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REVIEW ARTICLE

# Progression in Keratoconus

[1]Paolo Vinciguerra, [2]Raffaele Piscopo, [3]Fabrizio Camesasca, [4]Riccardo Vinciguerra

## ABSTRACT

The study of keratoconus progression was once based upon slit-lamp study, keratometry, and placido disk image examination. Today we have a lot of new corneal devices and indexes wich can help the ophthalmologist to make earlier the diagnosis and also to recognize as much is possible a progressive keratoconus. Only a deep knowledge of the meaning of all these indexes and values, together with the ability to interlock one another, increases reliability in the evaluation of Corneal Ectasia. Some pratical instructions are provided to help the early diagnosis of progressive Keratoconus.

**Keywords:** Corneal tomography, Corneal topography, Ectasia, Keratoconus.

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## INTRODUCTION

In the keratoconic cornea, any nonphysiological modification of the anatomical features can be suspected for ectasia progression.

The study of keratoconus progression was once based only on the analysis of the corneal anatomical features and their possible modifications through slit-lamp, keratometry, and placido disk image examination.

Today the parameters that are commonly examined in order to evaluate whether the keratoconus is progressing are corneal curvature, corneal thickness, anterior and posterior corneal elevations, and refractive modifications.[1]

This study is facilitated by the use and interpretation of a large number of corneal tomographic and topographical indices and maps, each of which is the numeric expression of specific corneal characteristics. Moreover, in many contemporary clinical trials, the criteria to assess keratoconus progression involve one or more of these indices ($K_{max}$ ≥1D increase, $K_{max}$–$K_{min}$ ≥1D increase, $K_{mean}$ ≥0.75D increase, pachymetry ≥2% decrease in central corneal thickness, corneal apex power > 1D increase, manifest refractive spherical equivalent > 0.5d).[2]

[1-3]Eye Center, Humanitas Clinical and Research Center Rozzano, Milan, Italy

[4]Department of Surgical and Morphological Sciences University of Insubria, Circolo Hospital, Varese

**Corresponding Author:** Raffaele Piscopo, Eye Center Humanitas Clinical and Research Center, Rozzano, Milan, Italy Phone +390282244680, e-mail: raffaele.piscopo@humanitas.it

Nevertheless, new examinations methods that are developing today allow us to monitor the ectasia progression also by studying a single corneal layer (epithelial optical coherence tomography (OCT)) or by examining other corneal characteristics (corneal hysteresis).[3-6]

In order to perform a more complete corneal study, several tests are available; each one providing specific information about different characteristics of the examined cornea, and following an ideal order from the more external to the internal corneal area as follows:

- The single epithelial appearance through the epithelial maps
- The corneal biomechanical indices
- The corneal curvature through topographical indices
- The corneal thickness through the tomographical indices
- The anterior and posterior corneal profiles through the anterior and posterior elevation maps.

The challenge that the ophthalmologist faces is to recognize the corneal modifications due to keratoconus progression as early as possible by utilizing these different examinations.

Some practical instructions for understanding and interpreting the aforementioned indexes and for improving the use of some new corneal diagnostic tools will be provided in this article.

## EPITHELIAL MAP INDICES

The new generation of Fourier-domain OCT generates a detailed corneal epithelial thickness map of the 6 mm surrounding the central corneal area (Fig. 1).

Modifications and irregularity in the corneal epithelial thickness map may be an important, early feature of keratoconus progression.[3] The normal epithelial thickness value is about 50 to 55 µm.[4] When the ectasia is ensuing or progressing, epithelial thickness on the cone apex begins to decrease over the keratoconic protrusion.[3]

Use of this device may help in early recognition of initial epithelial thickness modifications already identifiable, while topographic and refractive modifications are not yet pathognomonic (Fig. 2).

## CORNEAL BIOMECHANICAL INDICES

Current clinical instruments, such as topography and tomography, can detect alteration in the shape of the cornea but cannot measure the mechanical stability, which is thought to be the initiating event of the disease.

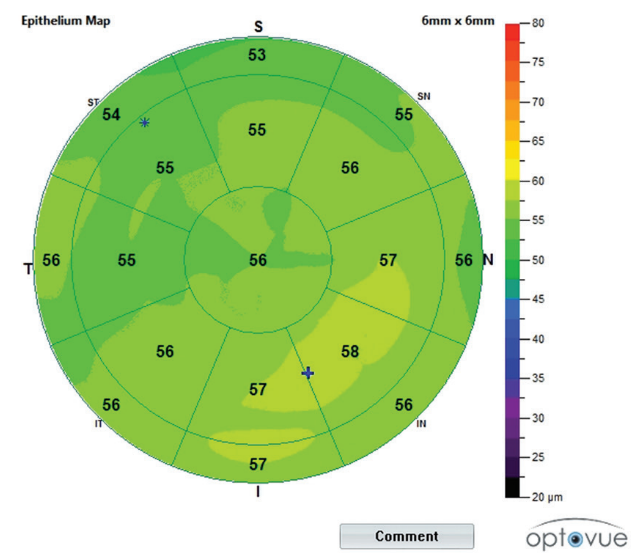



**Fig. 1:** Epithelial thickness map in a normal cornea

A new theory for biomechanical decompensation, based on the existing biomechanical models and clinical topographic and tomographic data,[7] proposed that the initiating event in keratoconus is a focal reduction in biomechanical properties, accompanied by thinning. Based on this theory, it might be therefore possible to diagnose the ectatic disease at a stage where only biomechanical alterations are present.

Therefore, there has been increasing interest in developing instruments to measure the *in vivo* biomechanical properties of the cornea. The first one to be developed was the Ocular Response Analyzer (ORA, Reichert Inc., Depew, NY).[8] The ORA is an adapted noncontact tonometer (NCT) designed first to provide a more accurate measurement of intraocular pressure (IOP) through compensation for corneal biomechanics. It examines corneal behavior during a bidirectional applanation process induced by an air jet,

