



Profils d'évolution des différents paramètres de la cornée dans le kératocône progressif

Joy Tellouck-Morincomme

► To cite this version:

Joy Tellouck-Morincomme. Profils d'évolution des différents paramètres de la cornée dans le kératocône progressif. Médecine humaine et pathologie. 2014. dumas-01089121

HAL Id: dumas-01089121

<https://dumas.ccsd.cnrs.fr/dumas-01089121>

Submitted on 1 Dec 2014

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Université de Bordeaux

U.F.R DES SCIENCES MEDICALES

Année 2014

N° 3093

Thèse pour l'obtention du

DIPLOME D'ETAT DE DOCTEUR EN MEDECINE

DISCIPLINE : OPHTALMOLOGIE

Présentée et soutenue publiquement le 06 octobre 2014 par

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Née le 13 Février 1985 à BORDEAUX

**EVOLUTION PROFIL OF DIFFERENT CORNEAL PARAMETERS IN
PROGRESSIVE KERATOCONUS**

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REMERCIEMENTS

Je dédie ce travail à notre maître, Monsieur le Professeur Colin auprès de qui ce fut un honneur et un plaisir de débuter l'ophtalmologie. Sa pratique restera un exemple pour moi durant toute ma carrière.

Mes remerciements vont également à Monsieur le Professeur Korobelnik pour avoir accepté de participer à ce jury de thèse et pour l'intérêt que vous avez porté à mon cursus.

Je tiens aussi à remercier mon directeur de thèse, David Smadja, pour la confiance que tu m'as accordée en acceptant d'encadrer ce travail ainsi que pour tes multiples conseils. J'aimerais également te dire à quel point j'ai apprécié ta grande disponibilité tout au long de cette année passée ensemble. Enfin, j'ai été extrêmement sensible à tes qualités humaines d'écoute et de compréhension durant cette collaboration.

Je souhaiterais aussi adresser ma gratitude à David Touboul qui a su être disponible tout au long de mon internat.

A Monsieur le Docteur Bourges, merci d'avoir accepté de rapporter ce travail et d'avoir apporté votre avis clairvoyant.

A monsieur le Professeur Hoffart, merci d'avoir accepté de participer à cette thèse en tant que membre du jury.

A Marie-Noelle Delyfer et Marie-Benedicte Rougier, merci de m'avoir fait découvrir les plaisirs de la rétine chirurgicale et médicale, plaisirs qui jusque là m'étaient insoupçonnés !

A Cédric Schweitzer, merci de m'avoir fait autant apprécier le glaucome et d'avoir été à l'écoute lorsque nécessaire.

A Madame Malet, merci de m'avoir transmis le goût de la contacto et de m'avoir dispensé une précieuse formation.

A Séverine, merci d'avoir géré d'une main de maître les rendez-vous des patients « protocole Joy » !! Ce ne fut pas une mince affaire, et je te remercie d'avoir été aussi rigoureuse et présente.

A Nicolas, Aurélie et Emilie, merci pour vos précieux conseils sur cet outil encore très mystérieux pour moi qu'est excel... et merci pour votre accueil si sympathique dans votre bureau !

A Fanny et Tania, merci pour votre aide et votre collaboration.

A Sandrine, merci pour ton précieux apport en statistiques.

A l'ensemble du personnel paramédical du service, de l'hospit et du bloc : merci de m'avoir accompagnée durant toutes ces années d'internat. Ce fut un plaisir de travailler à vos côtés.

Je tiens aussi à remercier tout particulièrement ma famille.

A Papa et Maman, merci pour votre soutien inconditionnel et votre amour. Merci de nous avoir encouragés et soutenus dans tout ce que nous avons entrepris. Papa merci d'avoir toujours été là et de nous avoir supportées dans les grands moments (matin des examens !!!). Je sais à quel point ce jour résonne de manière si particulière pour toi. Maman, merci de nous avoir transmis ta rigueur et surtout donné ton incommensurable affection. Tu es pour beaucoup dans notre parcours professionnel et rien n'aurait été possible sans ton soutien et ta présence constante.

A Laury : aucun mot ne saurait décrire notre relation si particulière et si magique. Rien de ce que j'ai fait n'aurait été possible sans toi alors merci pour tout.

A Florent, merci pour ta bonne humeur communicative, ton humour toujours acerbe mais surtout ton amour bienveillant.

A Papi et Mamette, merci pour vos conseils toujours pertinents mais surtout merci pour tout l'amour que vous nous avez donné. Vous avez su nous guider dans toutes les décisions importantes de notre vie.

A Mathieu qui a su me soutenir, me supporter, m'encourager... depuis tant d'années et plus particulièrement durant les derniers mois de rédaction de cette thèse qui n'ont pas toujours été des plus agréables.

A Sam, merci d'avoir agrandi la famille et d'avoir toujours été comme un grand frère pour moi.

A Frank, Eva, Stephane et Kaerenne, merci pour tous les bons moments passés ensemble. Vous avez su nous accompagner lors de toutes les étapes importantes de notre vie et nous couvrir de votre affection.

A Erick et Jacqueline, merci pour tous les bons moments passés dans notre enfance.

A tata Lyliane, merci pour ton soutien et ta présence constante à mes côtés. Ta gentillesse et ta bienveillance me sont très chères.

A Didier, Françoise, Bruno, Sandrine et Cathy, merci d'avoir su nous accompagner lors de tous les moments importants de notre vie.

A mes beaux-parents, Esther et Gérard ainsi qu'à Maxime et Julie, merci de m'avoir si bien accueillie au sein de votre famille.

A tous mes cousins et cousines, petits comme grands, merci pour tous ces supers moments partagés : les vacances ensemble, les nombreux fous rires lors des repas de famille et cette bonne humeur permanente.

A Elodie, merci pour ton aide providentielle en ce soir de mois d'août !!

A Sarra, Clémént, Clémence et David, merci pour toutes ces années d'internat partagées, nos nombreuses discussions et fous rires autour des repas oh combien succulents du relai h !!!

A Bérénice et Edith, merci pour votre amitié sans faille depuis nos débuts communs sur les bancs de la fac.

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ABBREVIATIONS

UCVA : uncorrected visual acuity

CXL: corneal collagen cross linking

LASIK : laser in situ keratomileusis

Kmax ant/post : maximal anterior/ posterior keratometry

IS ratio : Inferior-Superior ratio

SRAZ : skew radial axis index

AUROC : area under the receiver operating characteristics

RMS : root mean square

SimKs : simulated steep keratometry

SimKf : simulated flat keratometry

Mean K : mean keratometry

BFS : best fit sphere

BFTA : best fit toric aspheric

MAE : maximum anterior elevation

MPE : maximum posterior elevation

TP : thinnest point

TCP : total corneal power

CHOA : corneal higher order aberrations

SA : spherical aberrations

Tang : tangentiel

ICR : intracorneal ring

Keratop : keratoplasty

Coma V / tot : Vertical / total coma

AAI : asphericity asymmetry index

KPI : keratoconus prediction index

AC : anterior chamber

Pac : pachymetry

Ecc : eccentricity

AA : area analyzed

ACP : average central power

CSI : central/ surround index

DSI : differential sector index

IAI : irregular astigmatism index

OSI : opposite sector index

SAI : surface asymmetry index

SDP : standard deviation powers

SRI : surface regularity index

DALK : deep anterior lamellar keratoplasty

PK : penetrating keratoplasty

WTW: white to white

CCT: central corneal thickness

ACD: anterior chamber depth

REMINDERS ON KERATOCONUS

Keratoconus is a bilateral and asymmetrical corneal dystrophy. It begins with a curvature of the posterior surface before reaching the front face where bulging occurs and thinning. Disease begins in adolescence and progresses until the third decade.

Many factors are involved in the development of keratoconus: genetic(1)(2)(3)(4), chromosomal(5)(6) or atopic(7)(8)(9) but also mechanical(10) (eye rubbing).

1. CLINICAL SIGNS

In biomicroscopy we find 5 signs:

- Vogt streaks
- Fleisher ring
- Corneal opacities
- Visibility of corneal nerves
- Munson sign

2. PARACLINIC DIAGNOSTIC

It is now established that a tomographic examination can detect earlier the first corneal signs of keratoconus(11). Indeed, the first detectable signs of keratoconus are on the posterior side only and therefore are detected by tomography.

Many studies have highlighted the role of the corneal epithelium that hides topographic irregularities and thus prevents early detection of keratoconus on the anterior surface of the cornea(12)(13).

Again, the tomographic examination provides many details on pachymetric data, biometric, volume or curvature, elevation and wavefront derived parameters.

3. ABERROMETRIC SIGNS

Three systems measure optical aberrations : Hartmann-Schack system(14)(15), Tscherning system and OPD Scan system(16).

They are essentially CHOA like coma and spherical aberrations(17)(18).

Vertical coma is the first to appear in the course of the disease that means that early vertical asymmetry resulting in subclinical disease stages(19)(20)(21).

4. CLASSIFICATIONS

There are a lot of classifications of keratoconus. Oldest are Amsler classification based on the corneal deformation and the Krumeich one based on pachymetry, central keratometry, the spherical or cylindrical power and the corneal transparency(22).

Table 1 Clinical classification of keratoconus by stage

Stage	Characteristics
I	Eccentric steepening Induced myopia and/or astigmatism of ≤ 5.00 D Keratometric reading ≤ 48.00 D Vogt's lines, typical topography
II	Induced myopia and/or astigmatism >5.00 to ≤ 8.00 D Keratometric reading ≤ 53.00 D Pachymetry ≥ 400 μm
III	Induced myopia and/or astigmatism >8.00 to ≤ 10.00 D K-reading >53.00 D Pachymetry 200 to 400 μm
IV	Refraction not measurable Keratometric reading >55.00 D Central scars Pachymetry ≤ 200 μm

Stage is determined if one of the characteristics applies. Pachymetry is measured at the thinnest site of the cornea.
D, dioptres.

Figure 1 : Amsler-Krumeich classification

New classifications based on topography and aberrometry have also emerged(19)(23)

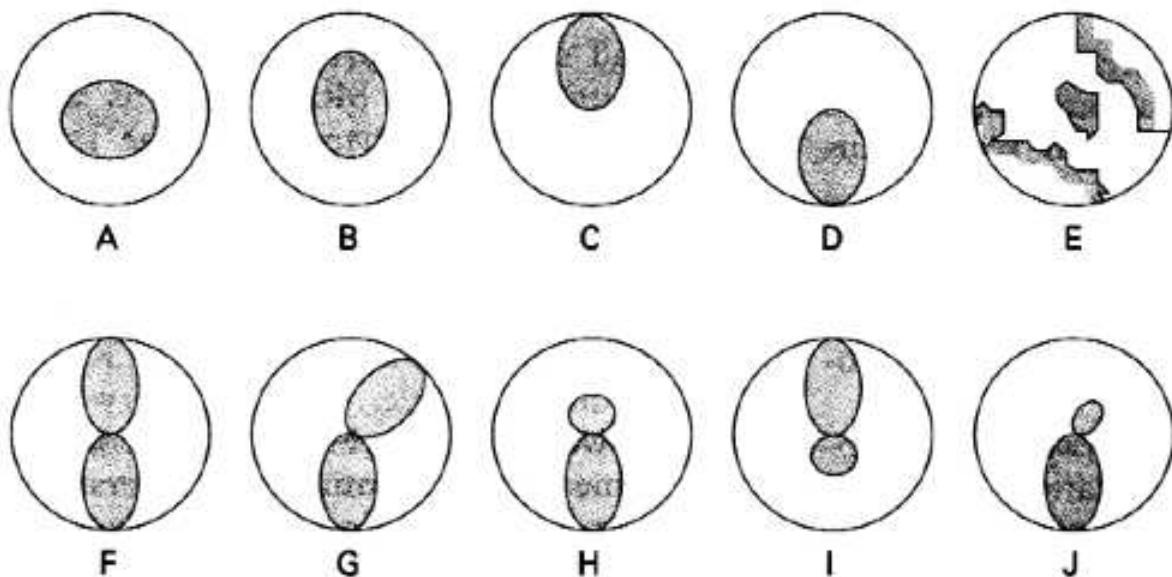


Figure 1 Videokeratography pattern classification scheme based on the absolute scale: A, round; B, oval; C, superior steepening; D, inferior steepening; E, irregular; F, symmetric bowtie; G, symmetric bowtie with skewed radial axes; H, asymmetric bowtie with inferior steepening (AB/IS); I, asymmetric bowtie with superior steepening; J, asymmetric bowtie with skewed radial axes (AB/SRAX).

Figure 2 : Rabinowitz classification

5. THERAPEUTIC ATTITUDE

5.1. Treatment of the scalability : CXL

CXL is a treatment involving the photochemical effect of UVA light source after a period of photosensitivity of the anterior stroma by riboflavin. This results in polymerization of the collagen with creation of covalent bonds between the fibrils and thus slow the progression of keratoconus(24)(25)(26).

CXL can also have a refractive effect with hypermetropisation secondary to a cone flattening (27), sometimes gain in BCVA (28)(29).

5.2. Correction by rigid gas-permeable contact lenses

Due to often significant astigmatism, equipment in glasses is often insufficient.

Rigid gas-permeable contact lenses remain the standard treatment for keratoconus(30). They help smooth out corneal irregularities restoring regularity of corneal anterior surface thereby correcting HOA(31).

5.3. Correction by intracorneal rings

For many years ICR has become a standard of care in treatment of keratoconus. This is a conservative treatment that can be added or subtracted to rigid gas-permeable contact lenses. It reduces irregular astigmatism by refocusing the cone(32)(33).

5.4. Keratoplasty

This treatment is reserved for patients with advanced keratoconus where the visual acuity is limited despite previous treatments. There are 2 types of keratoplasty: lamellar or total ; in 2 cases, visual acuity is improved(34). DALK now replaced penetrating keratoplasty because the risk of endothelial rejection is less important(35).

INTRODUCTION

Keratoconus is an idiopathic corneal dystrophy characterized by a progressive ectasia and a corneal thinning. The estimated prevalence in the general population is 54/100000 and its annual incidence is about 1/2000(36).

