10.5005/jp-journals-10025-1007

ORIGINAL ARTICLE

The Challenges of the Detection of Subclinical Keratoconus at Its Earliest Stage

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ABSTRACT

Undetected subclinical keratoconus (KC) is the main risk factor for iatrogenic ectasia. Many parameters have been proposed to help differentiate normal from subclinical KC corneas. Linear discriminant analysis is a technique that models the difference between different classes of data by looking for linear combinations of variables which best explain the data. The association of surfaces elevation, corneal thickness profile and anterior curvature indices leads to the best sensitivity and specificity for the discrimination between normal and early subclinical KC corneas.

Keywords: Keratoconus, Ectasia, Topography, Tomography.

How to cite this article: Gatinel D, Saad A. The Challenges of the Detection of Subclinical Keratoconus at Its Earliest Stage. Int J Keratoco Ectatic Corneal Dis 2012;1(1):36-43.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

The accurate detection of early keratoconus (KC) is a major concern for the refractive surgeon for many reasons. First, iatrogenic ectasia remains the most difficult complication after LASIK and similarity with ectatic corneas (KC or pellucid marginal corneal degeneration) is the main independent risk factor.[1-3] Second, early KC can benefit from new therapeutic modalities that can stop or delay the evolution.[4,5] Finally, the detection of true early KC is essential to avoid rejecting eyes from undergoing surgery as they have been falsely detected as early KC.[6]

Detecting clinical KC can be easily suspected with slit lamp examination and confirmed by corneal topography. The realization of a corneal topography is mandatory before refractive surgery and most clinicians are now aware of the topographical signs of subclinical KC. However, one major difficulty is to detect subclinical KC in its earliest stages.[6-9] Understanding current terminology employed to describe the earliest stages of the KC disease, and developing more appropriate automated detection methods are essential in order to overcome the challenge of subclinical KC detection. Despite the lack of precise taxonomy, the detection of early subclinical KC requires the design of appropriate statistical method and the elaboration of pertinent classes of data.

FACING THE CHALLENGE OF TERMINOLOGY

Several terms have been employed to describe the early stages of KC condition including, keratoconus suspect (KCS) and forme fruste keratoconus (FFKC).

Initially, the term KCS was introduced to describe Placido-based videokeratography that the clinician considered to be at high risk for progression to KC, based solely on subjective impression. Thus, the term KCS was initially reserved for corneas that exhibit some anterior topographically detectable features evocative of subclinical KC. For example, a topographic pattern of an asymmetric bowtie with a skewed radial axis is suggestive of subclinical KC (Fig. 1). These features were first described in a pure qualitative approach by Rabinowitz et al.[10] However, this approach was limited by the smooth transition in topographical phenotypes from normal to suspect and subsequent KC. The use of quantitative videokeratography-derived indices represents a more reproducible way of quantifying KC and its early phenotypes and reduces the complexity of proper classification.[11,12] Subsequently, these authors introduced semi quantitative indices and proposed cutoffs to better identify KCS.

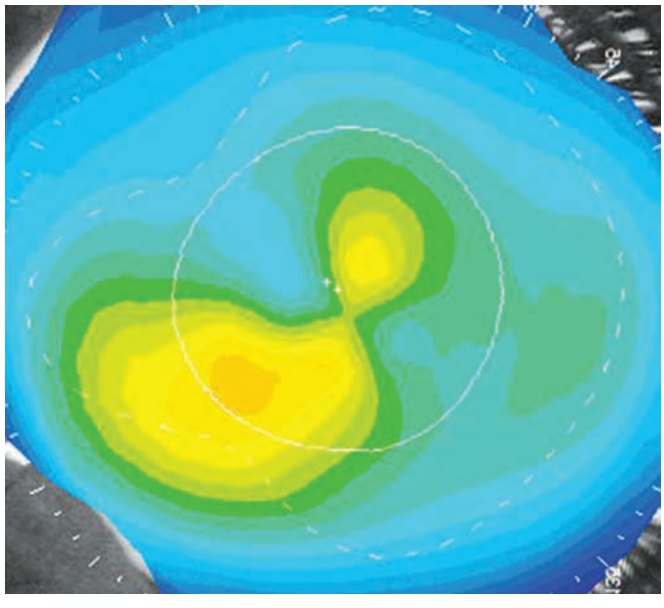


Fig. 1: Placido topography of axial curvature in right eye computed with the OPD-scan (Nidek, Japan) showing an asymmetric bowtie associated to a skewed radial axis

The definition of a form fruste is 'an incomplete, abortive or unusual form of a syndrome or disease'.[13] Klyce[8] has proposed the term FFKC for corneas that may exhibit subtle topographic characteristics suggestive of an early subclinical KC but that are not pronounced enough to reach the threshold of KC suspicion with automated classification. Hence, Klyce's definition of FFKC corresponds to a false negative for KC detection using Placido topography, whereas the term KCS may correspond to a subclinical KC (true positive) or not (false positive) (Fig. 2). These denominations can be confusing and have been employed interchangeably; however, for the refractive surgeons, all of these terms are clearly synonyms of increased risk of post-LASIK ectasia (true positive for KCS and FFKC).