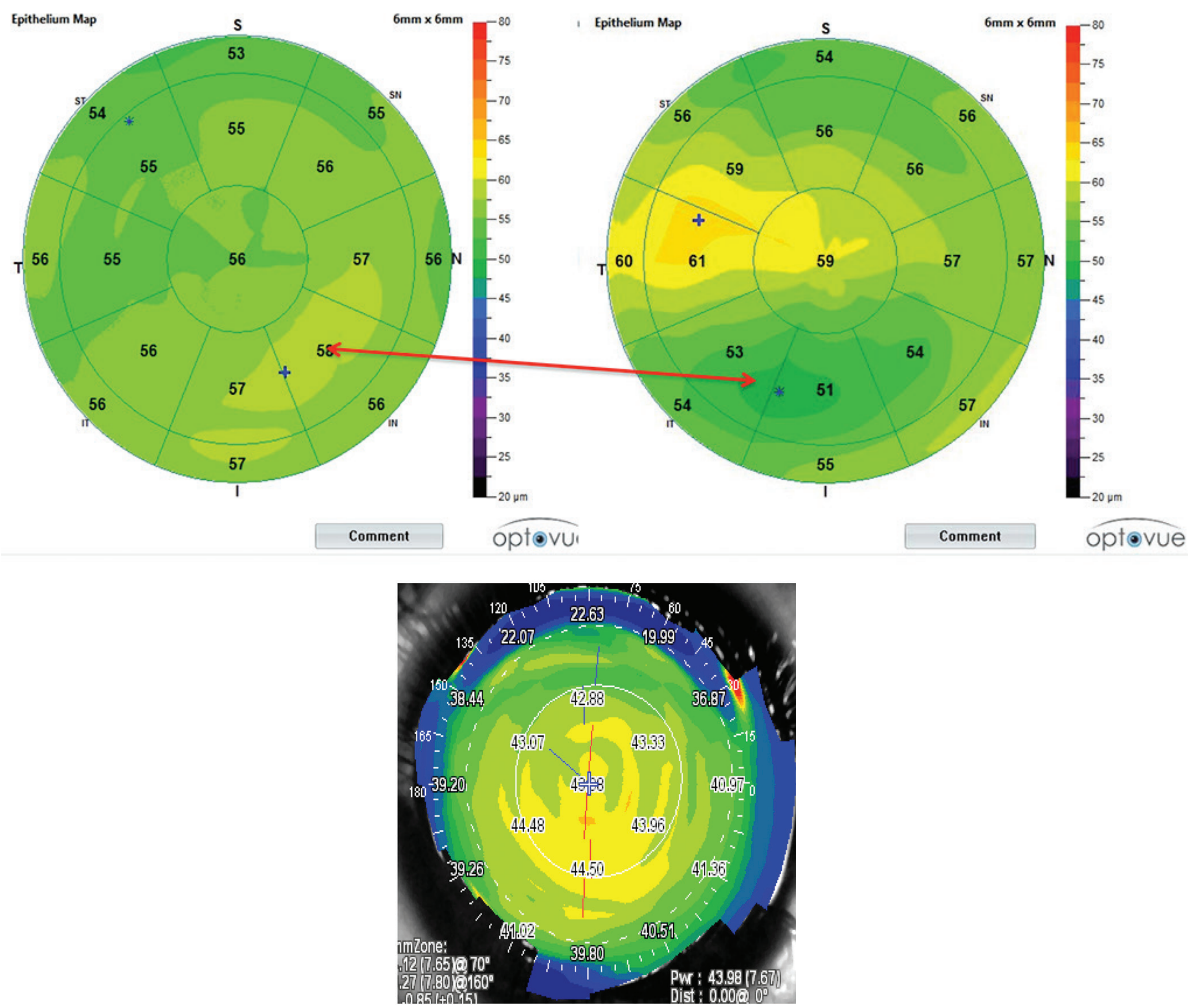



**Fig. 2:** Epithelial thickness modifications in a forme-fruste keratoconus. The conventional topography map of the same eye shows a less clear picture of corneal irregularity

**Fig. 3:** Ultra High-Speed Scheimpflug Technology takes 4.330 frames/sec with 8 mm horizontal coverage. It monitors corneal deformation response to a symmetrically metered air pulse

and produces estimates of corneal hysteresis and corneal resistance factor, along with a set of 36 waveform-derived parameters.[9-11] The most recent version of the device enables the measurement of two new keratoconus-specific parameters: the keratoconus match index (KMI) and the keratoconus match probability (KMP). The capability of ORA to diagnose keratoconus was tested in several articles[11-13] but never reached the gold standard.

The Corvis ST (OCULUS Optikgeräte GmbH; Wetzlar, Germany) was later introduced as an NCT, which monitors the response of the cornea to an air pressure pulse using an ultra-high speed (UHS) Scheimpflug camera (Fig. 3), and uses the captured image sequence to produce estimates of IOP and deformation response parameters.[14]

Several articles have been recently published on the possible applications of the Corvis ST, particularly evaluating possible biomechanical differences in the cornea after undergoing refractive surgery procedures,[15-20] between normal and keratoconic patients[21-24] and after cross-linking.[25]

Those demonstrated that corneal deformation parameters differ between normal eyes and keratoconic eyes,[25,26] especially considering defined parameters such as deformation amplitude (DA), highest concavity, and corneal applanation velocity[5] (Figs 4 and 5).

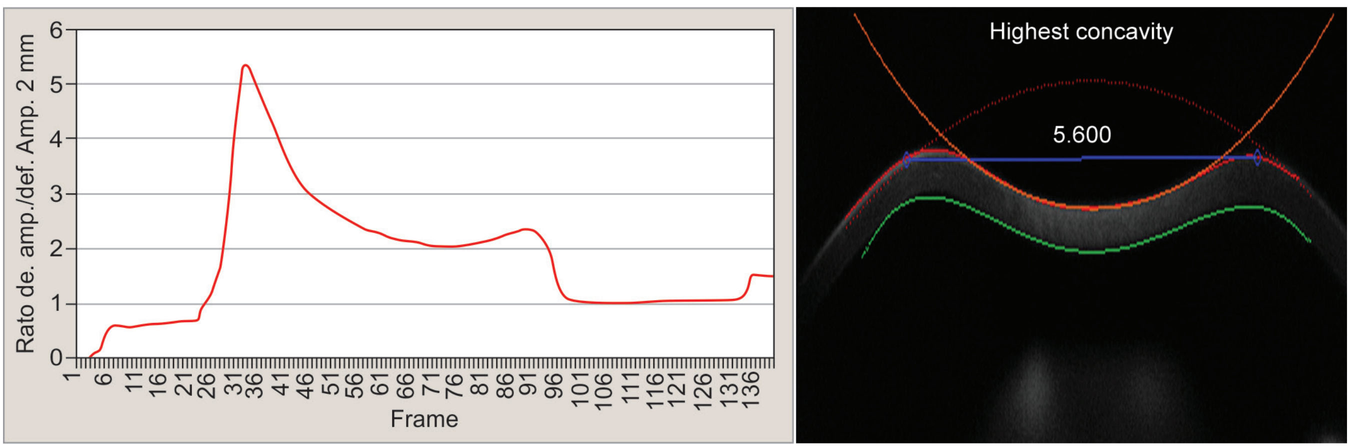



**Fig. 4:** Corvis parameters. CP ratio (central–peripheral deformation): describes the ratio between deformation aplitude at the apex and at 1 mm; DA ratio (deformation aplitude ratio): describes the ratio between deformation amplitude at the apex and at 2 mm