The age of onset is typically during puberty, and the disorder is progressive until the third to fourth decade of life, when it usually arrests. Disease progression is manifested with a loss of visual acuity due to an increase of refractive error (myopia and irregular astigmatism). Management varies with disease severity; nonsurgical alternatives are used primarily in treating patients with keratoconus (KC). Although the visual disturbances in keratoconus may be managed with spectacles early in the disease process, rigid gas-permeable contact lenses are the treatment of choice for irregular astigmatism associated with the disease(1). If rigid gas-permeable contact lenses are not well tolerated we can use intracorneal rings segments in order to reduce corneal irregularity and flatten keratometry with improvement in UCVA and best corrected visual acuity(37).

Corneal ectatic disorders are secondary to a decrease in biomechanical resistance. Corneal collagen crosslinking (CXL) is used to slow or even to stop the progression of these pathologies creating additional covalent bonds between collagen molecules, with consequent biomechanical stiffening of the cornea.(38),(39)

This procedure is currently the only approach in ectatic eyes that can stop the process of cornea destabilization, reducing the necessity for keratoplasty.

Diagnosing an early progression remains an important challenge due to the clinical and therapeutic attitude in young patients who must maintain a certain visual acuity.

1- DEFINITION OF A PROGRESSIVE KC AND CURRENT CRITERIA FOR MONITORING THE DISEASE

Although some guidelines for monitoring KC progression have been published(40)(41), to date, there is still no consensus on the most appropriate clinical, morphological or biomechanical parameter to track, in order to closely monitor the disease and detect the earliest manifestation of progression.

The parameters indicating the progression and the period of time in which these parameters were observed varied. Raiskup-Wolf and al., consider that progression indicating the necessity for treatment was based on an increase in K_{max} at the apex of keratoconus of 1 diopter (D) in 1 year, deterioration of visual acuity, or the need for new contact lens fittings more than once in 2 years(28).

Others like Vinciguerra(42) defined keratoconus progression as a change in either myopia and/or astigmatism of ≥ 3 D in the previous 6 months, a mean central K-reading change of ≥ 1.5 D observed in 3 consecutive topographies during the preceding 6 months, or a mean central corneal thickness decrease of $\geq 5\%$ in 3 consecutive tomographies performed in the previous 6 months.

Hersh and al.(29) suggested that a CXL procedure would be reasonable when one or more of the following changes over a period of 24 months were noted: an increase of 1 D or more in the steepest K measurement, an increase of 1 D or more in manifest cylinder, or an increase of 0.5 D or more in manifest refraction spherical equivalent.

Table 1 : Criteria of Keratoconus evolution derived from literature

	Kmax ant	Pachymetry	Cylinder	Visual acuity
Raiskup-Wolf(28)	>1D in 1year			Loss of BCVA
Vinciguerra(42)	>1,5D in 6 months	< 5% in 6 months	> 3D in 6 months	
Hersh (29)	>1D in 1 year		>1D in 1 year	Variation of SE: +/- 0,5D in 1 year
Choi(41)	>1,5D in 1 year			

Commonly accepted values are variations of $K_{max} > 0.5$ D 6 months or $> 1D$ 1 year. Nevertheless all topographic criteria to determine scalability is based on the evaluation of the anterior surface of the cornea and all those current criteria have many limitations.

2- PROBLEMATICS AND LIMITATIONS WITH THE CURRENT CRITERIA FOR MONITORING KC PROGRESSION

As illustrated in the above paragraph, most of the parameters used in the definition of a progressive keratoconus are based on subtle modifications of anterior corneal topographic

parameters (anterior keratometry and corneal astigmatism). However, it has been shown that the obtention of a reliable and repeatable topographic map in highly irregular corneas remains challenging with anterior Placido technology(43), which is based on the reflection of Placido rings on the lacrymal film. As a consequence, the definition of a progressive state should rely on corneal measurments with high repeatability and predictability. A lot of studies try to evaluate the repeatability and the reliability of all the topographic and tomographic examinations.

Szalai and al. (44) show that a measurement error exists corresponding to the within-subject standard deviation (SD). In this study, in control group they found for the steep keratometry a SD closed to 1,7 for rotating Scheimpflug system imaging. This value increases with the severity of the keratoconus: repeatability is higher for healthy corneas than for keratoconic eyes for every K value and the thinnest and center pachymetry measurements.

In a same way, Chen(45) analyzes intra-observer and inter-session repeatability using Pentacam; they capture three consecutive scans and then, the same procedure is repeated on a different day at approximately the same time of day for analysis. For the steepest keratometry they describe a SD of 1,4 and conclude to a good inter-observer repeatability. The inter-session repeatability of Sim K is also comparable to the inter-observer repeatability reported by Shankar(46).

Table 2 : Reliability and repeatability of devices for different parameters: data from litterature

	Type of device	Type of corneas	Parameters studied	Conclusions
Szalai(44)	AS-OCT Pentacam	Healthy eyes KC eyes	Ks and Kf, cyl, pachymetry, ACD	Significant differences between 2 devices
Chen (45)	Pentacam	Healthy eyes	SimK, corneal curvature of anterior and posterior surfaces	Good intra-observer reliability
Shankar(46)	Pentacam	Healthy eyes	Corneal curvature, AC parameters, pupil, pachymetry	High repeatability except for pupil
Chen (47)	Lenstar Sirius	Healthy eyes	CCT, ACD, Km, WTW	Excellent repeatability for both devices
De Sanctis (48)	Pentacam US pachymetry	KC eyes	CCT	Good repeatability and reproducibility
Sideroudi (49)	Pentacam	Healthy eyes KC eyes CXL eyes	Curvature and aberrometric parameters	Precise measurements and goog repeatability
Shetty (50)	Pentacam Galilei Sirius	KC eyes	Km ant and post CCT ACD	Repeatability of pentacam and Sirius better than galilei

Many articles have also studied the reliability and repeatability of Galilei which is the device used in this study.

These studies are summarized in the table below.

Table 3 : Reliability and repeatability of Galilei for different parameters: data from literature

	Number et type of corneas	Number of measurements	Parameters studied	conclusions
Al-Mohtaseb(51)	77 healthy eyes 39 post refractive surgery(PRS) eyes	3	CCT	High reliability and repeatability in both groups
Güler(52)	20 healthy eyes 20 KC eyes 20 PRS eyes	2	CCT TCT TCP, PCP BFS ant and post eccentricity	Good repeatability and reproducibility for 3 groups
Savini (53)	45 healthy eyes 15 PRS eyes	3	Iridocorneal angle Spherical aberrations	High repeatability, no change after refractive surgery
Wang (54)	20 healthy eyes	3	Corneal curvature Aberrations Pachymetry ACD	Excellent repeatability

Whereas the indices of anterior surface of the cornea, it is difficult to know if a patient moves or if the variation is part of the standard deviation of the examination

3- DIAGNOSIS OF KERATOCONUS

The first symptoms appear typically during puberty with an impairment of vision due to myopia and astigmatism, and in most cases, it's assumed that the disease no longer changes after 35 years-old.

According to Rabinowitz(36), keratoconus is an association between clinical and topographical criteria based on four main indexes that allow to distinguish 98% of keratoconus from a group of normal control using videokeratographs. Those indexes are

- the central keratometry which is the descriptive of central steepening
- the I-S value that describes the inferior-superior dioptric asymmetry
- the Simulated K value
- the SRAX value that quantifies the irregular astigmatism

Since a few years, new studies have shown that the earliest signs of disease reached the posterior face and not the anterior corneal surface.

Tomidokoro and *al.* in 2000(55) showed that not only the anterior but also the posterior corneal curvature is affected in keratoconus and these changes are observed from the early stage of this disorder. They describe that for the posterior surface, spherical power, regular astigmatism, asymmetry, and higher order irregularity of the keratoconus group were significantly greater than those of the control group. Likewise, Kamiya and al confirm that the posterior surface can discriminate keratoconus from normal corneas(22).

In a same way, Ishii in 2012 showed that both anterior and posterior corneal surface data obtained by elevation-based tomography provide useful information in improving keratoconus diagnostic accuracy but also in grading the severity of keratoconus(56). Indeed, cases of larger elevation differences in the anterior and posterior corneal surfaces were staged higher in Amsler-Krumeich classification. Cases of lower staging in the Amsler-Krumeich classification had a larger AUROC in the posterior elevation differences than in the anterior elevation differences, suggesting a greater diagnostic value of the posterior elevation measurement.

In keratoconus-suspects eyes, Schlegel and al (13) showed that there were also changes in the posterior surface including a higher posterior toricity, a more negative asphericity and a higher posterior elevation.

Fukuda (57) in 2013 showed that posterior elevation is the best parameter to diagnose forme fruste keratoconus with both corneal and anterior segment optical coherence tomography and a rotating Scheimpflug camera combined with a Placido topography.

More recent studies confirm the interest of using indices derived from the posterior surface whatever the device used. Saad and Gatinel(11) with Orbscan developed a score based on posterior central elevation to detect mild ectatic corneas. In an other study in 2012(58), they conclude that indices generated from corneal and ocular wavefront can identify very mild forms of ectasia.

Smadja and *al.*, in 2013(59) describe with Galilei, that using BFTA instead of BFS reference surface increases the ability to discriminate between normal cornea and forme fruste keratoconus . They added that posterior elevation measured by BFTA had a significantly higher predictive accuracy for forme fruste keratoconus than anterior elevation. They also created a new algorithm to detect subclinical KC based on posterior surface asymmetry and thickness spatial distribution(60).

Other studies done with Sirius(61) confirm that parameters derived from the posterior surface improved precision to detect KC especially in cases of subclinical keratoconus.

Concerning Pentacam, a Turkish team conducted by Muftuoglu(62) concluded that posterior elevation parameters were best in discriminating subclinical keratoconus eyes from normal eyes.

Detecting the earliest manifestation of progression in the ectatic disease remains the main challenge in this disease. Because of the young age of the patients, this disease often has a dramatic effect on quality of life and life planning. The treatment options available to date have not been encouraging, as they have not always been able to avoid the progression of the keratoconus. Thus, keratoconus, because it's a progressive disease, has been one of the most common indication for keratoplasty.

Based on these considerations, it seems therefore reasonable to question the use of anterior corneal parameters to monitor the disease for tracking the first manifestations of progression, while posterior surface modifications have been considered as a key parameter for detecting the earliest stage of the ectatic disease(55).

Therefore, the objective of our study was to compare the evolution profiles of various corneal parameters using a combined Placido-Dual Scheimpflug imaging system and to determine whether alternative parameters than the current gold standard (anterior keratometry) may be more appropriate to monitor the keratoconus progression.

MATERIEL AND METHODS

This prospective study was conducted at the University Hospital of Bordeaux, France, in the National Reference Center for Keratoconus (NRCK) and approved by an Institutional Review Board. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

1. SUBJECTS

A total of 109 eyes of 55 patients were prospectively enrolled in the study and imaged with the GALILEI Dual Scheimpflug Analyzer System (Ziemer Ophthalmic Systems AG; Port, Switzerland) as part of the keratoconus follow-up visits.

Eyes with keratoconus were enrolled among patients that were referred to the NRCK for a regular control visit for mild to advanced keratoconus. Diagnosis of clinical keratoconus was previously defined and includes a combination of findings characteristics of keratoconus(63)(1): Corneal topography with asymmetric bowtie pattern or localized steepening, irregular cornea determined by distortion of the retinoscopic or ophthalmoscopic red reflex and at least one of the following slit-lamp findings: Stromal thinning, Fleischer ring greater than 2mm arc, Vogt striae and corneal scarring consistent with keratoconus. Eyes that wear contact lenses and eyes that have already underwent a specific treatment for keratoconus, such as collagen cross-linking, intracorneal rings or keratoplasty, as well as marginal pellucid degeneration were excluded from the study.

All patients had a detailed ophtalmic evaluation including uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), manifest refraction, slitlamp examination, applanation tonometry and fundus examination.

All patients were imaged with the Galilei Dual Scheimpflug Analyzer System (Ziemer Ophtalmic Systems AG; Port, Switzerland) and followed every 3 months as part of the scheduled visit protocol for monitoring the disease progression: at the inclusion, 3, 6, 9 and 12 months.

2. DUAL SCHEIMPFLUG ANALYZER SYSTEM AND PROCEDURE

Measurements were performed with the Galilei (Ziemer Ophtalmic Systems AG; Port, Switzerland) dual Scheimpflug analyzer system (software version 5.2.1) according to the manufacturer's guidelines. The device was first brought into focus (Placido rings into sharp focus) and aligned with the patient visual axis (central fixation light). Then, patients were asked to blink just before the measurement. Only measurements that satisfy the minimum quality required by the system were included in this study.

Galilei is a rotating Scheimpflug tomography based device combining dual-channel Scheimpflug cameras and a Placido disk. The system acquires between 15 to 60 Scheimpflug images per scan and 2 Placido top view images at 90° apart, as the cameras rotate around the central axis. Placido and Scheimpflug data are acquired simultaneously, and then a motion correction algorithm is applied to the combined dataset.

The combination of both technologies, Placido disk and Scheimpflug imaging has been designed to improve the accuracy of the anterior corneal curvature calculation. Height data from the Scheimpflug images and slope data, converted into height data from the placido, are merged to provide a surface fitted to the anterior corneal data whereas posterior corneal surface data are measured using edge detection in images provided by the dual-Scheimpflug system.

In addition, the Galilei software has enhanced the posterior edge location and used ray-tracing with a Snell's Law refraction through the anterior surface to locate and help in reliably reconstructing the posterior surface. The ray tracing algorithm takes into account the 45° camera viewing angle relative to the anterior surface and calculates the pathway through the cornea using the relative indices of refraction, 1,376 for the cornea and 1,336 for the aqueous humor.

Indeed, such correction process is needed to overcome the images distortion created by the camera optics and the cornea itself (effect of magnification of the anterior cornea to the path of the ray of light).