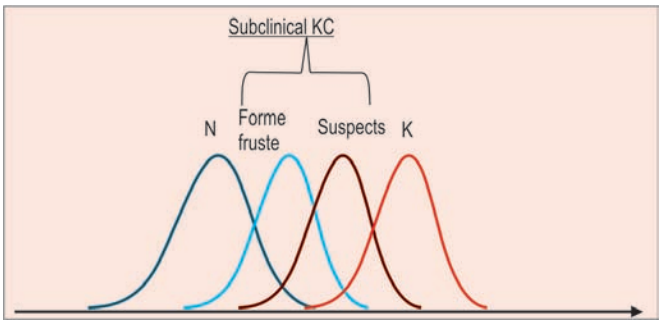


Fig. 2: Schematic representation of the distribution of quantitative variables in the normal (N), forme fruste keratoconus (forme fruste), keratoconus suspects (suspects) and keratoconus (K) eyes. For any quantitative variable, there is significant overlap between these different population. Forme fruste keratoconus and keratoconus suspects belong to the category of subclinical keratoconus

FACING THE CHALLENGE OF AUTOMATED DETECTION

Beyond the lack of consensus on the academic definition of early subclinical KC, this redundant terminology reflects the difficulty of diagnosing the earliest manifestation of KC. Within the proposed terms for labeling early KC, 'subclinical' is certainly the most consensual, as it is related to the stage in the development of a disease before the symptoms are observed, and thus is not detectable by routine clinical tests, such as maximal contrast visual acuity measurements or slit lamp examination. In this paper, we will therefore restrict our terminology to 'subclinical keratoconus', as diagnosing subclinical KC in its earliest form seems to be an important practical goal, beside any semantic debate.

With the current diagnostic tools, the classification of a cornea as normal may not indicate the absence of a subclinical KC (Figs 3 to 5). Thus, the sensitivity of computer assisted Placido-based videokeratotopography is not sufficient. Similarly, an abnormal inferior keratometry

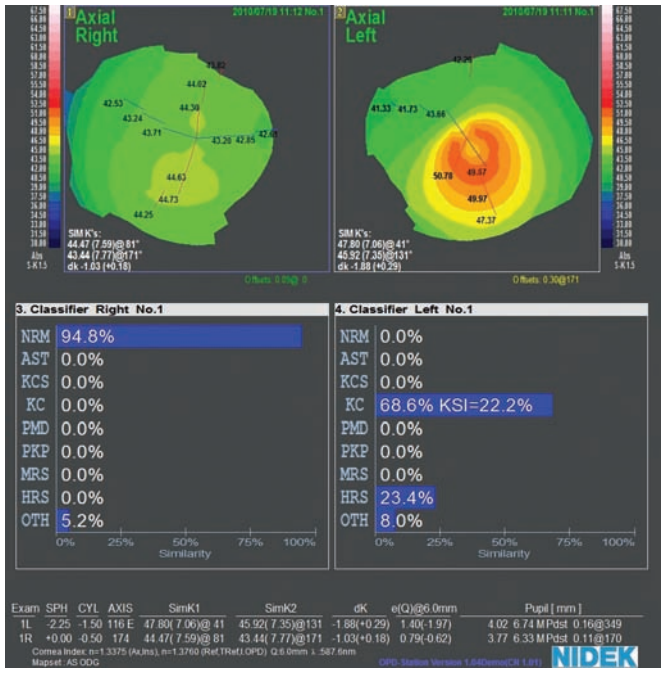


Fig. 3: Example of FFKC according to Klyce's definition:[8] The left eye of this patient presents an evident KC while the right eye is classified as NRM (normal) based on Placido topography analysis. The slight asymmetric bowtie does not reach the cutoff for Placido detection