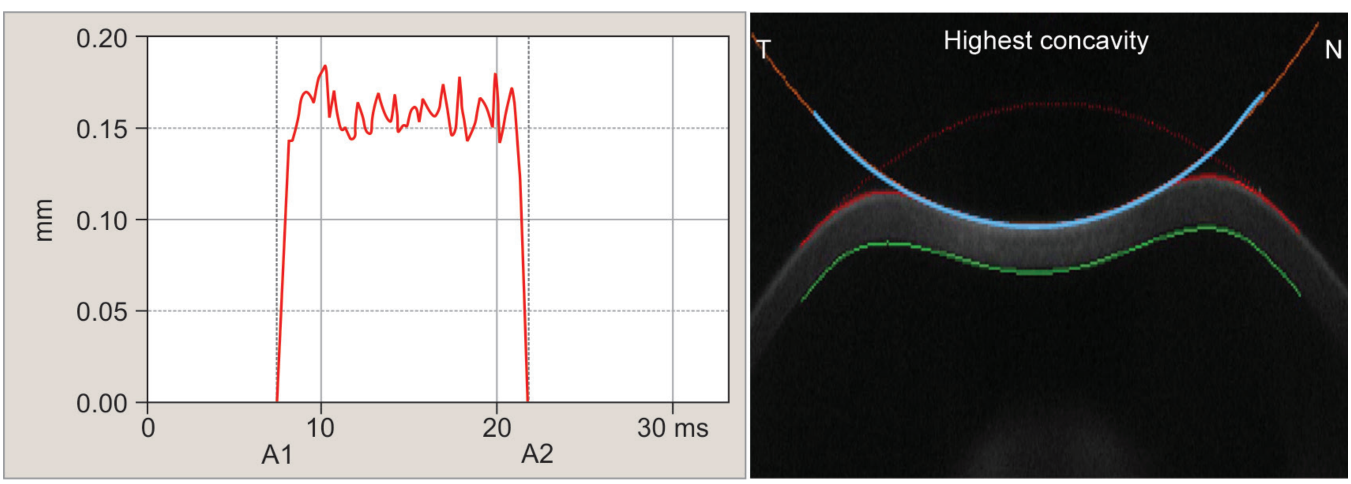



**Fig. 5:** Corvis parameters. ICR (inverse concave radius): the maximal value of the inverse radius of curvature during the concave phase of the deformation (max concave power = max inverse radius)

Corvis can be used in the evaluation of possible keratoconus progression: A deterioration of corneal biomechanics may be revealed with a numerical increase of this set of parameters.

New parameters, such as inverse concave radius (the maximal value of the inverse radius of curvature during the concave phase of the deformation) and deformation amplitude ratio (the ratio between deformation amplitude at the apex and at 2 mm) may increase the sensitivity of this novel instrument.

## TOPOGRAPHICAL INDICES

In corneal topography, the various color map codifications of corneal curvature (altimetric, refractive, tangential) provide an excellent and immediate idea of the corneal curvature and its power distribution, but several different corneal topographical indexes increase sensibility and specificity in the diagnosis of keratoconus.

The numerical index value quantifies in an objective manner several aspects of corneal curvature.

*Differential sector index (DSI)*: The corneal surface is divided into eight areas, and in every area the mean curvature power is calculated. This index quantifies the highest difference in mean power between the highest power area and the lowest power area.

*Surface asymmetry index (SAI)*: Detects alteration of corneal symmetry investigating for curvature differences between two specular areas of the cornea. It represents the asymmetry of instantaneous curvature of the surfaces of the two hemi-meridians opposing along each meridian. In the ideal cornea it is equal to 0. In the case of asymmetry, the mean instantaneous curvature of the flatter hemisphere is colored blue, while the most curved is red, while the SAI indicates the difference between the two. The normal value in the ideal spherotoric surface ranges from 0.10 to 0.42; if this number increases, then the visual acuity and its quality worsen.

*Irregular astigmatism index (IAI)*: Reports the average inter-ring variation in power along semi-meridians, normal values range between 0.19 and 0.49.

*Opposite sector index (OSI)*: The entire corneal surface is divided into eight areas, the mean power of each area is calculated and the index quantifies the maximum difference from the opposite area.

*Center-surrounded index (CSI)*: It represents the difference between two rings: The 3 mm central diameter and the near ring until 6 mm diameter.

*Corneal eccentricity index (CEI)*: This value is positive for a prolate surface and negative for an oblate surface.

*Symmetry vertical index (SI)*: Symmetry vertical index is calculated by measuring the mean curvature power of two 3 mm zones: one on the superior and the other on the inferior corneal hemisphere.

*Surface regularity index (SRI)*: It is calculated by confronting the variation in curvature among several points near the 10 central rings. Values superior to 1.5 diopters underscore irregularity in the optical zone.

Progression of keratoconus can be detected and demonstrated by observing the increase of one or more of these indices in successive examinations taken at different times. Often, modifications in these indexes are synchronous with modifications in refraction (Fig. 6).

Also the modern devices utilizing a Scheimpflug camera can provide several topographic indexes, calculated on the basis of a tridimensional model from as many as 250,000 elevation points.

This type of measurement ensures high precision, because the observer, recorder, and recorded planes are not on the same axis, in order to provide a tridimensional image with great accuracy.

The Ambrosio indices are eight very sensitive values designed to disclose the development of keratoconus. Every index investigates in a peculiar manner the corneal anterior surface.

- *Index surface variance (ISV)*: This index is elevated in all types of corneal surface irregularity (astigmatism, warpage, keratoconus, etc.), and expresses the deviation of individual corneal radii from the mean value.
- *Index of vertical asymmetry (IVA)*: this index is elevated in case of oblique astigmatism, in keratoconus or ectasia. It provides the degree of symmetry of the corneal radii with respect to horizontal meridian when taken as an axis of reflection.
- *KC index (KI)*: this value is elevated in keratoconus.
- *Center keratoconus index (CKI)*: Center keratoconus index increases with severity of central keratoconus.
- *Index of height asymmetry (IHA)*: Analogous to IVA, this index calculates the symmetry of height data and thus is more sensitive.
- *Index of height decentration (IHD)*: This index provides the degree of vertical decentration, and is elevated in keratoconus.
- *Radius min:* Minimum sagittal curvature in the 8-mm zone.
- *Topographical keratoconus classification (TKC)*: Topographical keratoconus classification is based only on anterior corneal data.