Simultaneously, the system allows for corneal aberration analysis separately from the aberrations of the lens and displays the total higher order corneal wavefront aberrations calculated from the front and back surface. Both the displayed wavefront maps and the RMS indices are re-calculated recentered on the pupil center over a 6.0 mm optical zone. Individual Zernike coefficients for terms from second to sixth order are displayed in microns as well as diopters.

3. ANALYZED PARAMETERS

3.1. ANTERIOR CURVATURE PARAMETERS

Simulated keratometries SimK are calculated with the so called keratometric index, which is known from Placido topographers, and is equal to 1.3375. This does not correspond to the actual index of refraction of the cornea (1.376) since it takes into account the posterior surface parameters calculated with keratometric index are called simulated (SimKf, SimKs, ...).

SimK steep (**SimKs**) and SimK flat (**SimKf**) are calculated from the pair of meridians 90° apart with the greatest difference in average power, from 0.5 to 2.0 mm distance from the center. This maximizes the astigmatism parameter, which is the difference between SimKf and SimKs.

Eccentricity ϵ_2 : this term is one of four parameters by which the shape of a conic section, can be described: Q (asphericity), p value and E (corneal shape factor) are the others. These terms are mathematically related by the following equation: $\epsilon_2 = E = 1-p = -Q$

Galilei calculates the eccentricity ϵ_2 of the surface within a central diameter of 8 mm averaged over all meridians.

Kmax has been directly recorded from the curvature map and represents the maximal keratometric value at the top of the cone in keratoconic patterns.

Mean Keratometry (MeanK) is the average keratometry calculated over the analyzed area, central (0-4 mm), paracentral (4-7 mm) and peripheric cornea (7-10 mm). These values are derived from the axial curvature maps for the central cornea and from the tangential curvature maps for the paracentral or peripheric cornea.

IS ratio value is the amount of steepening of the inferior cornea compared with that of the superior cornea. It's calculated by subtracting the superior value from the inferior value. The inferior value was calculated by averaging 5 data points along the inferior cornea from the center of the cornea at 30-degree intervals (at 210, 240, 270, 300 &nd 330°). The superior value was derived from averaging 5 points on the superior cornea from the center of the cornea (at 30, 60, 90, 120 and 150°).

3.2. POSTERIOR CURVATURE PARAMETERS

These parameters are basically the same as the ones from the anterior surface. The only difference is that the K values are not simulated, but calculated with the real indices of refraction of the cornea (1.376) and the aqueous humor (1.336).

I-S posterior score has been designed for evaluating the curvature asymmetry of the posterior surface. It corresponds to the absolute value of the IS ratio of the posterior surface along the corneal circular ring 6.0 mm from the center. It's calculated by subtracting the superior value (average of 3 data at 60, 90 and 120°) from the inferior value (average of 3 data at 240, 270 and 300°).

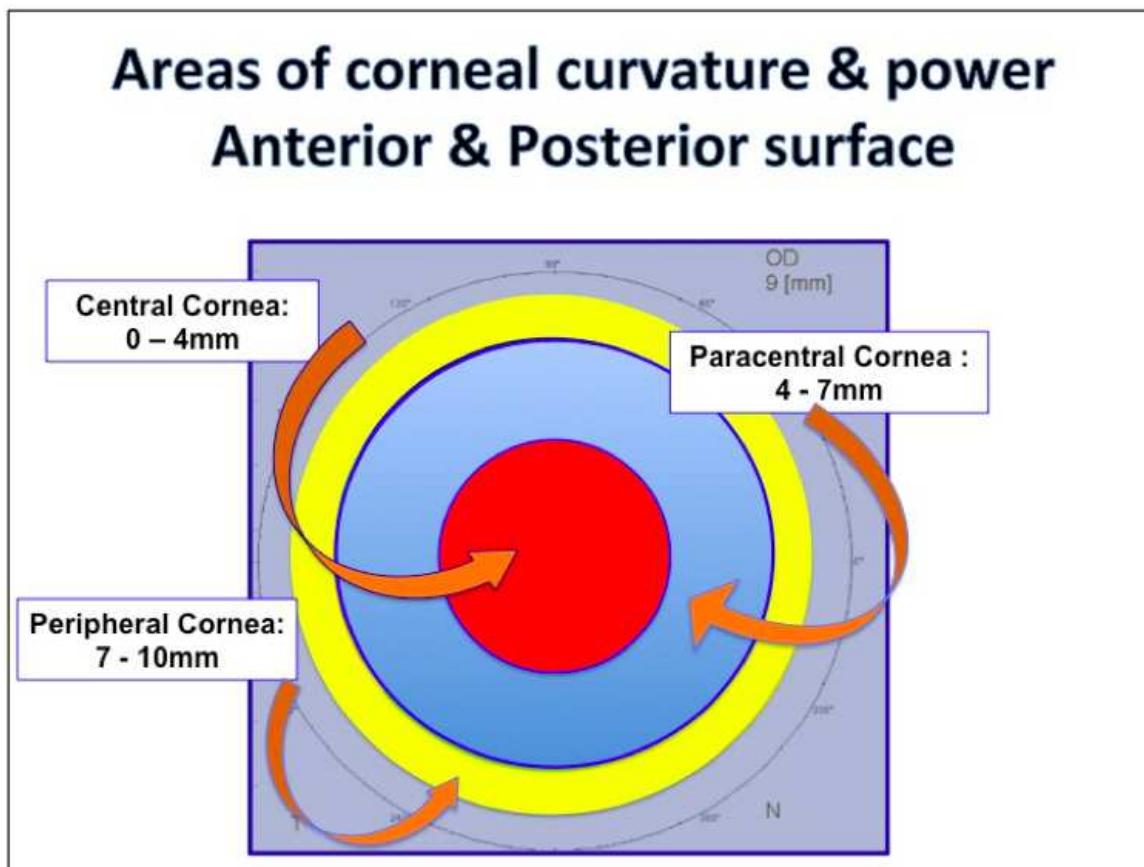


Figure 3 : Areas of corneal curvature and corneal power of the corneal surface

I-S Ratio Calculation

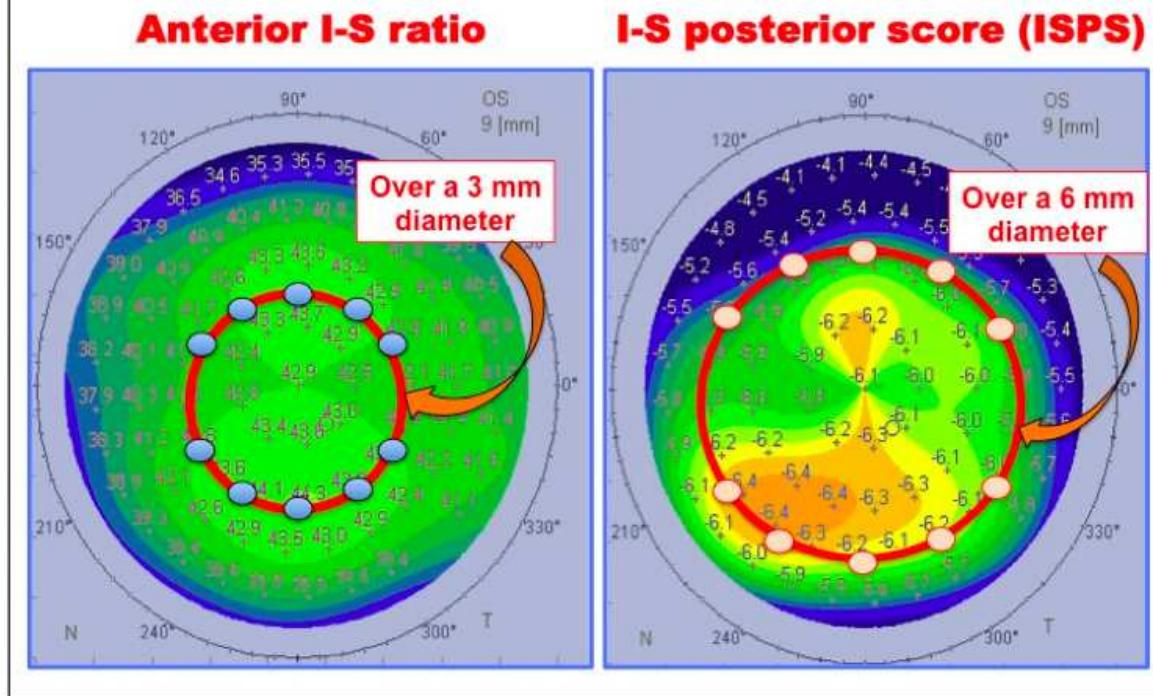


Figure 4 : Position of extracted data for calculating the IS ratio over the anterior and the posterior surfaces

3.3. KERATOCONUS INDICES

The keratoconus indices provided by the system are based on formulas in the litterature using a placido device(65), and simulated on the Galilei by translating the ring numbers used in the original Placido equations into corneal regions in the Galilei(66).

- **Area Analyzed (AA)** is the ratio of the actual data area to the area circumscribed by a circle 4.5 mm in radius.
- **Average Central Power (ACP)** is simulated as the average dioptric power of all points within the central 3 mm.
- **Central/Surround Index (CSI)** reports the difference between the average area-corrected power between the central area (3-mm diameter) and an annulus surrounding the central area (3–6 mm).
- **Differential Sector Index (DSI)** reports the greatest difference in average area-corrected power between any two 45° sectors.

- **Irregular Astigmatism Index (IAI)** is simulated as the average summation of area-corrected dioptric variations along every semi-meridian for the entire analyzed surface and normalized by the average corneal power and number of all measured points.
- **Opposite Sector Index (OSI)** reports the greatest difference in average area-corrected power between opposite 45°sectors.
- **Surface Asymmetry Index (SAI)** is simulated as the centrally weighted average of the summation of differences in corneal power between corresponding points 180°apart on all meridians.
- **Standard Deviation Powers (SDP)** is simulated as the standard deviation of all measured powers present on the map.
- **Surface Regularity Index (SRI)** is simulated as a difference in power gradient between successive points on a hemimeridian that is assigned a positive value and added to the running sum. This sum is divided by the number of points that went into the sum and then scaled.

3.4. ELEVATION PARAMETERS

Elevation values were measured with two different reference bodies over a 8 mm calculation zone: the best-fit sphere (BFS) in float mode and the best-fit toric and aspheric body (BFTA). Values were recorded in both anterior and posterior surfaces over 3 locations by manually guiding the cursor over the anterior and posterior elevation maps: highest elevation value within the 8mm diameter zone (MAE and MPE), elevation value at the thinnest point (MAETP and MPETP) and elevation value at the Kmax location (MAEKm and MPEKm).

The **posterior AAI** (asphericity asymmetry index) is a quantitative indicator of the posterior surface asymmetry and is calculated over the best-fit toric and aspheric (BFTA) surface. It quantifies the level of asymmetry of asphericity of a corneal surface. It's calculated as the absolute value of the difference between the maximum negative BFTA elevation and maximum positive BFTA elevation in the central 6mm-diameter data zone. This indice has been recorded for the anterior and posterior surfaces.

It was identified by Smadja in 2013 such as the most discriminant index to diagnose form fruste keratoconus(60) with a cutoff value of 21,5 µm, with a sensitivity of 93,7% and a specificity of 97,2%.

Reference bodies for calculating elevation data

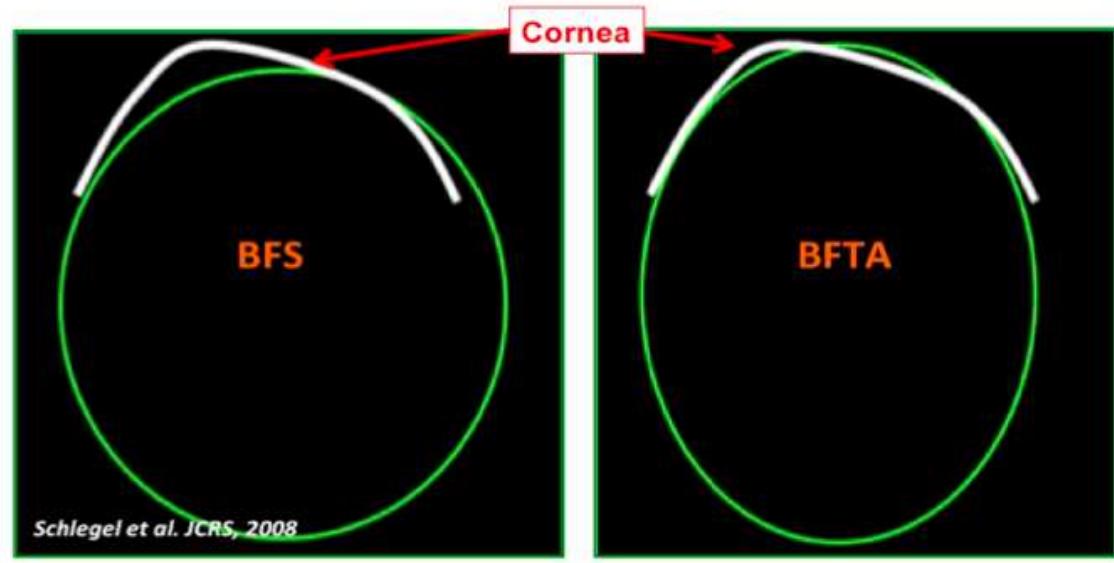


Figure 5 : Two different bodies used for calculating elevation data

Elevation derived parameters in Anterior and Posterior surfaces

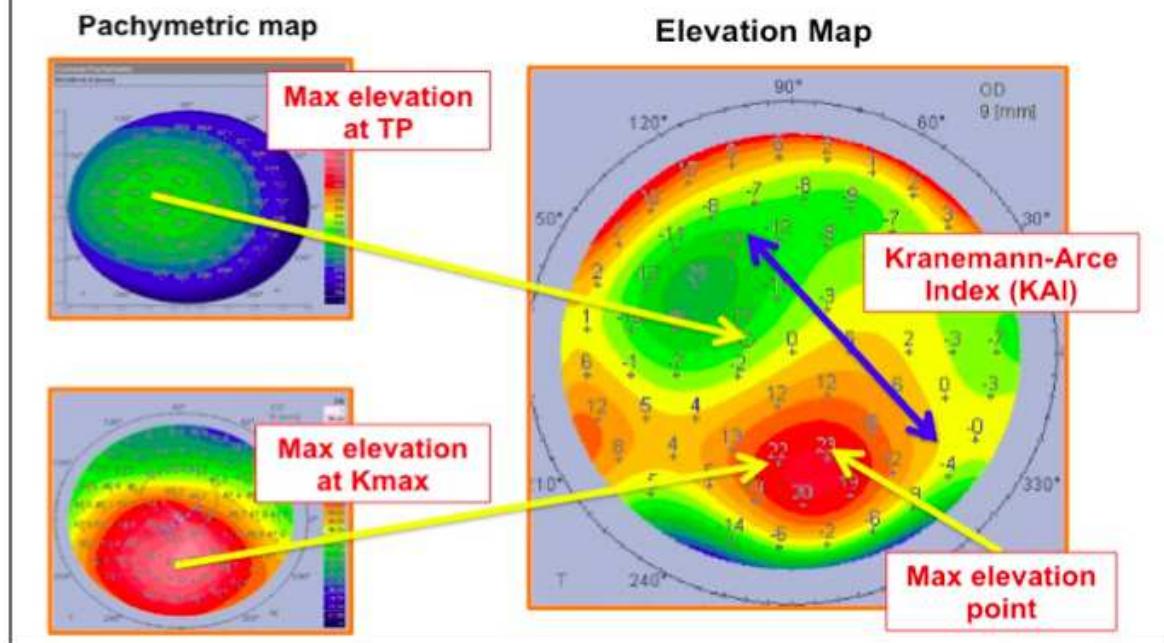


Figure 6 : Different positions where elevation data were collected over the anterior and posterior corneal surfaces

3.5. CORNEAL WAVEFRONT PARAMETERS

Total corneal HOAs root mean square (RMS) from the third to the sixth order as well as the RMS spherical aberration Z(4,0), RMS vertical Z(3,-1) and horizontal Z(3,1) coma and RMS total coma through a 6mm pupil size were recorded from the wavefront maps displayed in microns.