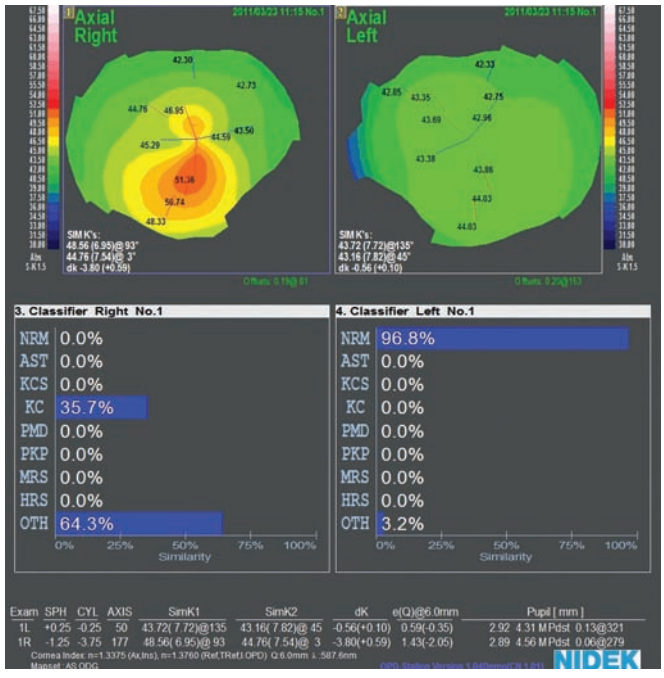
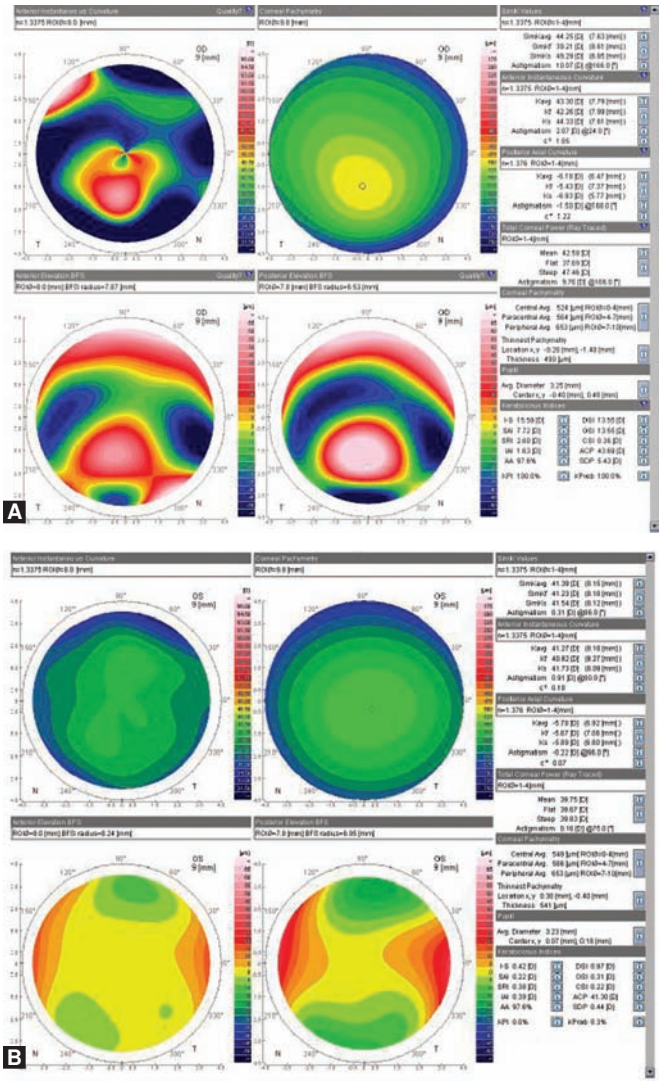


Fig. 4: Example of FFKC: The right eye of this patient presents an evident KC while the left eye is classified as NRM (normal) based on Placido topography analysis

minus superior keratometry (I-S) value as defined by Rabinowitz or a steep keratometry (>47 diopters) may merely represent a false positive, and is not necessarily an indicator of a keratoconic subtype (Figs 6 and 7). Thus, the specificity of Placido topography is not 100%. This lack of accuracy (insufficient sensitivity and specificity) does not



Figs 5A and B: Scheimpflug acquired topography images of a FFKC. The right eye (A) shows a clear KC while the left eye (B) classified as normal with only 0.3% probability of KC

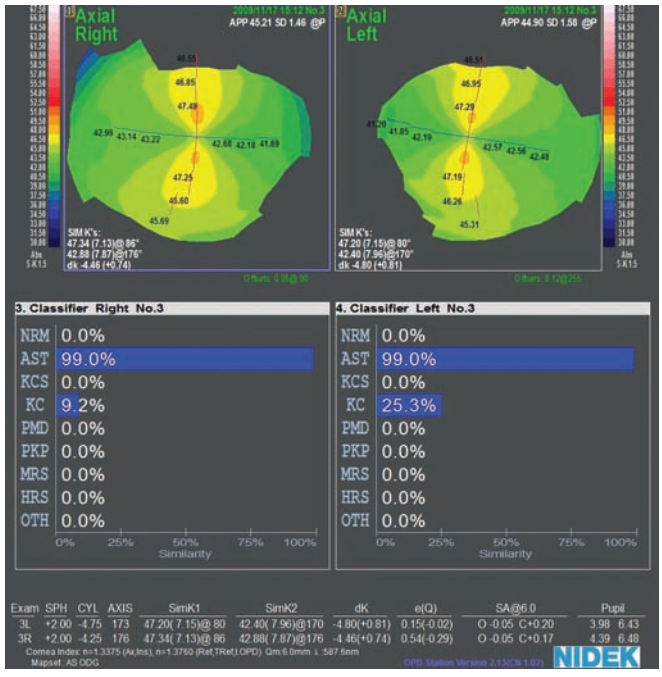


Fig. 6: Placido topography-based neural network (Nidek corneal navigator, Nidek, Japan) classifying these corneas with some degree of similarity to keratoconus because of a steep keratometry