The software reports and compares the measured values with the mean and standard deviation values of

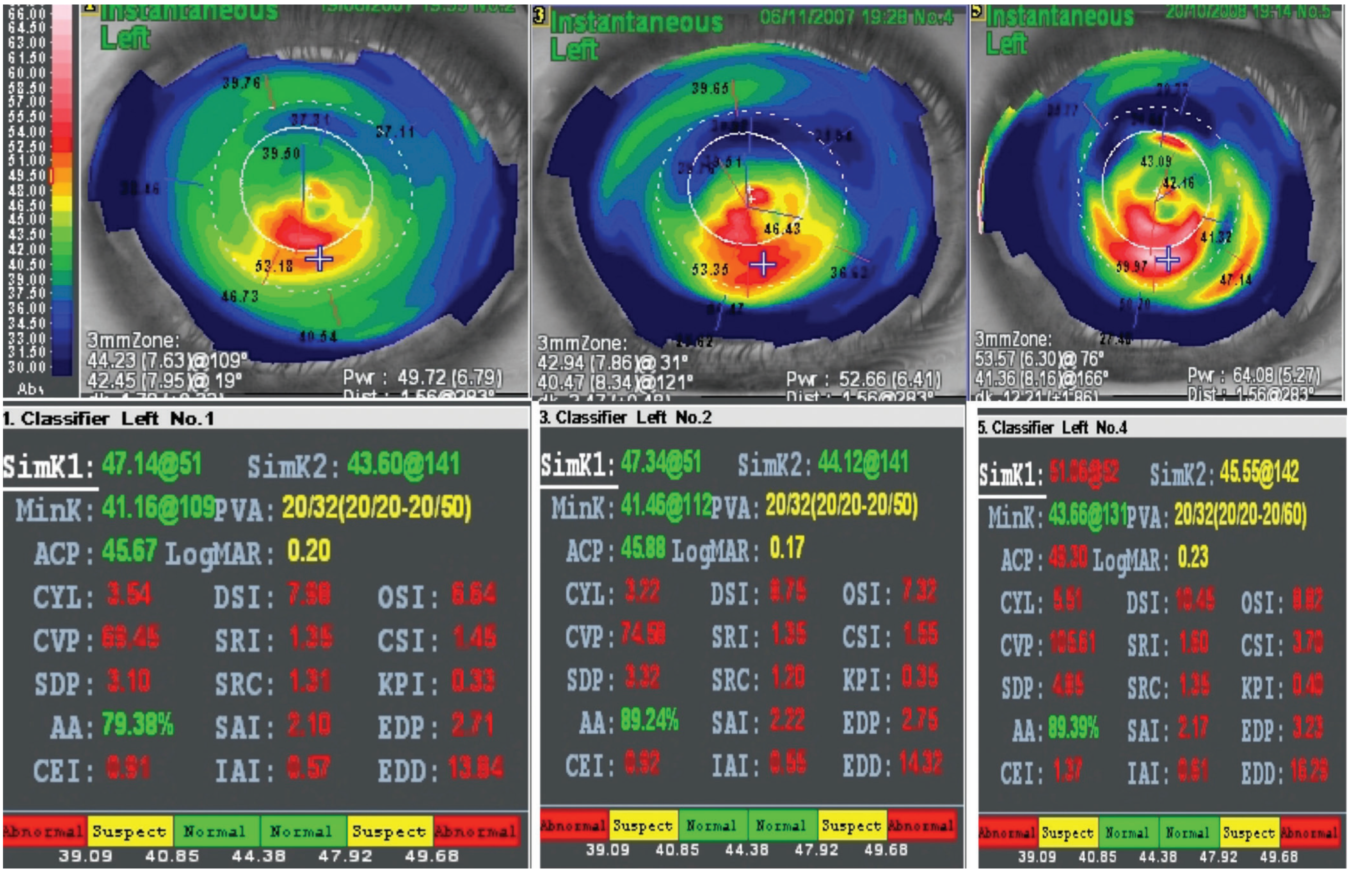



**Fig. 6:** Keratoconus progression observed in the instantaneous map and topographical index: CEI, SAI, IAI, Keratoconus prediction index (KPI) show a variation in three different topography in the same patient. Note that the visual acuity decreases only at a late stage. CEI: Corneal eccentricity index; SAI: Surface asymmetry index; IAI: Irregular astigmatism index

a normal population. The color reported in the number boxes immediately highlights the differences from the normality (yellow for more than 2.5/exceeding deviation standard: abnormal value; red for more than 3.0/exceeding deviation standard: Pathological value (Fig. 7)).

Once again, these indices provide an excellent monitoring system; every minimum increase in one or more of these values magnifies a possible corneal modification or keratoconus progression. Nevertheless, it is important to remember that the whole assessment is based entirely on anterior corneal surface topography.

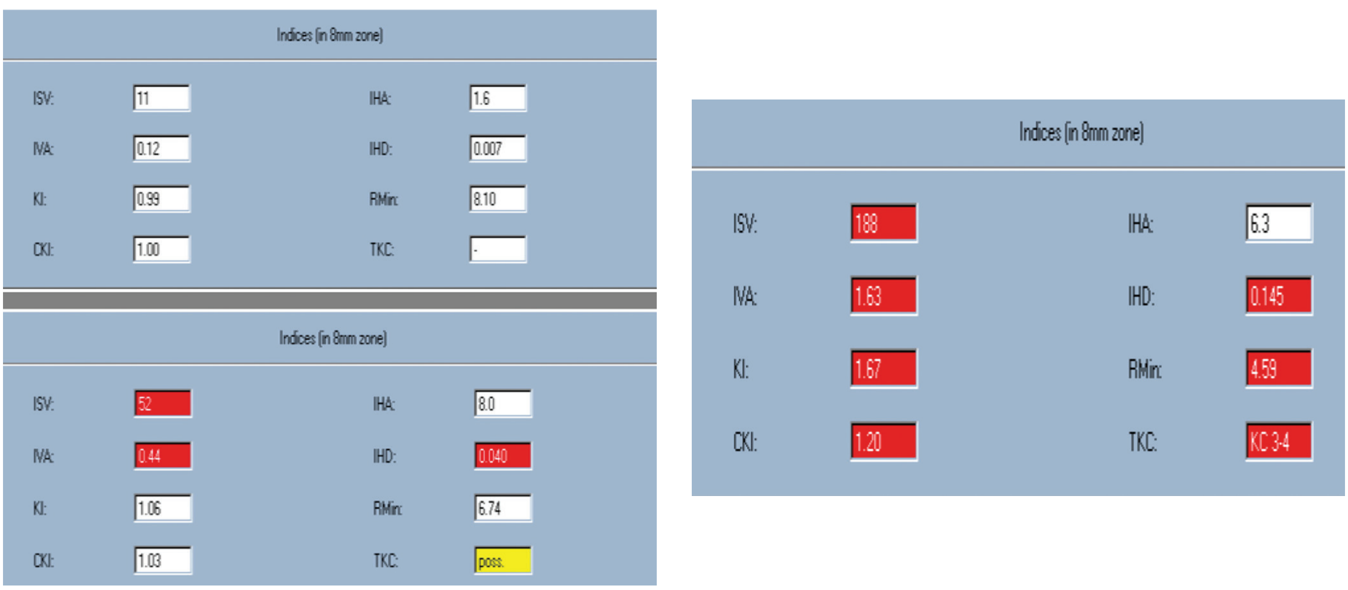



**Fig. 7:** Progression evidenced by Ambrosio indices increasing in three consecutive examinations in a suspect keratoconus