Enantiomorphism was neutralized by inverting the sign of the mirror-symmetric coefficients of the left eyes as shown in the following equations:

For all C_{n^m} if n is even and m<0 : $C_{n^m} = -(C_{n^m})$

For all C_{n^m} if n is odd and m>0 : $C_{n^m} = -(C_{n^m})$

3.6. CORNEAL POWER DERIVED PARAMETERS

The average total corneal power (TCP) over 3 different corneal zones respectively central (0-4mm), paracentral (4-7mm), and peripheral (7-10mm) were recorded.

The TCP, which is calculated by the galilei system, is the actual power of the cornea including both the anterior and posterior surfaces. The TCP power and map are calculated by tracking the path of incident rays of light through the 3-dimensional (3D) cornea using ray tracing. Ray tracing is a method of modeling the power of lens by tracing incident parallel rays of light through an optical system, such as the cornea. This method uses Snell's Law to refract the incoming rays of light and considers the 3D shape of the cornea and the difference in indices of refraction at each surface, which affect how the rays of light are bent. The 3D corneal shape is defined by the anterior surface curvature, the corneal thickness (pachymetry) and the posterior surface curvature, while the index of refractions used are n=1.0 for air, n=1.376 for cornea and n=1.336 for aqueous. Corneal power is then determined by n/f where f is the focal length, referenced to the anterior corneal surface and n the index of refraction of the aqueous (n=1.336).

In addition, the posterior-anterior corneal power ratio over the 3 different analyzed corneal zones was calculated as the ratio of the anterior value to the posterior value

3.7. PACHYMETRIC AND BIOMETRIC PARAMETERS

The thinnest point of the cornea as well as the corneal and anterior chamber volume calculated over a diameter of 8.0 mm, were recorded. Anterior chamber depth was calculated as the distance between the crystalline lens and the posterior cornea, measured among normals to the line between the outer iris endpoints.

Table 4: List of all parameters in the study

Curvature derived parameters	Elevation derived parameters	Wavefront derived parameters	Pachymetric derived parameters
	ANTERIOR DATA		
Kmax	With BFTA : Max elevation TP	RMS total corneal HOA	Thinnest point
Axial SimKs, Kf, Cyl	Max elevation Kmax	RMS corneal SA	Corneal Volume
Axial mean K (0-4mm)	Max elevation	RMS corneal vertical coma	
Tang mean K (4-7mm)		RMS corneal horizontal coma	
Tang mean K (7-10mm)	With BFS : Max elevation TP	RMS total corneal coma	
Eccentricity	Max elevation Kmax		
IS ratio	Max elevation		
	AAI		
	POSTERIOR DATA	Corneal Power (CP)	Biometric derived parameters
Kmax	With BFTA : Max elevation TP	Total CP (0-4mm)	Anterior chamber depth
Axial SimKs, Kf, Cyl	Max elevation Kmax	Total CP (4-7mm)	Anterior chamber volume
Axial mean K (0-4mm)	Max elevation	Total CP (7-10mm)	
Tang mean K (4-7mm)	With BFS :		
Tang mean K (7-10mm)	Max elevation TP		
Eccentricity	Max elevation Kmax		
IS ratio	Max elevation		
	AAI		
KERATOCONUS INDICES	DSI, SAI, OSI, SRI, CSI, IAI, ACP, SDP, AA		

4. DATA ANALYSIS

The data analysis was done in 3 steps.

We initially defined progressive keratoconus, all patients who had an increase superior or equal to 1D of Kmax ant, confirmed by 3 successive measurements, after 1year follow up.

Then, we selected all the progressive KC than met these criteria to constitute the progressive group (group 1), in contrast to the other eyes that did not meet these criteria and composed the group 2 of non-progressive eyes.

The change at every time-points was calculated for each parameter and the percentage of increase (PI) was then derived from this value in order to homogenize the different units for comparison.

The percentage of increase was calculated as follows:

$$(\text{Final value}-\text{initial value})/\text{initial value}.$$

For example at 12 months: percentage of increase= $(\text{Kmax M12}-\text{Kmax M0})/\text{Kmax M0}$

We compared the Delta of the Kmax ant (gold standard) to the delta of all the other parameters at every time-point (M3, M6, M9, M12) to determine whether a parameter was changing earlier than the Kmax ant. We used Student test with a p-value< 0,05.

Those analyzes were conducted under SAS and Excel.

Once the most relevant parameters were identified, we calculated ROC curves to obtain a threshold that could be informative of the scalability of Kmax ant at 1 year.

For each score, we:

- Analyze the sensitivity and specificity of the score in all groups
- Calculate the area under the ROC curve using the method of Hanley
- Estimate the sensitivities and specificities for each threshold score

Within each sample, a comparison of ROC curve method based on Delong nonparametric approach areas was made.

Those analyzes were conducted under Stata9 with a p-value<0,05.

RESULTS

1. DESCRIPTION OF THE POPULATION

1.1. AGE AND SEX OF THE POPULATION

The average age was 26,4 +/- 4,8 years.

There were 44 men for 19 women in our study.

1.2. POPULATION MONITORING OVER TIME

The characteristics of the subjects over time are on the table below.

Table 5 : Characteristics of the subjects over time

	Eyes lost	Cxl	ICR	Keratop.	Eyes studied
Baseline	0/126	10/126	2/126	5 /126	109
M3	20/109	14/126	2/126	5/126	85
M6	34/109	16/126	2/126	5/126	69
M9	31/109	20/126	2/126	5/126	68
M12	48/109	22/126	2/126	5/126	49

2. DATA OF OUR STUDY AT BASELINE

We studied 53 parameters in this study but we have chosen to focus only on certain values that were relevant after a first analysis

Key data are summarized in the table below.

Table 6: Main parameters: mean and standard deviation

	Kmax ant (D)	Kmax post (D)	Coma V (μm)	Coma tot (μm)	AAI post
Mean+/- SD	51,55+/-5,34	-8,11+/-1,15	-1,46+/-1,37	1,72+/-1,29	72,13+/-43,74

Large standard deviations witness to the diversity of the severity of the disease in our population.

Others data are summarized in the tables 4, 5, 6, 7 and 8.

Table 7: Anterior surface parameters: mean and standard deviation

Parameter (Anterior surface)	Mean N=109	Standard deviation N=109	Bounds N=109
BFTA MAETP	11,18	11,73	(-9 ;60)
BFTA MAEKs	17,18	14,26	(-3 ;130)
BFTA MAE	22,77	14,30	(-7 ;135)
BFS MAETP	11,96	9,58	(-8 ;43)
BFS MAEKs	12,18	11,46	(-3 ;56)
BFS MAE	16,47	11,98	(1 ;68)
AAI anterior	40,69	24,61	(14 ;205)
Kmax anterior (D)	51,66	5,34	(40,04 ;64,2)
Axial SimKs(D)	47,13	4,91	(38,29 ;60,47)
Axial SimKf (D)	42,91	6,91	(34,62 ;55,21)
Cylinder (D)	2,69	1,98	(0,48 ; 8,96)
Axial MeanK (0-4mm)	44,69	6,24	(37,79 ; 58,36)
Tang MeanK (4-7mm)	40,88	3,25	(38,31 ; 51,05)
Tang MeanK (7-10mm)	37,56	6,65	(38,05 ; 53,84)
Eccentricity	0,65	0,66	(0 ; 4,09)
IS anterior ratio	6,09	4,21	(0,88 ; 25,26)

Table 8 : Posterior surface parameters: mean and standard deviation

Parameter (Posterior surface)	Mean N=109	Standard deviation N=109	Bounds N=109
BFTA MPETP	23,29	23,69	(-15 ; 82)
BFTA MPEKs	32,60	25,19	(-3 ; 96)
BFTA MPE	41,31	26,34	(3 ; 101)
BFS MPETP	25,09	19,49	(0 ; 91)
BFS MPEKs	23,93	20,62	(0 ; 100)
BFS MPE	30,51	19,11	(2 ; 100)
AAI posterior	72,13	43,74	(17 ; 184)
Kmax posterior	-8,11	1,15	(-13,2 ; -5,73)
IS posterior ratio	5,54	4,22	(-3 ; 21,4)
Axial SimKs (D)	-6,97	0,84	(-11,74 ; -5,64)
Axial SimKf (D)	-6,30	0,81	(-8,62 ; -4,89)
Cylinder (D)	-0,57	0,41	(-11,46 ; -0,02)
Axial MeanK (0-4mm)	-6,66	0,66	(-9,34 ; -5,18)
Tang MeanK (4-7mm)	-5,53	0,65	(-7,08 ; -4,19)
Tang MeanK (7-10mm)	-4,85	1,03	(-11,56 ; -4,01)
Eccentricity	0,79	0,79	(0 ; 4,38)

Table 9 : Wavefront parameters: mean and standard deviation

Parameter (Wavefront analysis)	Mean N=109	Standard deviation N=109	Bounds N=109
Total CHOA	2,01	1,34	(0,33-5,18)
RMS SA	0,09	0,36	(-1,21 ; 0,93)
RMS COMA V	-1,46	1,37	(-7,43 ; 4,02)
RMS COMA H	0,10	0,68	(-3,32 ; 3,34)
TOTAL COMA	1,72	1,29	(0,14 ; 8,15)

Table 10 : Corneal power: mean and standard deviation

Parameter (Corneal power (cp))	Mean N=109	Standard deviation N=109	Bounds N=109
TCP (0-4mm)	44,02	5,41	(35,93 ; 55,24)
TCP (4-7mm)	43,46	2,32	(35,85 ; 51,19)
TCP (7-10mm)	43,52	2,95	(35,51 ; 62,57)

Table 11: KPI variables, pachymetric and biometric data: mean and standard deviation

Parameter	Mean N=109	Standard deviation N=109	Bounds N=109
KPI variables			
DSI	6,33	5,20	(0,90 ; 34,47)
OSI	5,69	5,12	(0,19 ; 31,08)
SRI	1,49	0,76	(0,24 ; 5,34)
CSI	1,02	1,44	(-2,92 ; 6,38)
IAI	0,76	0,39	(0,36 ; 2,72)
ACP	46,50	7,78	(34,38 ; 59,39)
SDP	2,46	1,72	(0,39 ; 9,44)
PACHYMETRIC DATA			
TP	500,66	40,16	(394,53 ; 592,63)
Corneal volume	31,91	2,05	(27,34 ; 46,90)
BIOMETRIC DATA			
AC depth	3,39	0,26	(2,74 ; 3,97)
AC volume	122,40	19,13	(86,69 ; 158,48)

3. STANDARD DEVIATION OF OUR EXAMS

For each eye, we repeated the examination 3 times and we have considered valid when it met the quality criteria of Galilei. The reliability and intra observer repeatability were tested for each variable with 3 measures. We find the same results as the article written by Koch and Wang (54).

The results are on the table below

Table 12: Standard deviation of the exams

	Kmax ant	Kmax post	Coma V	Coma tot	AAI post
Mean	49,35	-7,54	-1,38	1,15	56,66
Mean SD	0,31	0,03	0,08	0,08	1,5

4. OBSERVATIONAL STUDY

We retrospectively analyzed the evolution profiles of several parameters in patients who presented an increase of Kmax ant >1D at 12 months.

The percentage of progression between each time point was calculated for each parameter as followed. We have done so in order to homogenize the units for all the parameters. Then, we have compared the percentage of progression of each new parameter to the gold standard, the Kmax ant.

The percentage of increase was calculated as follows:

$$(\text{Final value}-\text{initial value})/\text{initial value}.$$

The four main parameters were: Kmax post, Coma V, coma tot and AAI post. We also studied, IS ant, anterior and posterior eccentricity and corneal pachymetry which are considered as gold standard parameters.

All the results are on the graphs below.

