying the same criteria and functions designed to detect subclinical KC. However, if corneal Zernike coefficients were weighted with newly generated discriminant function coefficients, discriminative ability was excellent.[11] These findings show that flexible classification schemes are needed to build an algorithm that detects eyes with subclinical KC and eyes that are at risk for ectasia. A study is currently underway at our institution investigating the application of advanced statistical classification methods to detect both disorders.

A promising approach for detecting subclinical KC are multimodal models that integrate data from the front and back surfaces of the cornea, pachymetry, biomechanical properties, and anthropomorphic data (eg, age, gender, and ethnicity) into a single metric or apply machine learning algorithms that are capable of automatically detecting KC or ectasia risk based on a set of multiple input data.

FOR THE CLINIC

For clinical use, I recommend the I-S value or primary vertical coma. An eye is suspicious for KC if C_3^{-1} is smaller than -0.2 µm (6-mm pupillary diameter and wavefront mode) or if the I-S value is greater than 0.55 D (Table). Eyes afflicted with KC or at risk for ectasia should eventually be evaluated with an approach that includes clinical data and by a physician who has experience with KC. For borderline cases in which the data are not conclusive, a follow-up visit might be helpful, and modern KC detection metrics can facilitate the diagnosis of early KC. ■

Section Editor Kathryn M. Hatch, MD, practices corneal, cataract, and refractive surgery at Talamo Hatch Laser Eye Consultants in Waltham, Massachusetts. She is a clinical faculty member at the Alpert Warren Medical School of Brown University in Providence, Rhode Island. Dr. Hatch may be reached at (781) 890-1023; kmasselam@gmail.com.

Section Editor Colman R. Kraff, MD, is the director of refractive surgery for the Kraff Eye Institute in Chicago.

Jens Bühren, MD, is an associate professor in the Department of Ophthalmology at Goethe University Frankfurt am Main, Department of Ophthalmology, Frankfurt am Main, Germany. Dr. Bühren may be reached at +49 69 6301 6588; buehren@em.uni-frankfurt.de.

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42(4):297-319.
2. Maeda N, Klyce SD, Smolek MK, Thompson HW. Automated keratoconus screening with corneal topography analysis. *Invest Ophthalmol Vis Sci*. 1994;35(6):2749-2757.
3. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. *J Refract Surg*. 1995;11(5):371-379.
4. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. *J Cataract Refract Surg*. 1999;25(10):1327-1335.
5. Bühren J, Kühne C, Kohnen T. Wellenfrontanalyse zur Diagnose des subklinischen Keratokonus. *Ophthalmologe*. 2006;103(9):783-790.
6. Bühren J, Kühne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. *Am J Ophthalmol*. 2007;143(3):381-389.
7. Bühren J, Kook D, Yoon G, Kohnen T. Detection of subclinical keratoconus by using corneal anterior and posterior surface aberrations and thickness spatial profiles. *Invest Ophthalmol Vis Sci*. 2010;51(7):3424-3432.
8. Ambrósio R Jr, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. *J Cataract Refract Surg*. 2006;32(11):1851-1859.
9. Ambrosio R Jr. Percentage thickness increase and absolute difference from thinnest to describe thickness profile. *J Refract Surg*. 2010;26(2):84-86.
10. Ambrosio R Jr, Caiado AL, Guerra FP, et al. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. *J Refract Surg*. 2011;27(10):753-758.
11. Bühren J, Schäffeler T, Kohnen T. Preoperative topographic characteristics of eyes that developed post-LASIK keratectasia. *J Refract Surg*. In press.