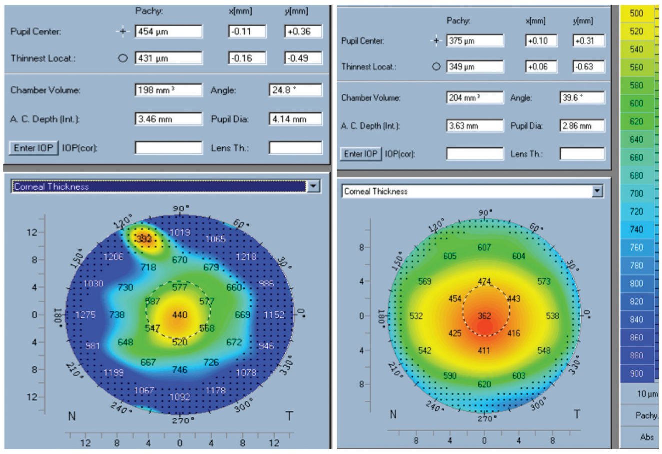


**Fig. 8:** Two different pachymetric patterns of two different patients

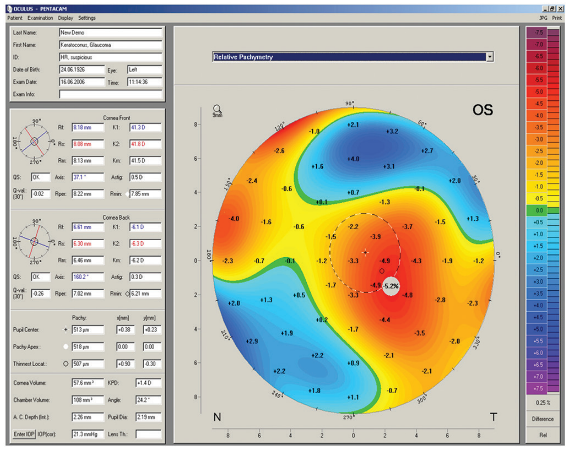



**Fig. 9:** This relative pachimetry map shows abnormal distribution of pachymetric values

## TOMOGRAPHICAL INDICES

### Pachymetric

The modern Scheimpflug cameras and anterior OCT perform manifold point pachymetry with high precision (Fig. 8). Any point can be selected and evaluated individually in different subsequent examinations with a differential map. A progression in keratoconus can be easily detected digitally comparing two pachymetric maps.

### Relative Pachimetry and Corneal Thickness Spatial Pachymetric Profile

With the modern tomographer, it is possible to compare the thickness of various corneal points with normal expected values, then show for each point the percentage of difference. This is determined by the difference in microns of height with that specific point features when compared to normality (relative pachymetry) (Fig. 9).

The pachymetric map shows physiological variability in thickness distribution (>520–540 µ), with concentric morphology around the thinnest point. Thickness increase from center to periphery is evaluated by the corneal thickness spatial profile (CTSP) diagram, where the *x*-axis represents the increase in thickness from the corneal center (left) to the corneal periphery (right), while the *y*-axis shows the pachymetry values in µm (Fig. 10).

The percentage of increase of thickness (PIT) diagram shows the averages of thickness values of the points on imaginary circles centered on the thickness point with increased diameters from 0.4 to 8.8 mm.

In this case, the *y*-axis represents the percentage of corneal points showing thickness progression.

Keratoconic eyes usually show thinner corneas (highlighted in the pachymetric and relative pachymetric indices) with less corneal volume. Also, CTSP and

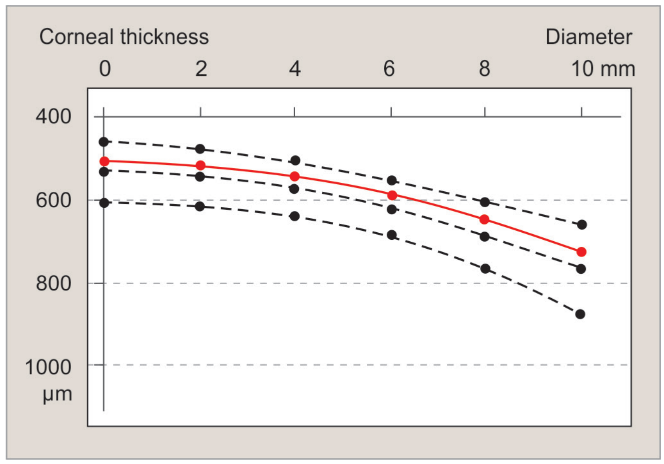



**Fig. 10:** Corneal thickness spatial profile. In this graphical representation, a central broken line indicates the change in thickness in a normal cornea and two broken lines above and below indicate ±2 to the SD respectively. In a normal cornea, the pachymetry gradient (red line) should be parallel to one of the broken lines

Percentage thickness increase (PIT) of keratoconic eyes show difference from normality: in the case of ectasia, the pachymetry gradient curve shows a faster and more abrupt increase from the thinnest point (TP) toward the periphery, when compared to normal corneas (Fig. 11).

If a progression is suspected, pachymetry, relative pachymetry, and pachimetric diagrams can be easily and objectively compared in subsequent examinations. Nevertheless, they have to be considered and interlocked: as you see in Figure 12, the single pachymetry map apparently shows a more serious thickness reduction in Patient A, while, comparing to pachymetric diagram and relative pachymetry, the ectasia is more considerable in patient B, whose pachymetry map is less dramatic.

## ELEVATION INDICES

The elevation-based topography map offers important advantages compared to Placido-based devices: The latter