Table 13: Data of patients who present an evolution of Kmax anterior > 1D Vs Control group: percentage of evolution

		N	Kmax Ant	Kmax Post	Coma V	Coma tot	AAI post	IS Ant	Ecc Ant	Ecc Post	Corneal Pach
M0 N=109	Progressive	0	0	0	0	0	0	0	0	0	0
	Non – progressive	109	0	0	0	0	0	0	0	0	0
M3 N=85	Progressive	4	-0.01	0	0.15	0.19	0.03	0.11	0.37	0.09	-0.01
	Non - progressive	81	0	0	0.01	0	0.13	0.05	0.17	-0.34	0
M6 N=69	Progressive	5	0	0.01	0.21	0.16	0.03	0.25	0.28	-0.07	0
	Non - progressive	64	0.01	0.01	-0.01	-0.02	0.15	0.05	0.99	-0.01	0
M9 N=69	Progressive	4	0.01	0.03	0.23	0.14	0.05	0.14	-0.11	-0.1	-0.01
	Non - progressive	64	0	0	0.01	-0.03	0.21	-0.02	0.34	0.5	0
M12 N=49	Progressive	6	0.03	0.06	0.27	0.24	0.03	1.8	-0.16	-0.19	0.01
	Non - progressive	43	0	0	-0.01	0.01	0.26	0.36	-0.2	-0.57	-0.14

4.1. GROUP WITH AN INCREASE OF KMAX ANT > 1D AT 12 MONTHS VS CONTROL GROUP

4.1.1. Kmax ant

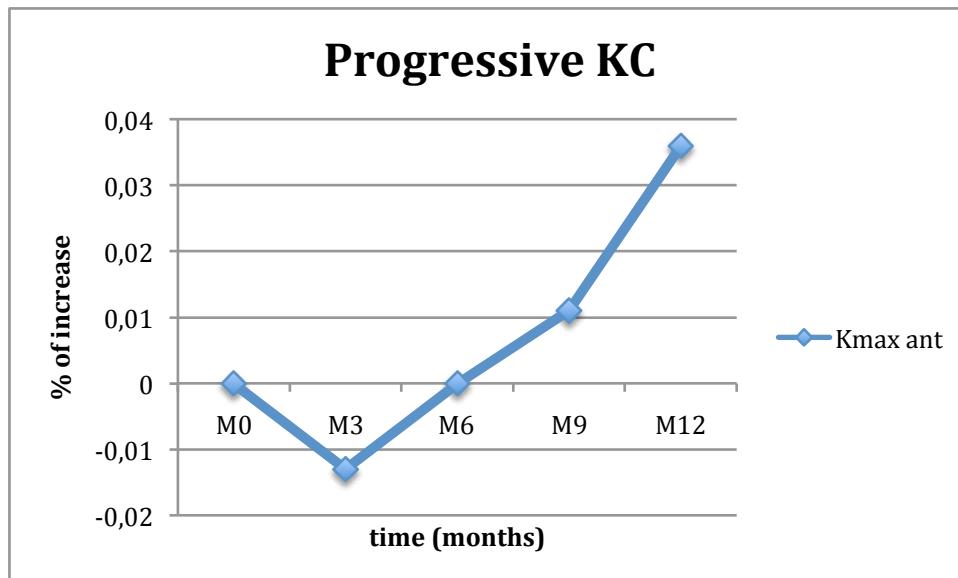


Figure 7: Kmax ant evolution over time: progressive KC

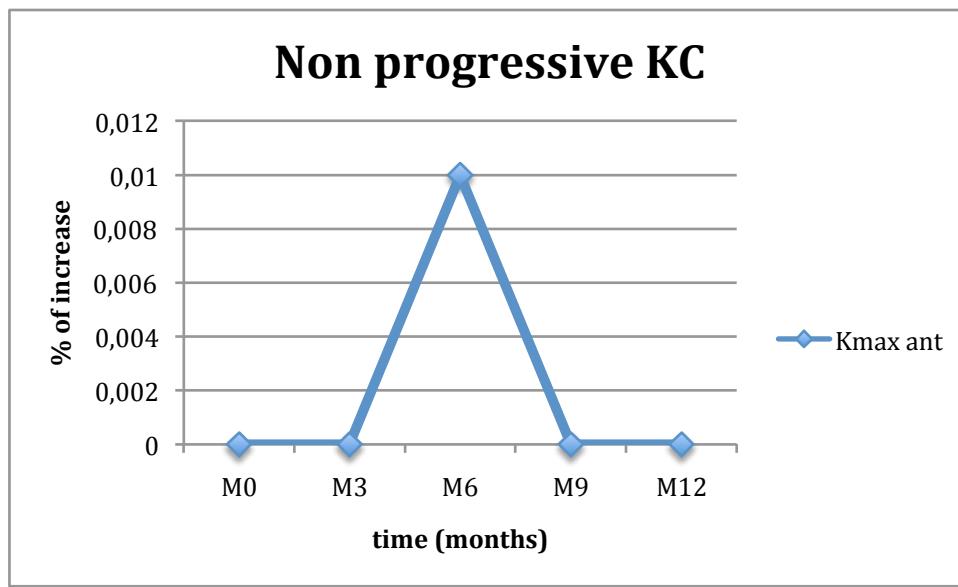


Figure 8: Kmax ant evolution over time: non progressive KC

4.1.2. Kmax post

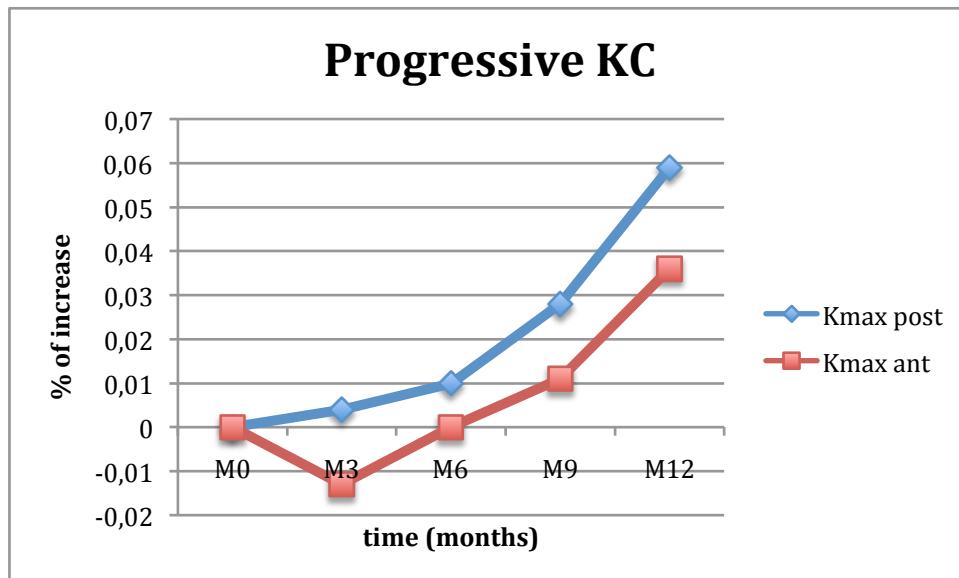


Figure 9: Kmax post evolution over time: progressive KC

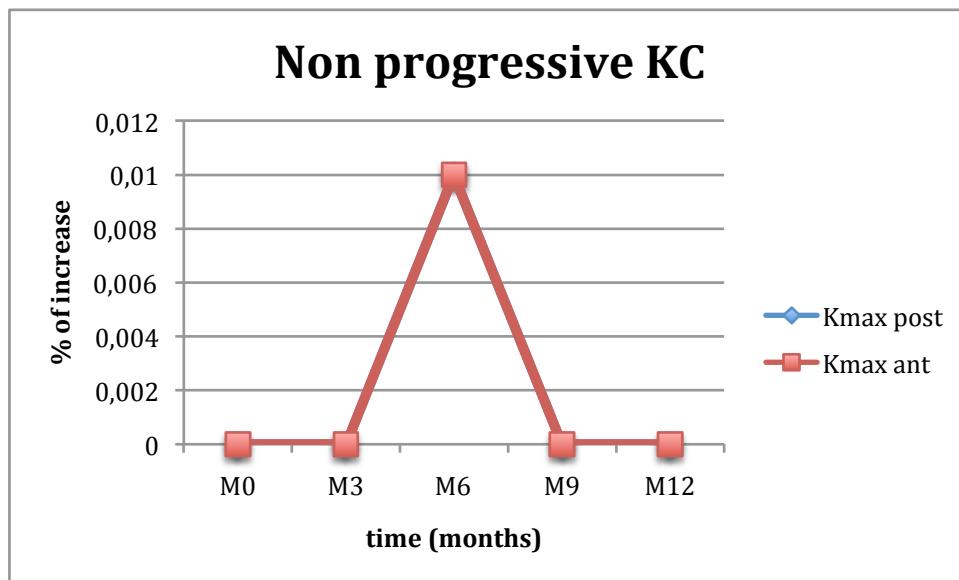


Figure 10: Kmax post evolution over time: non progressive KC

Increase of Kmax post seems to be more precocious than the Kmax ant and larger in the evolutionary group.

4.1.3. Coma V

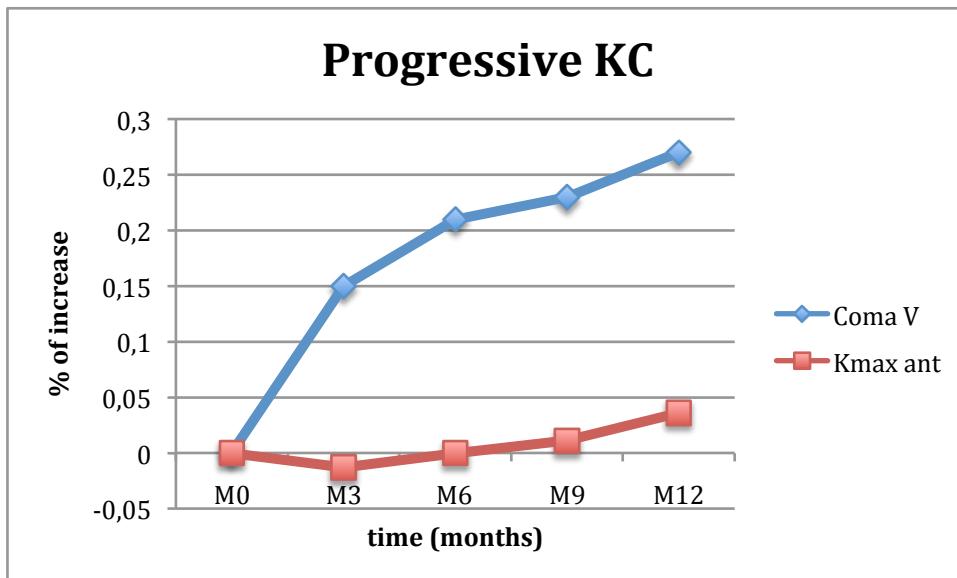


Figure 11: Coma V evolution over time: progressive KC

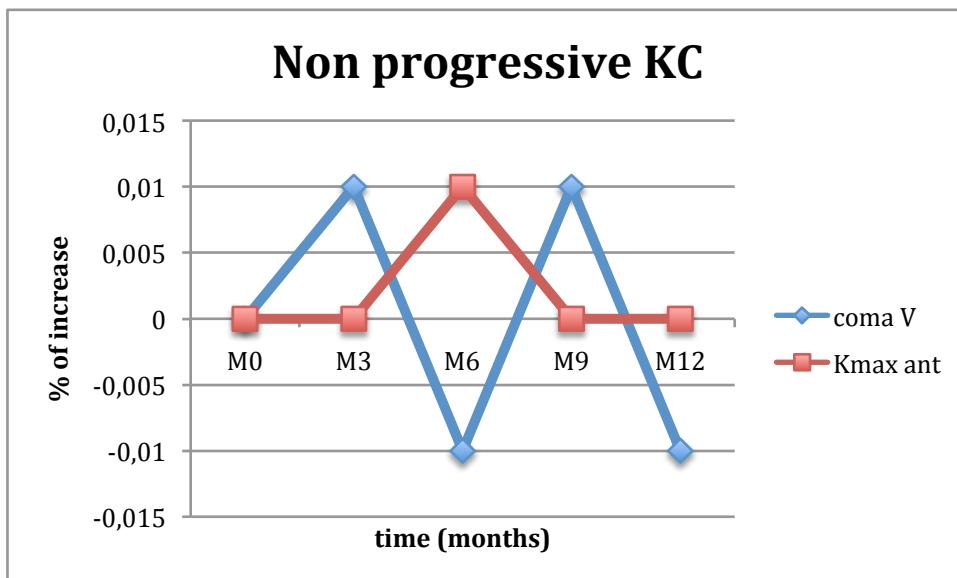


Figure 12: Coma V evolution over time: non progressive KC

Increase of Coma V seems to be more precocious than the Kmax ant and larger.