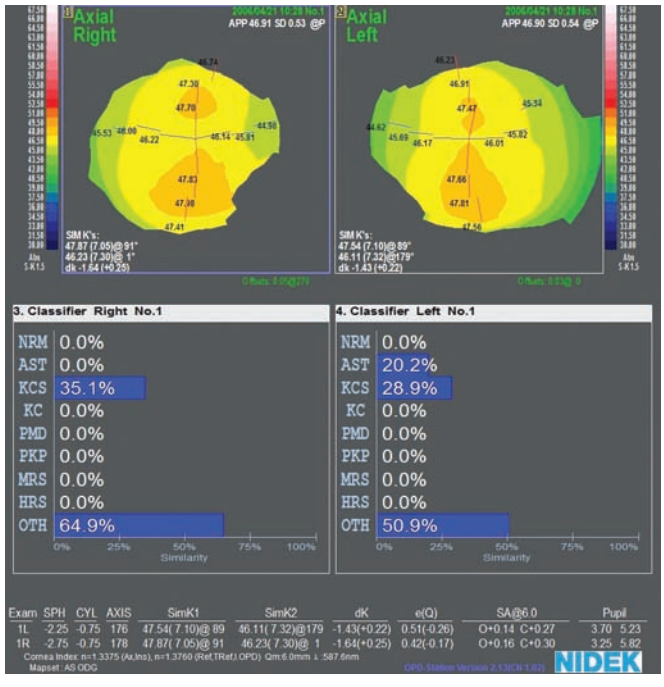


Fig. 7: Placido topography-based neural network (Nidek corneal navigator, Nidek, Japan) classifying these corneas with some degree of similarity to keratoconus suspect because of a steep keratometry associated to a slight asymmetric bowtie

allow this technique to be the gold standard to identify all subclinical KC.[6] The increase in the number of reported post-LASIK ectasias in the early 2000s seems to echo this impression, despite preoperative Placido-based topography screening.

An ideal diagnostic test aims to achieve 100% sensitivity and specificity. However, this is unrealistic in medicine, and a test which sensitivity and specificity are higher than 90% is considered acceptable. The Placido-based topographical diagnosis of subclinical KC relies on various indicators or 'markers', such as the I-S or skewed radial axis (SRAX) values. These markers are time-dependent and may only become pronounced after a certain lag time. Most topographical indexes represent continuous values (i.e. keratometry). They can artificially be made binary by defining a cutoff value, with test results being designated as positive or negative depending on whether the resultant value is higher or lower than the cutoff (i.e. keratometry superior to 47.2 diopters (D) was at one point selected as cutoff for KC detection).[14] After being a pure qualitative marker the asymmetric bowtie became the I-S and was used as a quantitative value to classify a cornea in the subclinical KC category.[10] An I-S between 1.4 and 1.9 diopters was defined as the range to classify an eye as KCS. The I-S threshold was lowered by Smolek et al[14] to reach a higher

sensitivity in the detection of KCS. At the same time, the introduction and the development of elevation based topography allowed clinicians to access new information about the corneal shape: Posterior elevation and continuous (nondiscrete, such as with ultrasound-based techniques) thickness data provided a lot of new quantitative information (corneal spatial profile). Recent studies suggested that the calculation of the change of the progression in meridionally averaged pachymetry from the thinnest point to the periphery could help to diagnose early forms of subclinical KC.[15] Similarly, the possibility of measuring viscoelastic properties of the cornea in clinical practice with the ocular response analyzer opened new paths for better early subclinical KC screening.[7,16-18] The advent of wavefront sensing was also used to investigate wavefront aberrations in keratoconic eyes and evaluate their use for KC screening.[19-21] However, most of the studies were based on a limited series or isolated case reports. In addition, some of the elevation or tomographic criteria were facing the same limitations as anterior curvature in terms of binary classification and cutoff definition with the absence of reported sensitivity and specificity being the major limiting factor for general acceptance. Despite these major advances in corneal investigational techniques, there is still a lack of consensus in the benefit of these techniques over conventional anterior computer-assisted videokeratotopography. Hence, refractive surgeons who stand in the front line of KC detection are often left alone with a simple question: Is it safe to perform LASIK in this eye? Is this eye susceptible to an ectatic outcome after corneal lamellar surgery?

Beside early undetected subclinical KC, some other risks have been identified for post-LASIK ectasia, such as the insufficient residual bed thickness, while some may remain unknown. In particular, recent work using viscoelastic measurements of the cornea suggests that despite large variability there may be corneas that present biomechanical weakness.[7] Further studies are necessary to identify more risk factors for post-LASIK ectasia. However, the proper detection of its major risk factor (undetected subclinical KC) requires specific salient methodology.

Using Appropriate Statistical Model: Linear Discriminant Analysis

Binary classification is the task of classifying the members of a given set of patients into two groups on the basis of whether they have a certain disease or not (the classification property is the disease). Besides medicine, it is used in a wide range of domains including quality control (good or bad product) or search engines result strategy. In the latter, the task is to decide whether a page or an article should be in the result set of a search or not: The relevance of the article will be computed from the presence of certain words in it.

Linear discriminant analysis is a technique which attempts to model the difference between different classes of data. It works when the measurements made on independent variables for each observation are continuous quantities, and looks for linear combinations of variables which best explain the data. Therefore, it is particularly adapted to model the difference between classes of data, such as normal corneas and early subclinical KC. To build such model, it appears crucial to have a set of observations with known class, called the training set. The classification problem is then to find a good predictor for classifying any sample of the same distribution (not necessarily from the training set) given only the topography. In the frame of early subclinical KC detection, the problem of classifying data is of importance, as it must provide pertinent training datasets. This will be addressed in section 2. Within these assumptions, linear discriminant analysis can be used to discriminate between a population of healthy *vs* early keratoconic corneas.