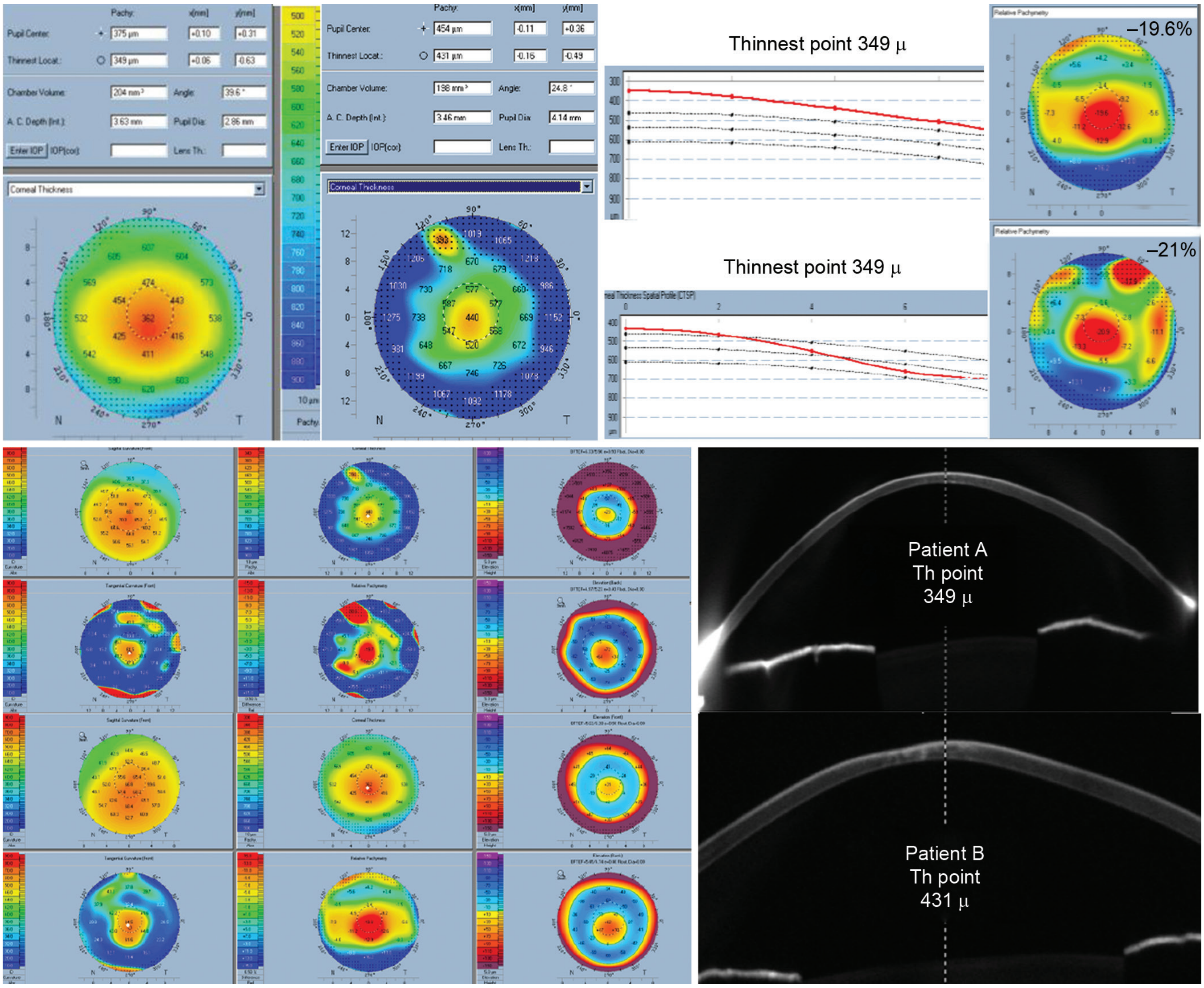



**Fig. 11:** Thickness is not always determinant! Here the most severe case (Patient B) has a higher minimal pachymetry value

systems are limited to providing information only about the anterior corneal surface.

In keratoconus, the posterior corneal curvature is also modified and early morphological changes may develop on the posterior surface.[27]

Elevation data from both the anterior and posterior corneal surfaces are provided by elevation maps; such maps show the distribution of the differences in elevation between a reference sphere and the corneal anterior and posterior surfaces examined. The peaks from the reference sphere are warm-colored, whereas the depressions from the reference sphere are cold-colored (Fig. 12).

## Belin Enhanced Ectasia

It is a comprehensive display that combines corneal anterior and posterior differences in elevation (from an ideal reference surface, spherical – Best Fit Sphere (BFS) – or toric ellipsoid (BFTE)) as well as an evaluation of the pachymetric distribution. The enhancement of ectasic variation in elevation is obtained, excluding a 4-mm circle around the thinnest spot from the BFS fit. With respect to the standard BSF, the new obtained BSF (enhanced BFS) is more similar to the peripheral area of the examined cornea and more regular than the excluded zone so as to enhance elevation differences from the expected values.

The maps on the left side of the display report the deviation from normality of corneal anterior and posterior elevations, calculated in relation to BSF and enhanced BSF values. Next are shown the pachymetric distribution and vertical displacement of the thinnest point in relation to the apex (Fig. 12).

Several studies demonstrated that a simultaneous evaluation of the elevation and pachymetric data is a highly sensitive method for the early detection of keratoconus.[28,29]

These data show a progressing decrease in thickness and increase in elevation in keratoconic progression.

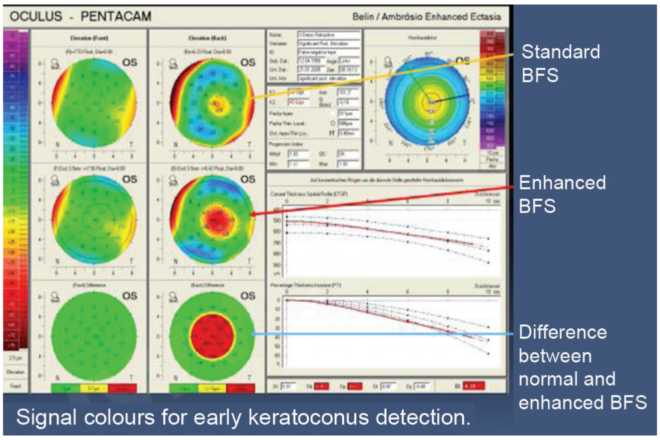



**Fig. 12:** Standard BFS: The upper two elevation maps are the normal elevation maps where a best fitted sphere (BFS) is used. In this pair of maps, the whole cornea is used to fit the BFS. Enhanced BFS: The two elevation maps in the middle are the "enhanced" elevation maps. The lower two elevation maps are the difference of the upper elevation maps

## RECOMMENDATIONS IN ASSESSING KERATOCONUS PROGRESSION

### Differential and Pattern Map Indices

Keratoconus progression may be detected with extreme precision evaluating various types of differential maps. These are obtained by comparing the same type of map performed at different times (pachymetric, anterior and posterior elevation map, instantaneous map) and generating a digital differential map. Furthermore, different types of map can be interlocked.

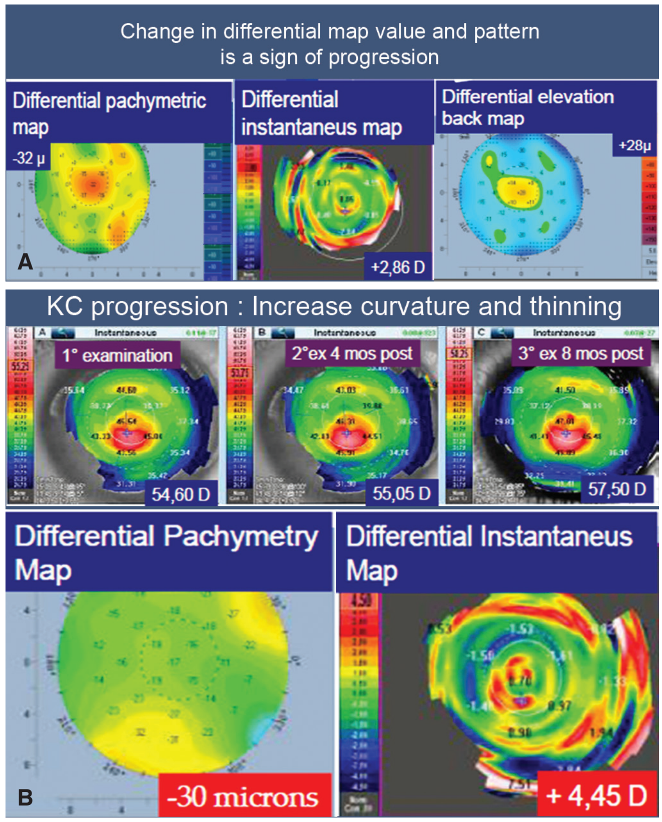
A cornea showing an interconnection among increase of differential curvature, reduction of pachymetry as well as a positive differential elevation map in a localized area is highly suspicious for keratoconus progression (Figs 13A and B).