4.1.4. Coma tot

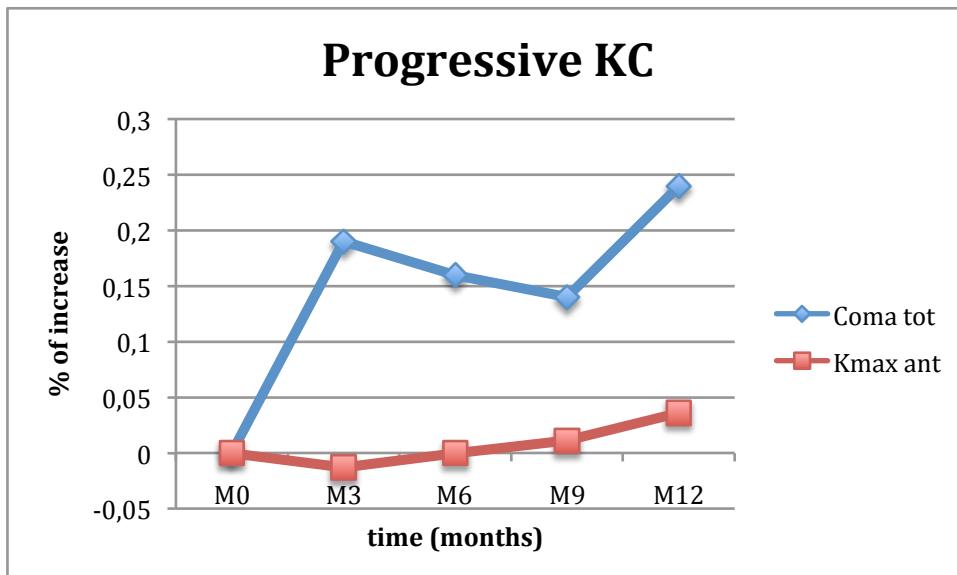


Figure 13: Coma tot evolution over time: progressive KC

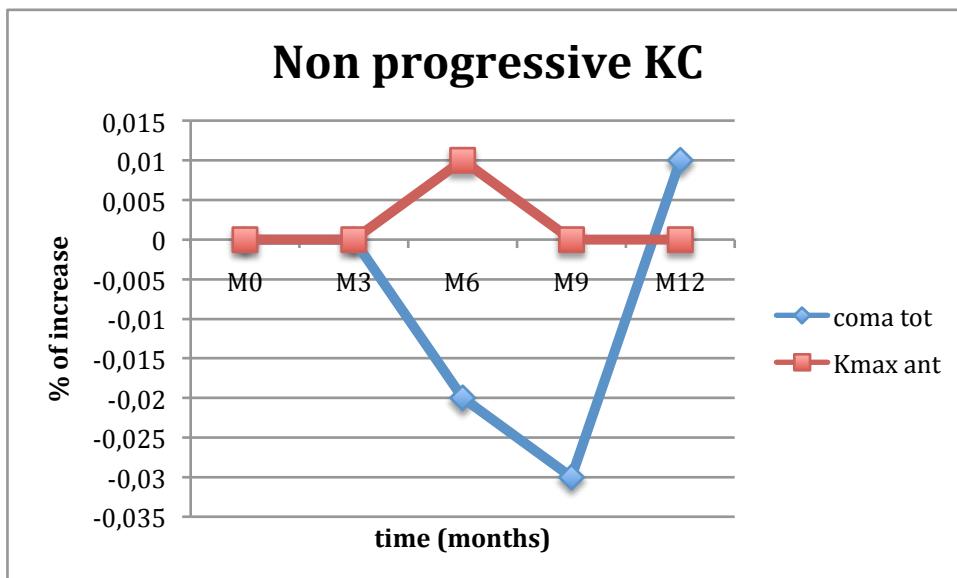


Figure 14: Coma tot evolution over time: non progressive KC

In the evolutionary group, the increase of Coma tot seems to be larger than these of Kmax ant. These results are not found in the control group.

4.1.5. AAI post

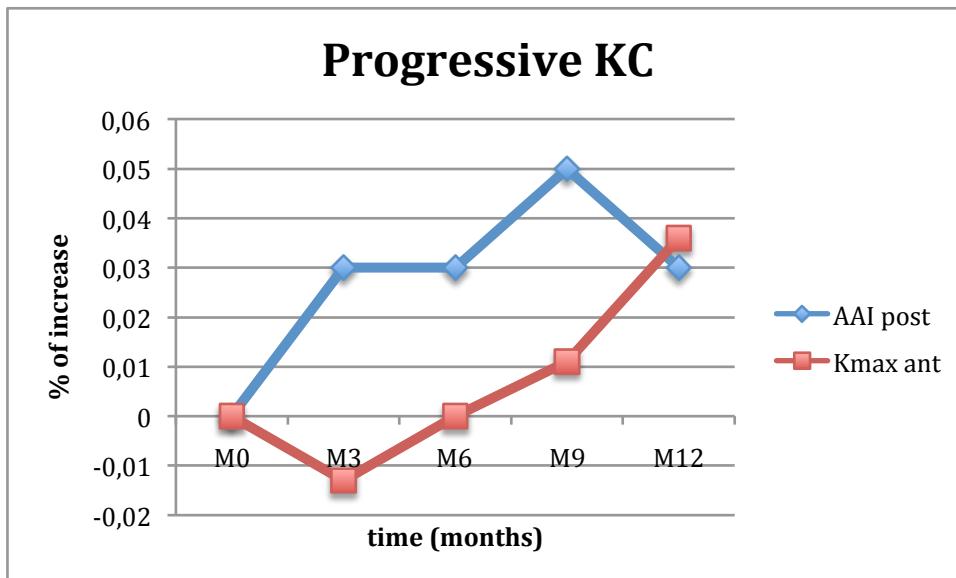


Figure 15: AAI post evolution over time: progressive KC

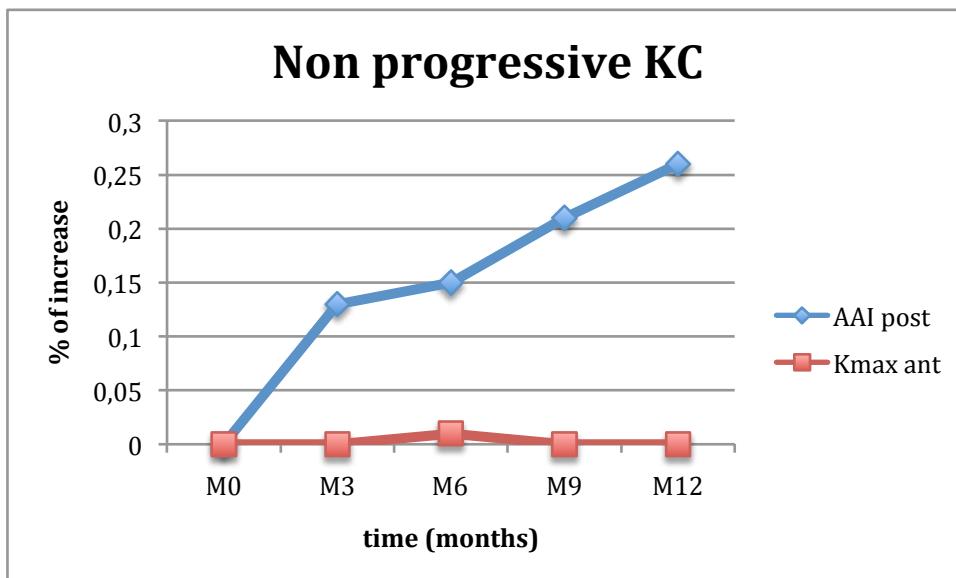


Figure 16: AAI post evolution over time: non progressive KC

Increase of AAI post seems to be more precocious than the Kmax ant and larger.

4.1.6. IS ant

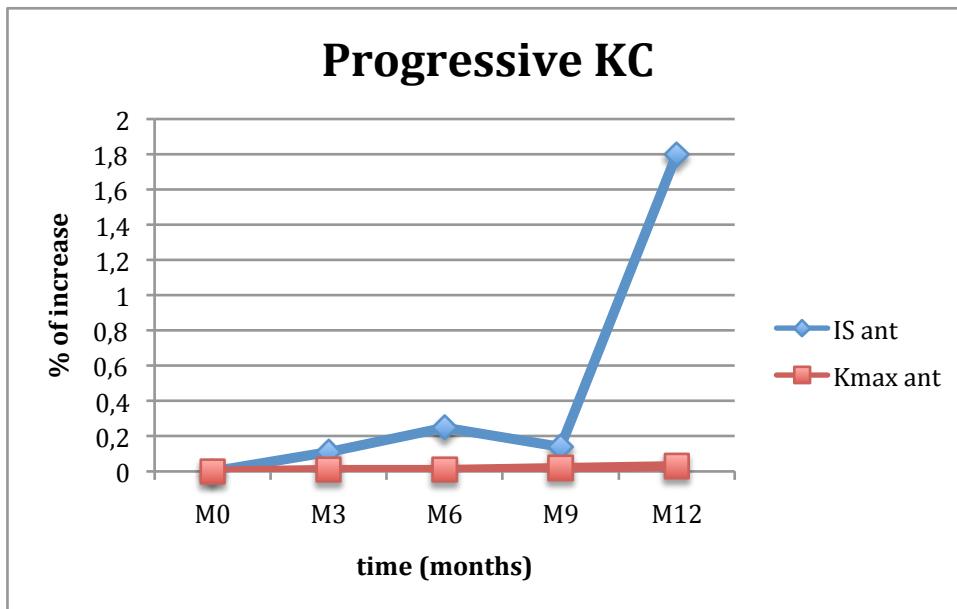


Figure 17: IS ant evolution over time: progressive KC

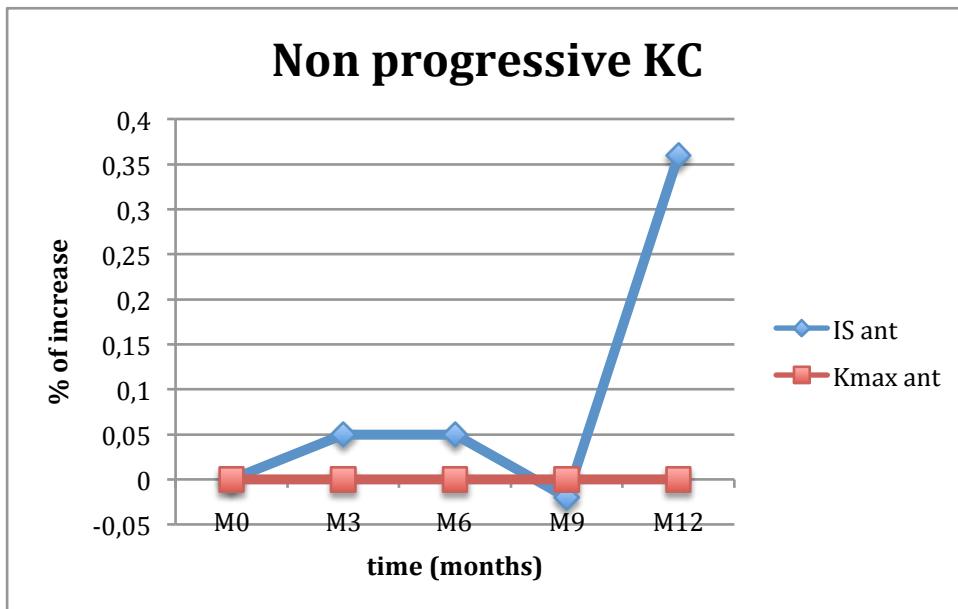


Figure 18: IS ant evolution over time: non progressive KC

The curves between the two groups (evolutionary and control) seem to have the same shape.

4.1.7. Eccentricity ant

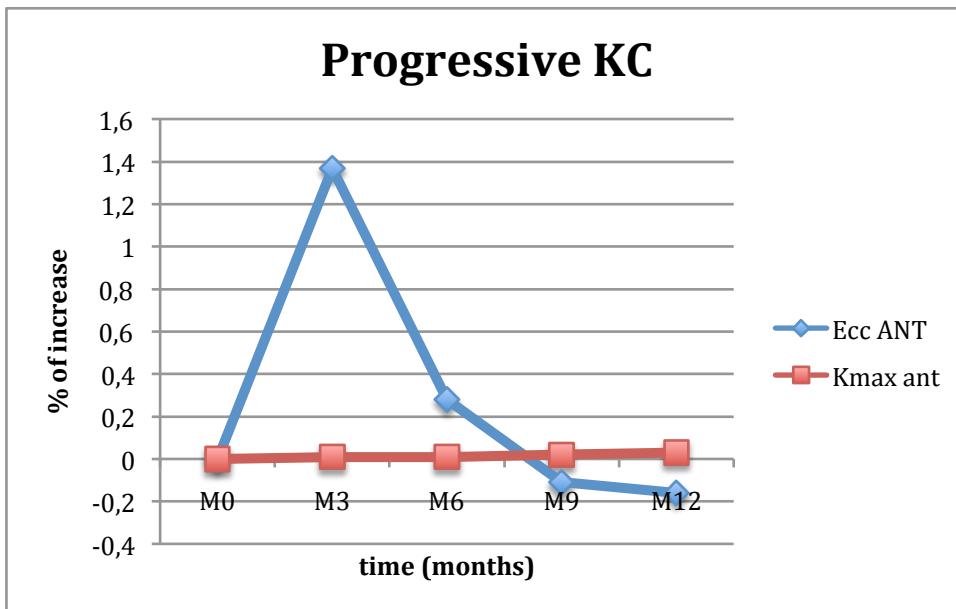


Figure 19: Eccentricity ant evolution over time: progressive KC

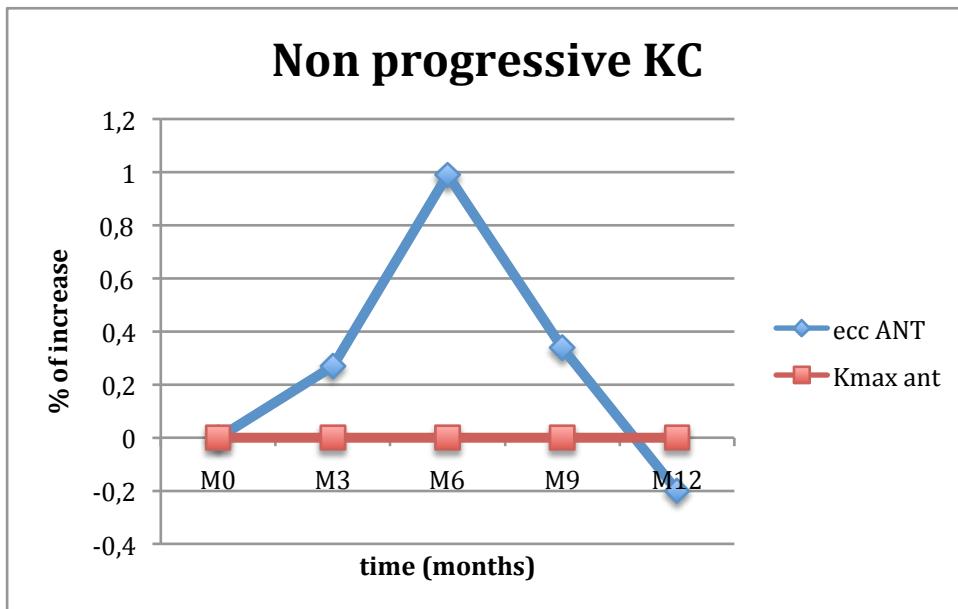


Figure 20: Eccentricity ant evolution over time: non progressive KC

The curves between the two groups (evolutionary and control) seem to have the same shape.