In linear discriminant analysis, a large number of specifically weighted independent quantitative variables can be used to calculate a score. The choice of the variables that participate to the calculation of the score is determined automatically using statistical algorithms. These variables are usually statistically significantly different between the tested populations. However, considered independently, they may not be truly clinically significantly different because of the large overlap between the numerical values obtained in normals and subclinical KC corneas. The included variables need to be normally distributed, but can relate to various features (topography, wavefront, biomechanics, etc.). Hence, they may not be expressed in the same units and eventually, the final score is a single number which contains composite quantitative information that characterizes each observation (i.e. corneal topography). It is important to realize here is that some of the variables that are linearly combined in the calculation of the score have numerical values, which, when considered in isolation, could not reach the same sensitivity and specificity than that of the score, whatever their cutoff value. Using the training set, an optimal cutoff value can be chosen for the score, in order to maximize sensitivity and specificity. For any discriminant test, there is usually a trade-off between the measures: For example, in an airport security setting in which one is testing for potential threats to safety, high sensitivity is more important than specificity. Similar priority arises in the field of early subclinical KC detection.

However, as metal detectors may be set to trigger on low-risk items like belt buckles and keys (low specificity), manual investigation permits confirmation of the nature of the suspect passenger and its items. In early subclinical KC screening, the need of preserving sufficient specificity is important in order not to exclude too many candidates from refractive surgery. This trade-off can be represented graphically as the receiver operating characteristic (ROC) curve which plots the relationship between sensitivity and specificity, as well as the performance of the test.

A resultant binary classification (e.g. normal *vs* abnormal) does not indicate the value in relation to its distance above or below the cutoff. In clinical practice, the numerical value of the score (its 'distance' below or above the determined cut-off value) may provide the clinician with additional information on the status of the analyzed cornea. This could help to analyze the natural progression of the keratoconus disease, and document the effect of new procedures, such as crosslinking in a more comprehensive fashion than when considering single parameters, such as simulated keratometry.

Using Pertinent Training Set

The populations to be separated are normal *vs* early subclinical KC. A set of normal patients can be established by including eyes that were judged normal and underwent LASIK without an ectatic complication, provided that sufficient time elapsed since the time of the surgery.

Constituting a group of eyes with true subclinical KC is more challenging and is at the heart of the problem. Ideally, one should try to collect the first examination maps of eyes with proven KC before the onset of the disease. This may not be feasible, as topography and advanced ocular examinations are usually performed when there is clinical suspicion, and they usually show some advanced stage. Also, collecting the preoperative examinations of eyes that developed post-LASIK ectasia may lead to the constitution of the desired dataset. However, this approach may also be difficult as many cases of post-LASIK ectasia are not reported, or not well-documented preoperatively. In addition, ectatic outcomes due to factors other than undetected subclinical KC, or those in which the diagnosis of subclinical KC was retrospectively obvious, should not be included.

Eventually, we found that eyes with no or low evidence of KC in patients in which the contralateral eyes has true KC currently represents the best approach for the detection of the mildest form of the disease.

Even if only one eye may be affected initially, KC is an asymmetric progressive disorder ultimately affecting both eyes. The incidence of 'true' unilateral KC is very low and its existence controversial.[22,23] Some longitudinal studies showed that if observed for a sufficient period of time signs of KC will develop in the opposite eye.[24] This is coherent as both eyes of unilateral KC have the same genetic makeup, and therefore the least affected eye already is known to have KC,[25] considering that KC is genetically described as a model of autosomal dominant transmission with complete penetrance but incomplete expression.[26] The estimated prevalence of unilateral KC ranges from 14.3 to 41% in several studies where only clinical parameters were considered.[27] In more recent studies, the reported frequencies based on computerized videokeratography diagnosis techniques, ranged from 0.5 to 4%.[28] Noteworthy, in patients with 'unilateral' KC, controlateral eyes with non-detectable evidence of KC using anterior videokeratoscopy should be labeled a forme fruste KC (FFKC), according to Klyce.[8]

Illustration of the Benefit of Linear Discriminant Analysis

In a recent paper,[6] we used linear discriminant analysis to build a model aimed at separating normal corneas from early subclinical KC, which we denominated FFKC in accordance to the definition proposed by Klyce. We used the Orbscan IIz topographer (Technolas Perfect Vision, Germany) to acquire elevation, Placido and tomography data. The normal group was composed of 72 eyes operated by LASIK with 2 years follow-up, without any complication, such as ectasia. These eyes had a score of 99% similarity to normality using a neural network analysis of Placido topography (OPD scan, Nidek, Gamagori, Japan) preoperatively. In addition, data provided by the Orbscan IIz for the normal group did not reveal topography patterns suggestive of KCS, such as focal or inferior steepening of the cornea or central keratometry greater than 47.0 diopters (D). The FFKC group was composed of 40 controlateral eyes of a unilateral KC. The neural network analysis indicated a null score similarity to KCS and KC for the selected eyes and a nonnull score similarity to KC for the controlateral eyes.