In addition to numeric increase in all of these differential maps, high attention should be focused on possible pattern changes: Often an enlargement of the ectatic area, though, with a stable or minimum variation of differential indices, can be a significant sign of progression (Figs 14 and 15).

The use of several differential maps can help in differentiating between a false positive and a real keratoconus progression. This is useful, i.e., in false positive cases due to contact lens warpage. In the case of Figure 16, the modifications of corneal instantaneous curvature do not show interlocking modifications on the relative/differential pachymetry or elevation maps, while the opposite is represented in Figure 17.

### Patient Indices: The Age

Keratoconus progression is strongly related to age, manifesting its changes mainly in the second decade of life.[30]




**Figs 13A and B:** Two cases of progression in a keratoconus demonstrated comparing differential pachymetry, instantaneous, and back elevation maps

The velocity of progression varies in relation with the age of the patient, and must be carefully monitored, especially in a younger patient who may show a rapid progression in a short time, as we explained in a previous study[31] (Fig. 18).

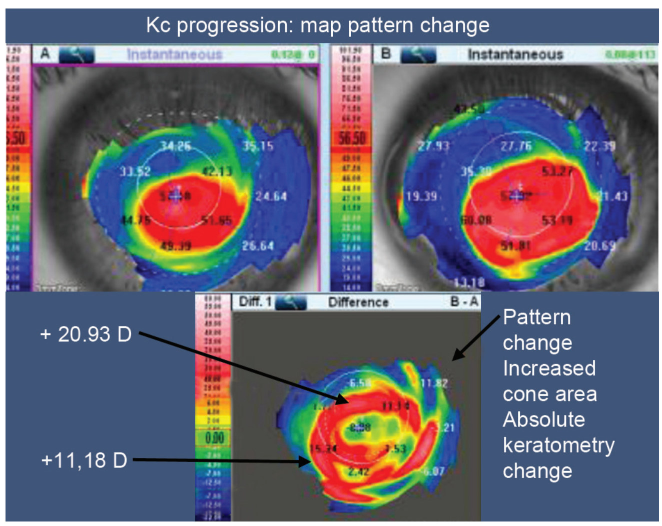



**Fig. 14:** Keratoconus pattern/change of progression. As you can see, the differential maps (B-A), obtained from two different instantaneous maps (A-B) of the same patient, a minimum increase in the central cone zone may be observed, while an enlargement of the ectatic area is apparent

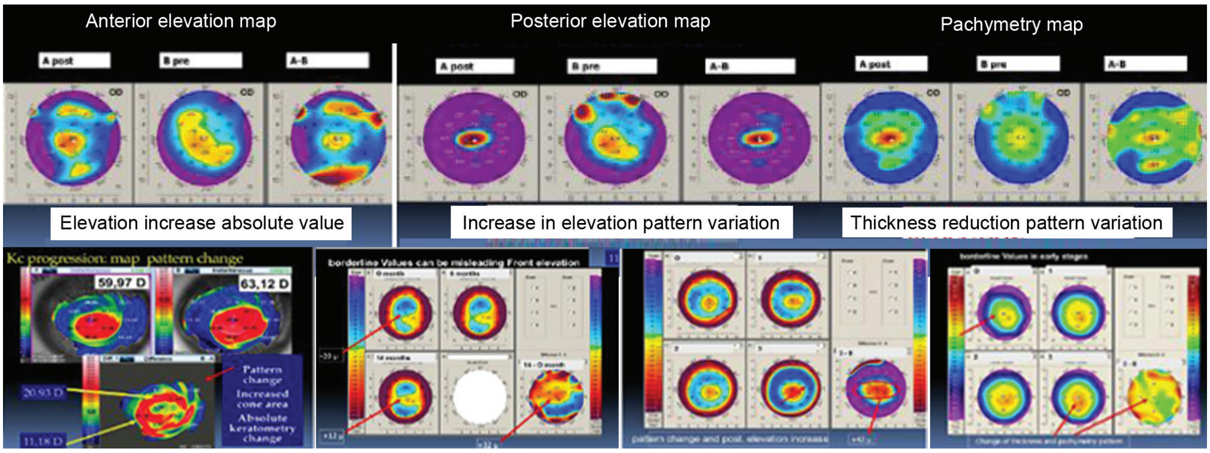



**Fig. 15:** Various appropriate methods to discover a progression in keratoconus observing differential and/or pattern changes

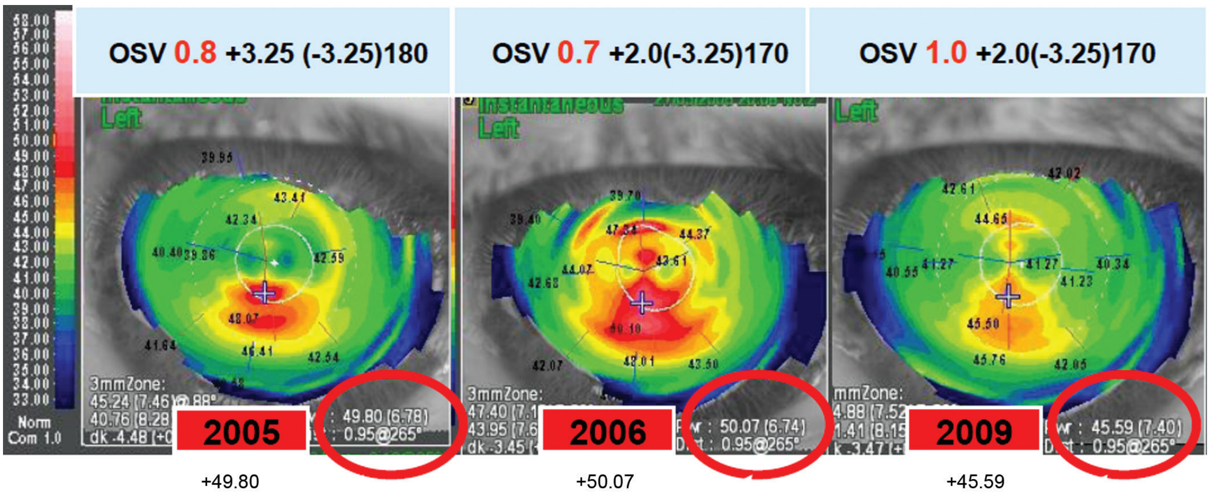



**Fig. 16:** False-positive keratoconus progression due to lens contact warpage. At 2005–2006 examinations, the relative pachymetric maps, the pachymetric gradient, and the elevation map were not abnormal. This patient reduced and normalized the instantan eous map over the years with appropriate wearing off period of contact lens (Fig. 17)

Age can be an insidious bias factor when evaluating keratoconus progression in an older patient: Figures 19A and B shows a possible rapid progression in the 6th–7th decade of life.