4.1.8. Eccentricity post

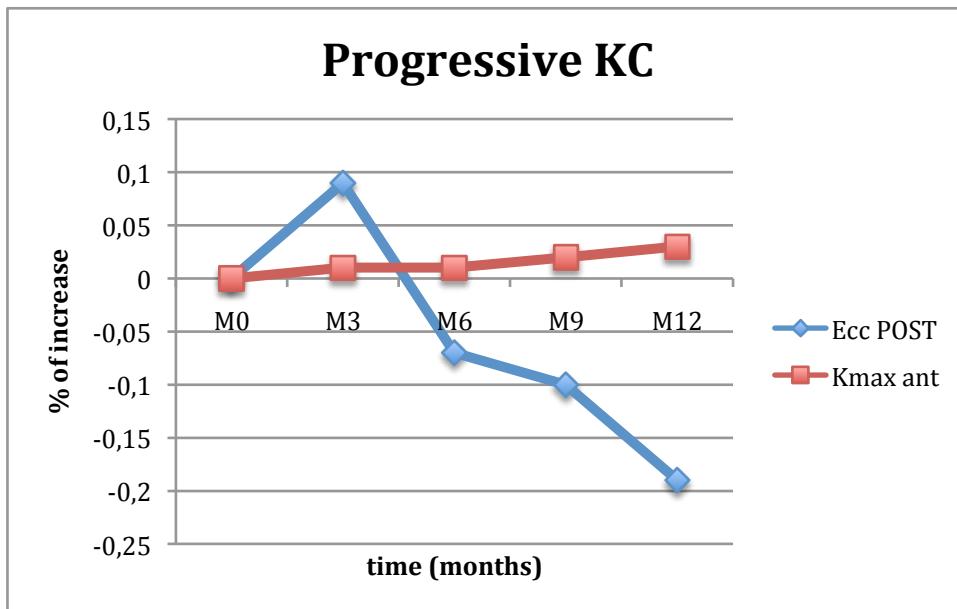


Figure 21: Eccentricity post evolution over time: progressive KC

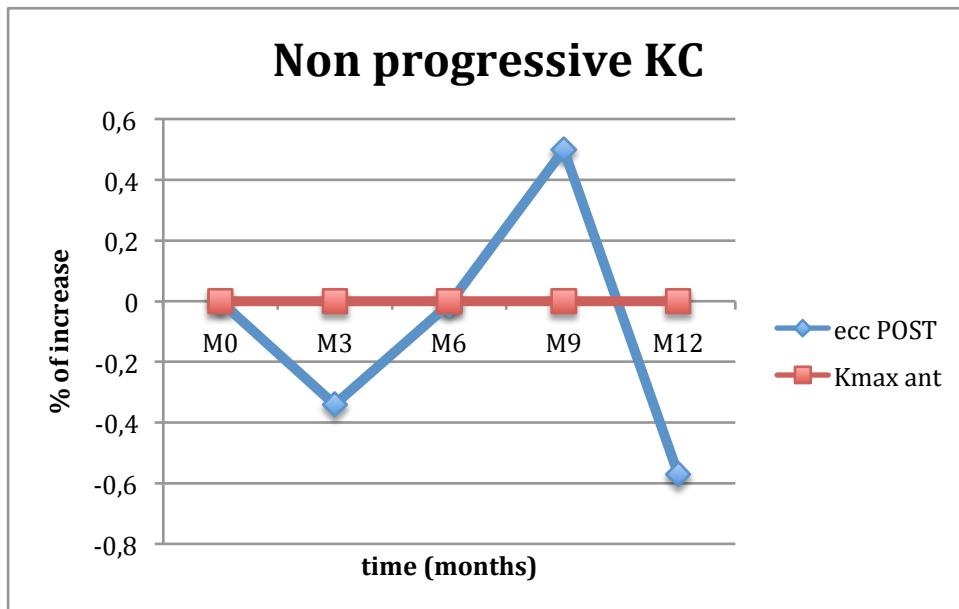


Figure 22: Eccentricity post evolution over time: non progressive KC

The evolutionary curve doesn't seem more precocious than the Kmax one in the progressive group.

4.1.9. Corneal pachymetry

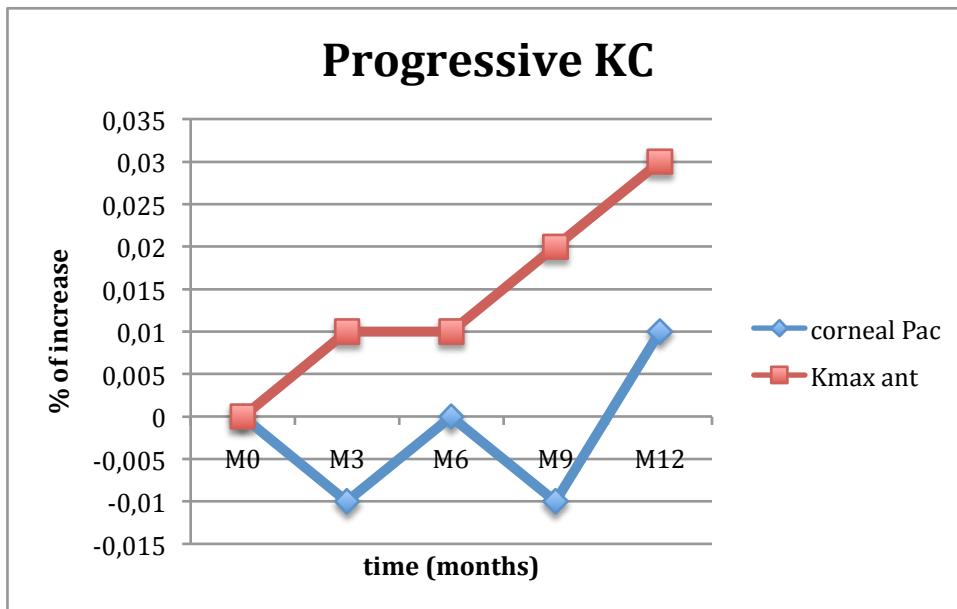


Figure 23: Corneal pachymetry evolution over time: progressive KC

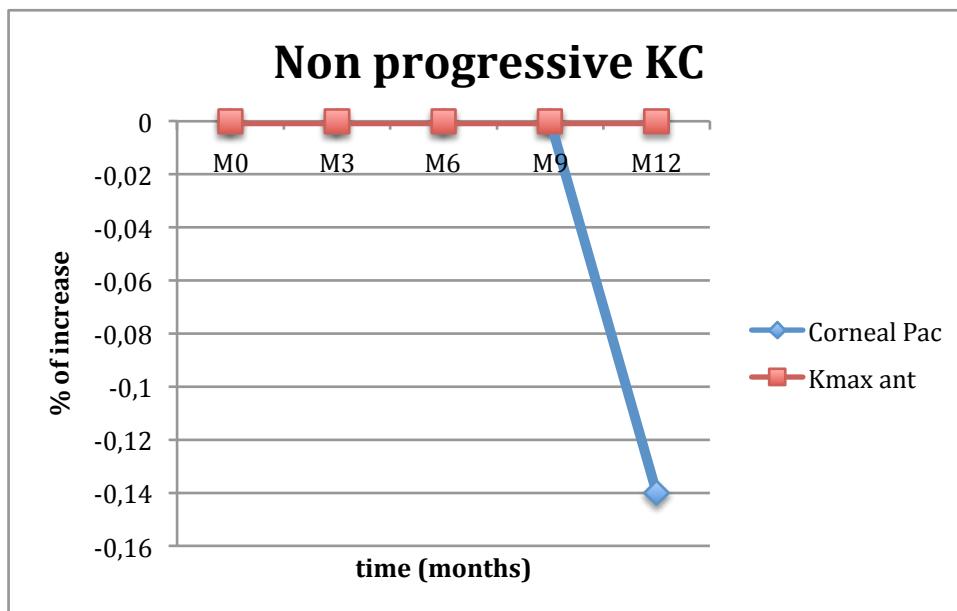


Figure 24: Corneal pachymetry evolution over time: non progressive KC

In the evolutionary group, the Corneal Pac curve isn't more precocious than the Kmax one.

5. STATISTICAL ANALYSIS

We made our analyzes using two softwares: SAS and excel.

We used the Student test and compare each parameter between the progressive group and the non progressive group.

We considered that our analysis were statistically significant when we found a p-value < 0,05.

5-3 Group with an increase of Kmax ant > 1D at 12 months VS control group

Table 14: Comparison of changes in the different parameters between the progressive and non progressive groups at each time point: Statistical significance (p value)

	M12	M9	M6	M3
Kmax ant	0,0000000013	0,0977	0,0614	0,2285
Kmax post	0,0009966306	0,0185	0,0485	0,8253
coma V	0,0373	0,0299	0,0317	0,0620
coma tot	0,0068	0,0268	0,0088	0,0164
AAI post	0,8231	0,9912	0,4224	0,4802
IS ant	0,0008	0,9926	0,1002	0,4406
Corneal pac	0,22085	0,4702	0,0756	0,8840
Ecc ant	0,0012	0,9281	0,1322	0,2508
Ecc post	0,0093	0,9401	0,0969	0,2725
Nb of active cases / control group	6/43	4/64	5/64	4/81

On the table we showed that Kmax ant becomes significant only at the twelfth month.

3 others parameters are significant before the Kmax ant: Coma tot in the third month, Coma V and Kmax post at the sixth month.

On curves, it was assumed that the Kmax post, coma V and Coma tot were earlier than the Kmax ant. Thanks to statistical analysis, it was confirmed this idea.

To conclude, for each evolutionary group, 3 parameters emerge as earlier than Kmax ant ie Kmax post, Coma V and Coma tot.

Now it remains to be determined from what threshold values we can talk about changing parameters.

Moreover, none of the following parameters showed any superiority compared to Kmax both on the charts and on the statistical analysis: IS ant, Corneal pachymetry Ecc ant and post.

AAI post seemed to be earlier than the Kmax ant on the curves but doesn't emerge as significant in the statistical analyzes.

6. AUROC curves

For each score, we made:

- an analysis of the sensitivity and specificity of the score in all 3 groups
- a calculation of the area under the ROC curve using the method of Hanley(67)
- an estimation of the sensitivities and specificities for each threshold score

Within each sample: comparison of ROC curve method based on Delong nonparametric approach areas(68).

Analyzes were conducted under Stata9.

6.1. GROUPS WITH AN INCREASE OF KMAX ANT >1D AT 12 MONTHS

6.1.1. Group with an increase of Kmax ant >1D at 12 months: Coma V

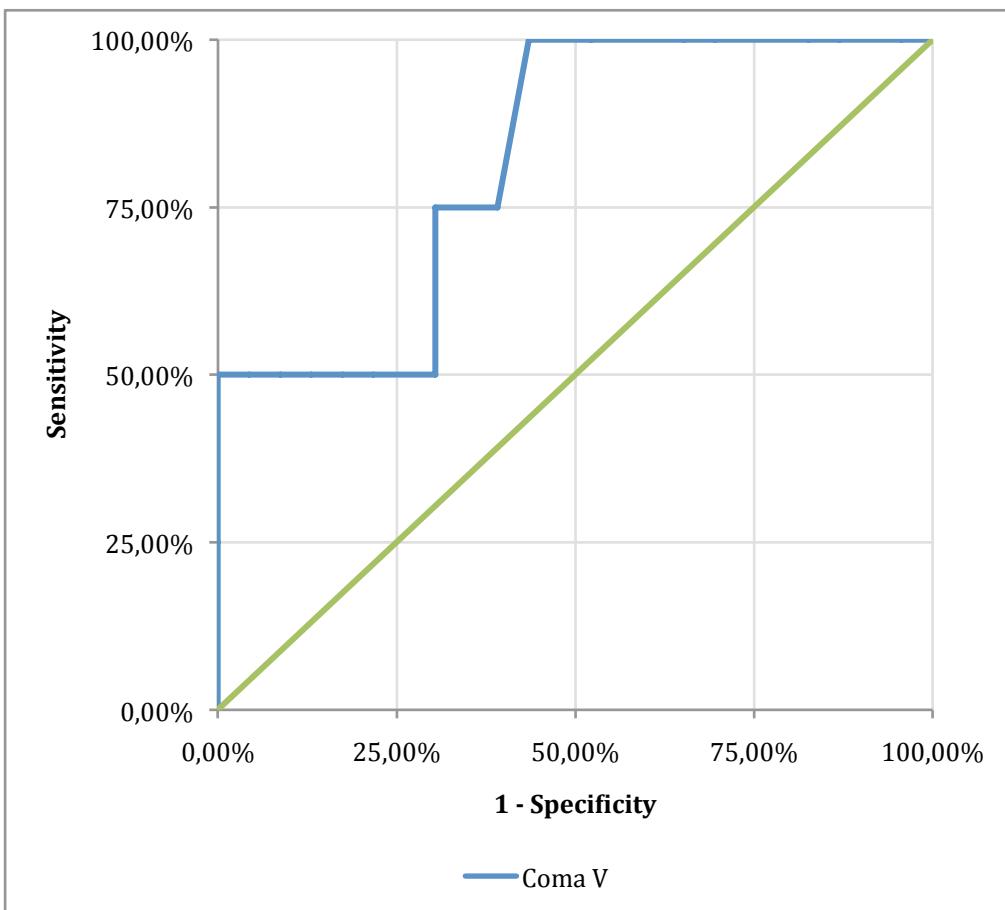


Figure 25: Coma V : ROC curve for group with an increase of Kmax ant > 1D at 12 months