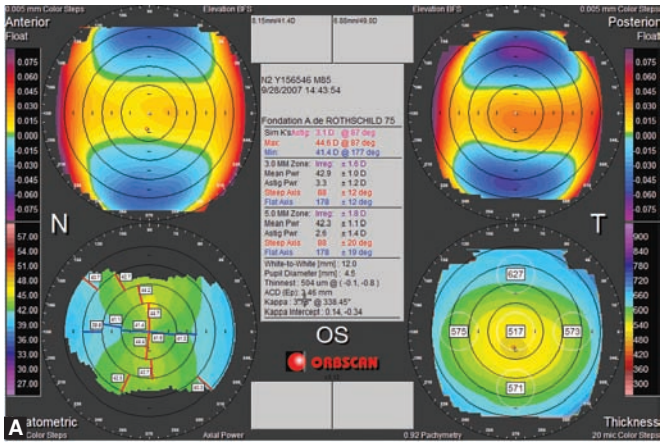
Hence, we had a training set constituted with a group of corneas with no (proven to 4 years of follow-up) risk of ectasia *vs* a group of early subclinical (and 'Placido negative') KC eyes. All the eyes in both groups were classified 'normals' using objective Placido analysis. However, eyes in the group FFKC were presumably at high risk for either spontaneous KC (apparition in the initially less affected eye overtime) or LASIK triggered ectasia (the surgery would certainly further compromise the weak biomechanical status of these corneas).

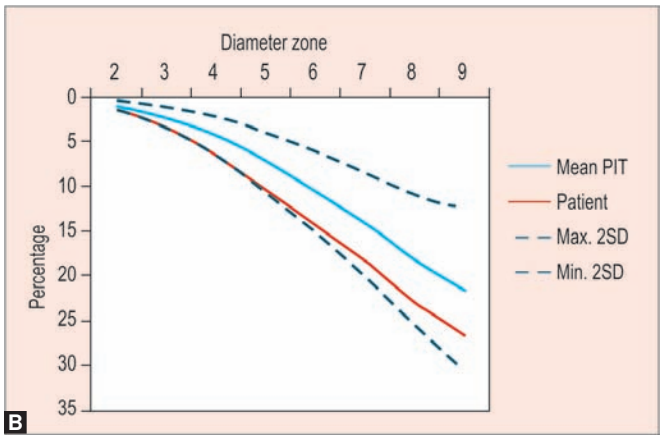
Our results showed that indices generated from corneal thickness and curvature measurements over the entire cornea and calculations of percentage of thickness increase and percentage of anterior and posterior curvature variation from the thinnest point to the periphery obtained with the Orbscan IIz could identify very mild forms of KC undetected by Placido-based neural network (Fig. 8). This approach suggests that the use of elevation and tomography data may allow for better sensitivity and specificity for the detection of early subclinical KC (FFKC) than Placido data alone. The correlation of these results was that using elevation and tomography data alone would not be as sensitive and specific than using all these variables (Placido and elevation derived data) in the same model (Figs 9 and 10).

FUTURE PERSPECTIVES

We hypothesize that applying the same methodology to any other investigational technique, such as corneal biomechanical evaluation or wavefront sensing, may lead to an increase in the specificity and sensitivity of early subclinical detection.

Using these most recent investigational techniques, corneal specialists are making valuable efforts to define a better classification for the KC disease. The existence of eyes that would just disclose posterior elevation and or pachymetric changes, without detectable anterior curvature changes is still debated. Defining early subclinical KC suspicion by the presence of abnormal thinning and posterior elevation is certainly more reflective of the physiopathogeny of the KC disease. However, there may be pertaining problems in trying to draw solid lines between categories





Figs 9A and B: Placido, elevation topography (A) and calculated percentage of modification in thickness (PIT) from the thinnest point to the periphery (B) The PIT appears below the mean of the normal population and based only on this indice, this cornea could wrongly be classified as subclinical keratoconus. However, the anterior and posterior elevations as well as the Placido topography are normal. The associations of placido and spatial profile indices in a discriminant function classify the cornea as normal. This patient underwent LASIK in 2007 without developing ectasia