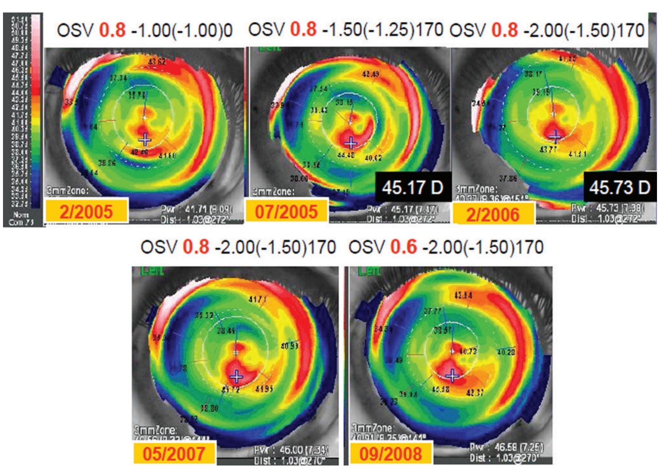



**Fig. 17:** Warpage in keratoconus progression. Warpage cannot hide the progression in instantaneous map

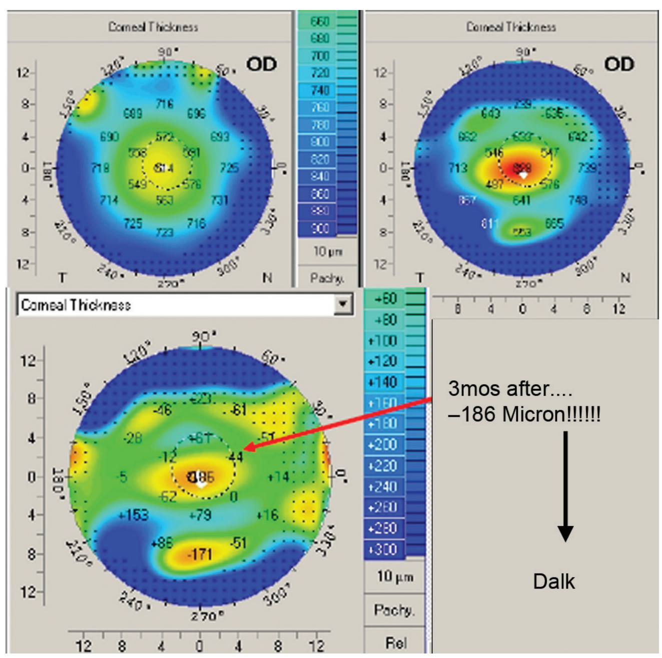
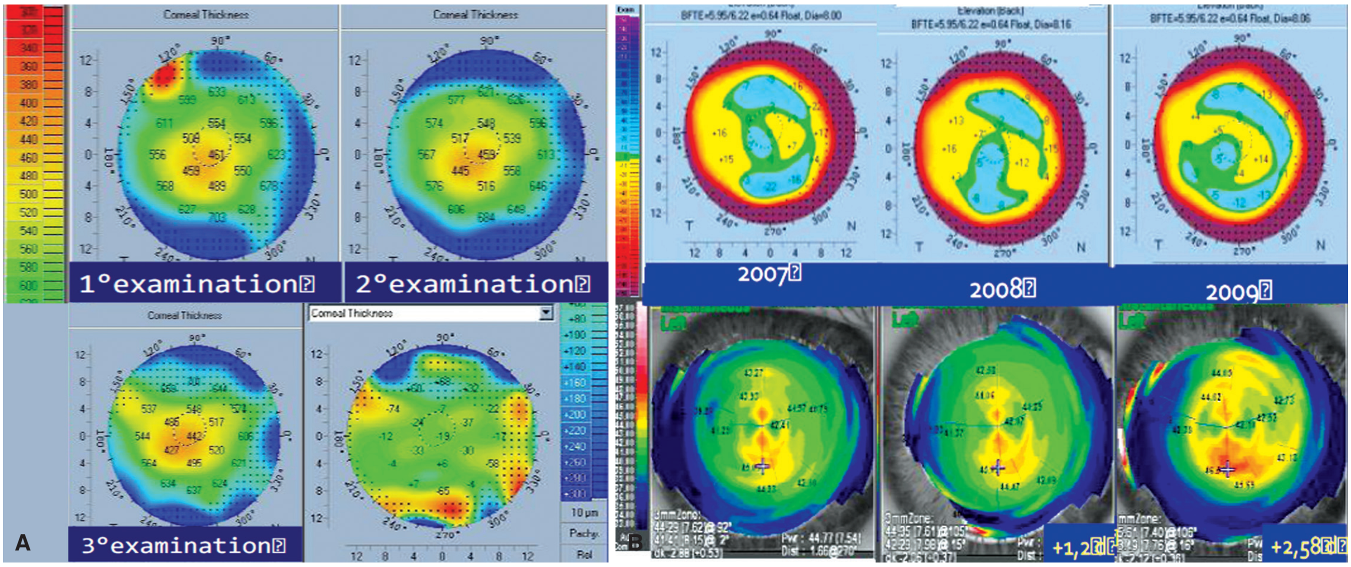



**Fig. 18:** See the extremely fast progression in this 12-year-old patient: In 3 months the differential pachymetric map showed a marked decrease in thickness




**Figs 19A and B:** (A) Pachymetry reduction from first examination to preoperative cross-linking in a 67-year-old patient, and (B) progression in instantaneous and back elevation map in a 72-year-old patient

## CONCLUSION

The diffusion of cross-linking has made early diagnosis essential in order to timely stop keratoconus progression and ensure a high – and previously unthinkable – quality of vision and life in these patients.

A large number of corneal tomographic or topographical indices and maps are available with modern topographers and tomographers. Such indices represent the numeric expressions of some peculiar corneal features.

The advantage of using such a wide number of indexes is to provide reproducible and comparable measurements, often at different time intervals, by objectively recording and analyzing corneal changes.

A possible disadvantage is represented by the lack of a single index synthesizing abnormality and summarizing the variety of possible corneal modifications. Only a deep knowledge of the meaning of all these indexes and values, together with the ability to interlock one another, increases reliability in the evaluation of keratoconus.

Differential maps allow immediate assessment of progression, i.e., ectasia diagnosis in borderline cases. A single topographic map is not a safe diagnostic instrument: Interlocking relationships are a safer and more sensitive tool for ectasia diagnosis.

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