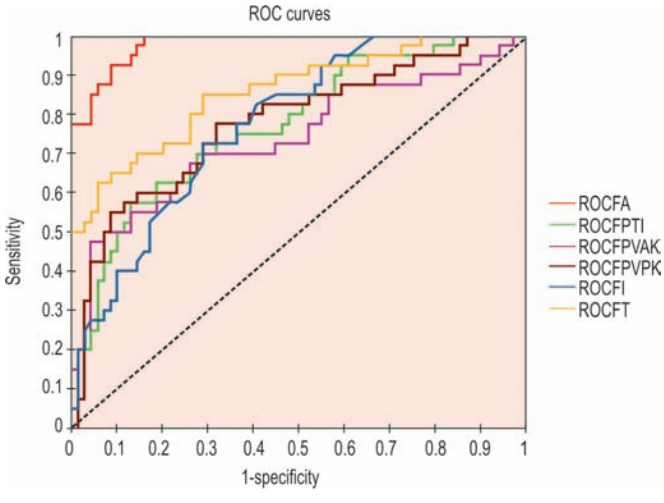
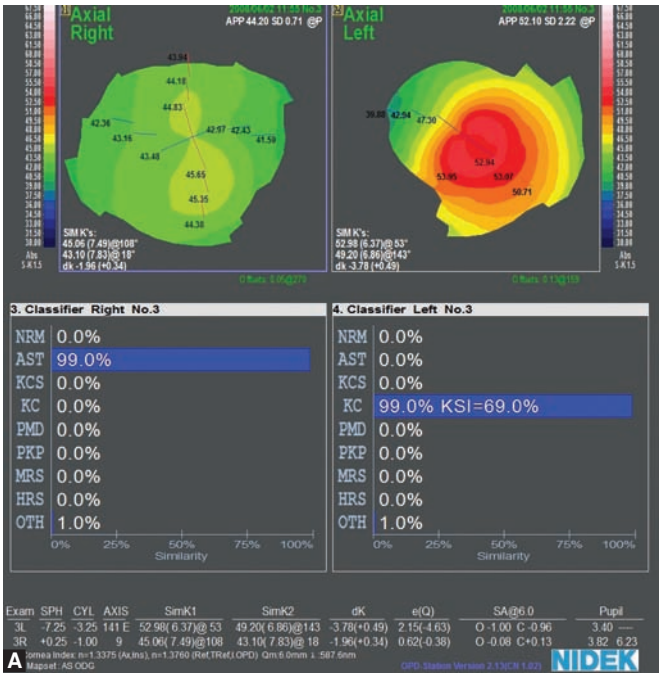
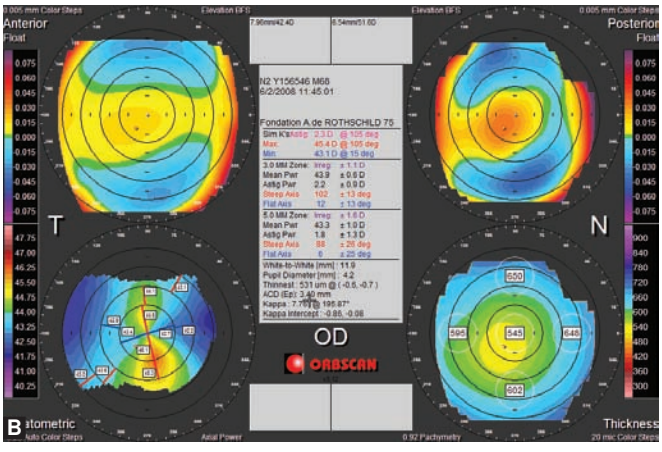


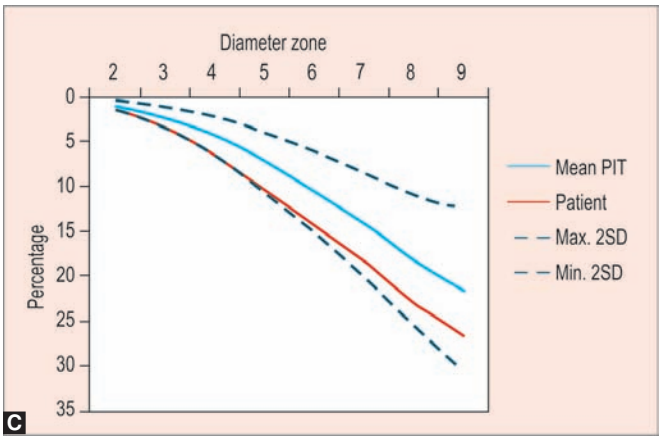
Fig. 8: ROC curves: The association of the corneal spatial profile indices and the Placido indices (FA) leads to the best sensitivity and specificity for the discrimination between normal corneas and FFKC corneas. All other indices alone (FPTI: Corneal spatial profile alone; FPVAK: Anterior curvature alone; FPVPK: Posterior curvature alone; FI: Placido irregularity alone; FT: Thickness indices alone) do not reach enough accuracy

of ectatic corneas, and more importantly, between mild ectatic and normal corneas. This classification suggests that anterior curvature modifications suggestive of KC should only be considered as such when accompanied by tomography and/or posterior elevation changes. Even if pachymetry and posterior surface float are more sensitive and specific in combination than Placido alone, they are not 100% sensitive and specific. In our study, the specificity of pachymetry and posterior float was less than when used in combination with Placido-based indices.

These findings may not be contradicting with the natural history of the KC disease. The cornea being a 'wall', one may postulate that the thinning of it would alter its biomechanical properties further. Any bulge of the corneal wall may incur a shape change that would transmit to the anterior surface and be seen by using a sensitive enough topography technique. We were the first to demonstrate *in vivo* that the corneal epithelial cell layer could change underlying Bowman specular topography,[29] and







Figs 10A to C: Placido (A, B), elevation topography (B) and percentage of modification (PIT) in thickness from the thinnest point to the periphery, (C) based only on the Placido images obtained with the OPD-scan, the right eye of this patient, whose left cornea has obvious keratoconus, is classified as normal (99% astigmatism). However, the PIT curve is distant from the mean of the normal population and the association of the corneal spatial profile indices and the Placido indices in a discriminant function allow the classification of this cornea as 'at risk' for ectasia

Reinstein et al reported data acquired with high speed ultrasound echography which suggest that what is induced by the KC disease may be reduced anteriorly.[30] In our experience, we have noticed that usually, slight Placido abnormalities under N admitted cutoff (e.g. I-S> 1 but <1.4) could raise some suspicion for the presence of early subclinical KC.

CONCLUSION

Trying to distinguish normal from early pathological cases is a common challenge in medicine. Multifactorial diseases are those for which it may be the most difficult to design efficient tests. Techniques, such as linear discriminant analysis, may help to increase the efficiency of screening tests for early subclinical KC identification. They provide sensitivity and specificity for each model. This approach can be extended to any investigational technique providing the acquisition of pertinent quantitative variables and the constitution of adequate datasets. The conjugation and integration of various investigational data in new models will certainly help to increase the sensitivity and specificity of the diagnosis of early subclinical KC.

REFERENCES

1. Binder PS, Trattler WB. Evaluation of a risk factor scoring system for corneal ectasia after LASIK in eyes with normal topography. J Refract Surg 26(4):241-50.
2. Randleman JB, Trattler WB, Stulting RD. Validation of the ectasia risk score system for preoperative laser in situ keratomileusis screening. Am J Ophthalmol 2008;145(5): 813-18.
3. Saad A, Hodge C, Lawless M, Gatinel D. Retrospective testing of a new method for detecting ectasia-susceptible corneas. J Cataract Refract Surg 37(10):1907-08.
4. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: The Siena eye cross study. Am J Ophthalmol 149(4):585-93.
5. Ashar JN, Vadavalli PK. Long-term results of riboflavin ultraviolet-A corneal collagen cross-linking for keratoconus in Italy: The Siena eye cross study. Am J Ophthalmol 150(4):588; author reply-9.
6. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. Invest Ophthalmol Vis Sci 51(11):5546-55.
7. Saad A, Lteif Y, Azan E, Gatinel D. Biomechanical properties of keratoconus suspect eyes. Invest Ophthalmol Vis Sci 51(6):2912-16.
8. Klyce SD. Chasing the suspect: Keratoconus. Br J Ophthalmol 2009;93(7):845-47.
9. Buhren 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 51(7):3424-32.

10. Rabinowitz YS, McDonnell PJ. Computer-assisted corneal topography in keratoconus. Refract Corneal Surg 1989;5(6): 400-08.
11. Rabinowitz YS, Rasheed K. KISA% index: A quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. J Cataract Refract Surg 1999;25(10):1327-35.
12. Klyce SD, Smolek MK, Maeda N. Keratoconus detection with the KISA% method-another view. J Cataract Refract Surg 2000;26(4):472-74.
13. Amsler M. The 'forme fruste' of keratoconus. Wien Klin Wochenschr 1961;73:842-43.
14. Smolek MK, Klyce SD. Current keratoconus detection methods compared with a neural network approach. Invest Ophthalmol Vis Sci 1997;38(11):2290-99.
15. Ambrosio 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):1851-59.
16. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg 2005;31(1):156-62.
17. Shah S, Laiquzzaman M. Comparison of corneal biomechanics in pre and postrefractive surgery and keratoconic eyes by ocular response analyser. Cont Lens Anterior Eye 2009;32(3): 129-32.
18. Touboul D, Benard A, Mahmoud AM, et al. Early biomechanical keratoconus pattern measured with an ocular response analyzer: Curve analysis. J Cataract Refract Surg 37(12):2144-50.
19. Schlegel Z, Lteif Y, Bains HS, Gatinel D. Total, corneal and internal ocular optical aberrations in patients with keratoconus. J Refract Surg 2009;25(10 Suppl):S951-57.
20. Buhren J, Kuhne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. Am J Ophthalmol 2007;143(3):381-89.
21. Alio JL, Shabayek MH. Corneal higher order aberrations: A method to grade keratoconus. J Refract Surg 2006;22(6):539-45.
22. McMonnies CW. The evidentiary significance of case reports: Eye rubbing and keratoconus. Optom Vis Sci 2008;85(4):262-69.
23. Phillips AJ. Can true monocular keratoconus occur? Clin Exp Optom 2003;86(6):399-402.
24. Shirayama-Suzuki M, Amano S, Honda N, et al. Longitudinal analysis of corneal topography in suspected keratoconus. Br J Ophthalmol 2009;93(6):815-19.
25. Wang Y, Rabinowitz YS, Rotter JI, Yang H. Genetic epidemiological study of keratoconus: Evidence for major gene determination. Am J Med Genet 2000;93(5):403-09.
26. Rabinowitz YS, Maumenee IH, Lundergan MK, et al. Molecular genetic analysis in autosomal dominant keratoconus. Cornea 1992;11(4):302-08.
27. Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes in unilateral keratoconus patients. Ophthalmology 2004;111(3):440-46.
28. Wei RH, Zhao SZ, Lim L, Tan DT. Incidence and characteristics of unilateral keratoconus classified on corneal topography. J Refract Surg 27(10):745-51.
29. Gatinel D, Racine L, Hoang-Xuan T. Contribution of the corneal epithelium to anterior corneal topography in patients having myopic photorefractive keratectomy. J Cataract Refract Surg 2007;33(11):1860-65.
30. Reinstein DZ, Gobbe M, Archer TJ, et al. Epithelial, stromal and total corneal thickness in keratoconus: Three-dimensional display with artemis very-high frequency digital ultrasound. J Refract Surg 26(4):259-71.

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