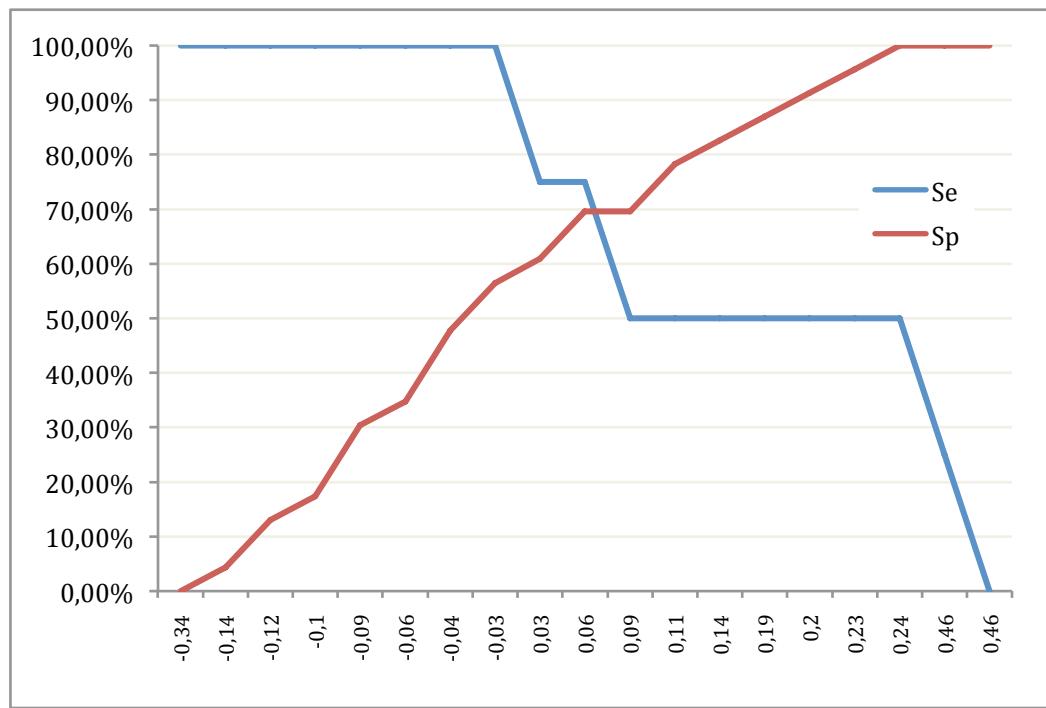


Figure 26: Curves of sensibility and specificity

We find a cut-off value of 0,06 with a sensitivity of 75% and a specificity of 69% for Coma V for patients that evolve at twelfth month.

6.1.1. . Group with an increase of Kmax ant >1D at 12 months: Coma tot

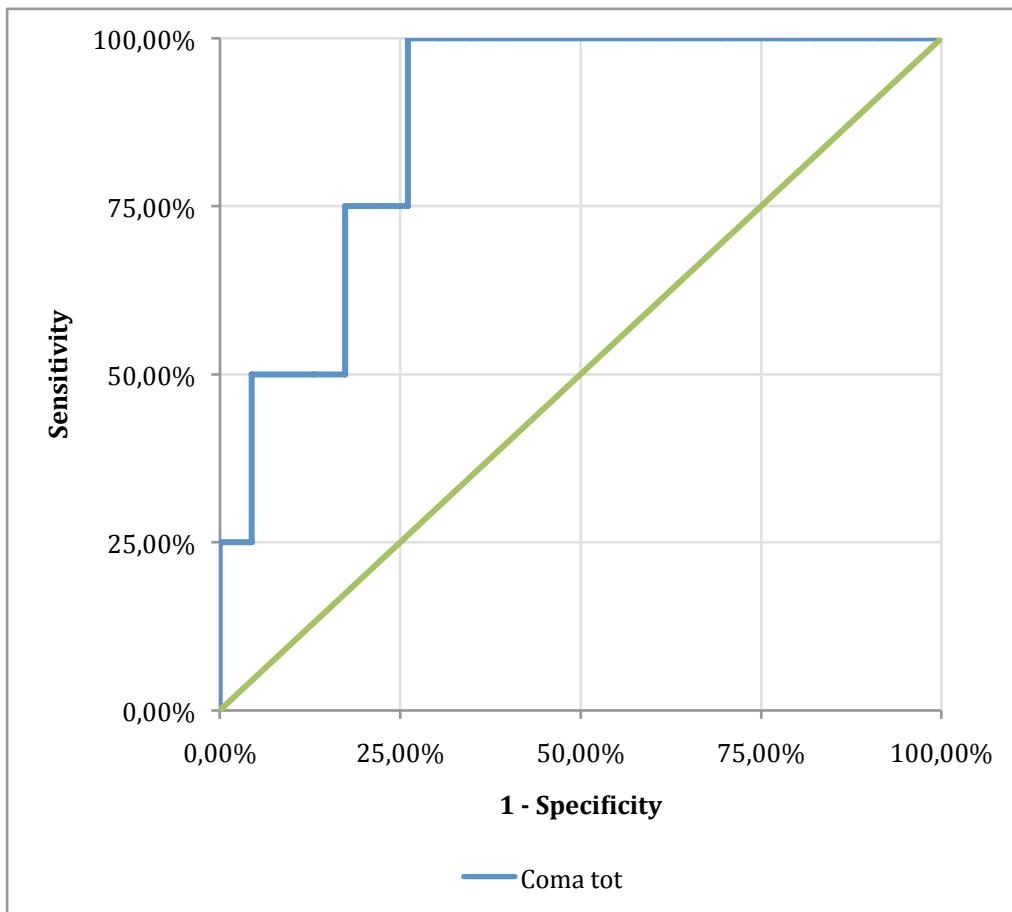


Figure 27: Coma tot : ROC curve for group with an increase of Kmax ant > 1D at 12 months

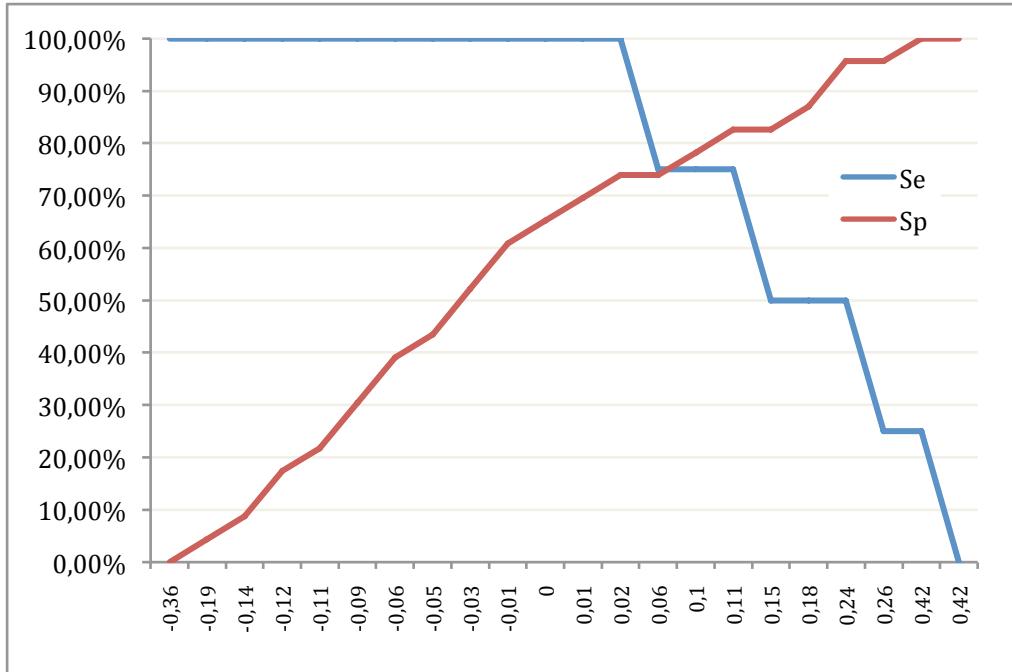


Figure 28: Curves of sensibility and specificity

We find a cut-off value of 0,11 with a sensitivity of 75% and a specificity of 82,6% for Coma tot for patients that evolve at twelfth month.

6.1.2. Group with an increase of Kmax ant >1D at 12 months: Kmax post

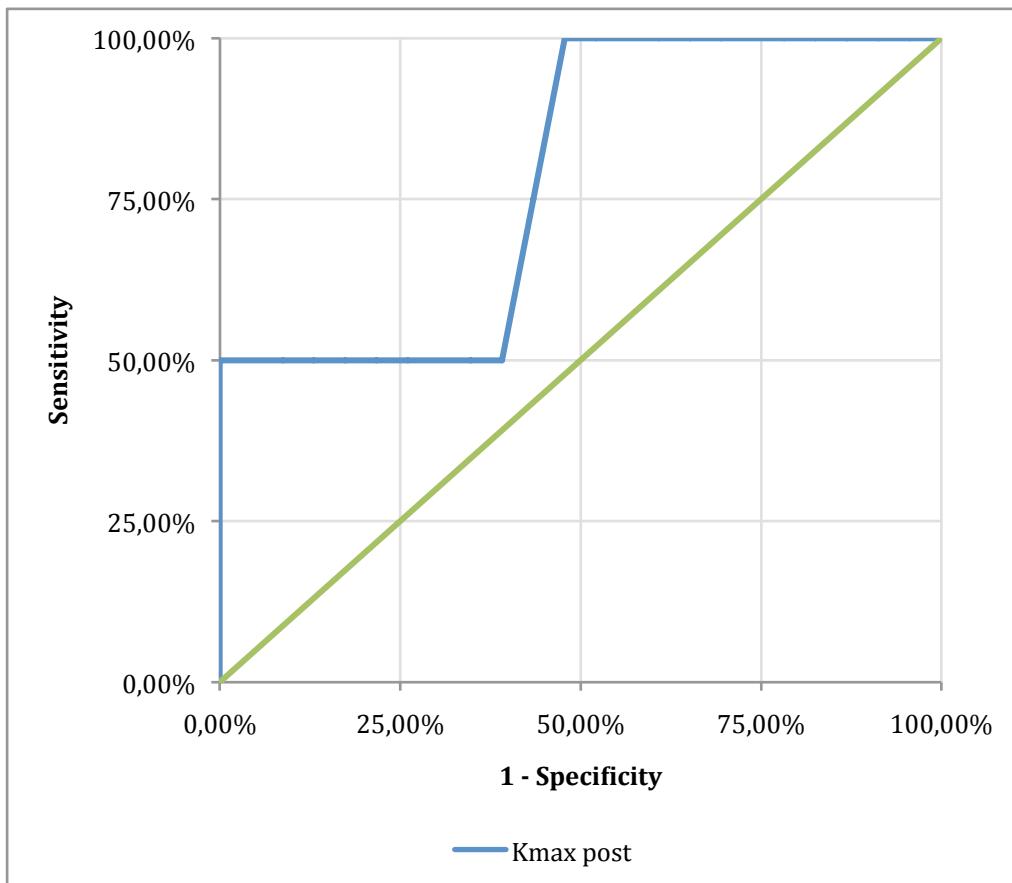


Figure 29: Kmax post : ROC curve for group with an increase of Kmax ant > 1D at 12 months

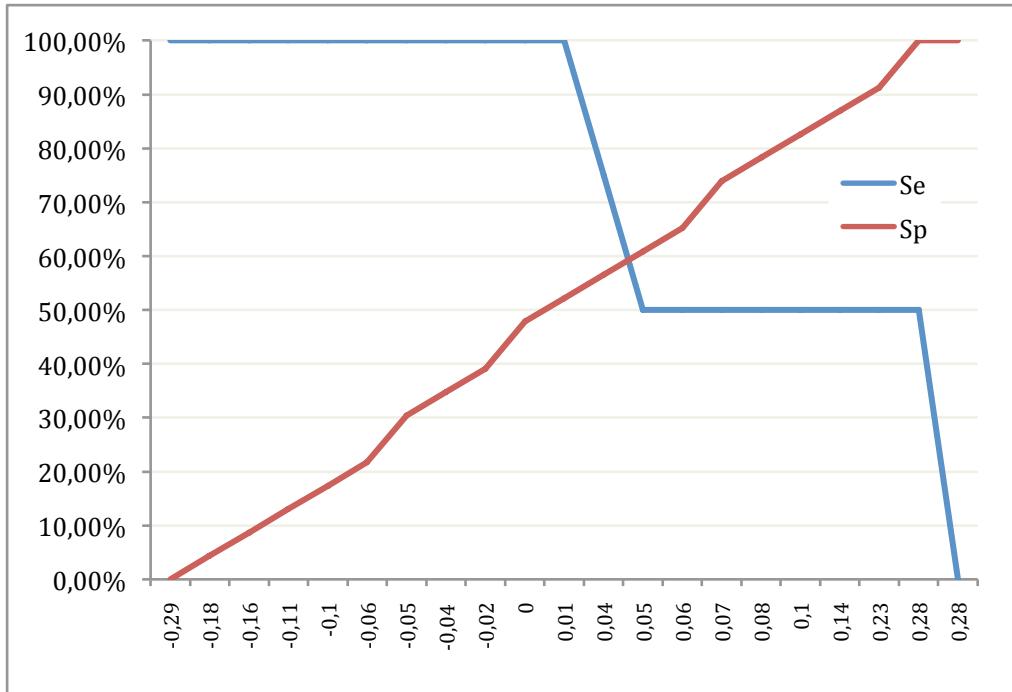


Figure 30: Curves of sensibility and specificity

We find a cut-off value of -0,04 with a sensitivity of 75% and a specificity of 56% for Kmax post for patients that evolve at twelfth month.

In summary,

Table 15 : Thresholds found

N=27	
Nb of active cases	4
D RMS coma V	$\geq 0,06$ (Se=0,75 Sp=0,69)
D total coma	$\geq 0,11$ (Se=0,75 Sp=0,86)
D Kmax post	$\leq -0,04$ (Se=0,75 Sp=0,56)

Se : sensitivity – Sp : specificity

Table 16 : AUROC curve

N=27	
Nb of active cases	4
D RMS coma V	0,82
D total coma	0,88
D Kmax post	0,78
Comparaison test (p-value)	0,610

The area under the curve indicates the discriminating power of each parameter. The higher the value is to 1, the setting is more discriminating. No difference was significant between the parameters studied (p-value greater than 0.05)(69).

DISCUSSION

Determine the evolution of keratoconus at an early stage remains an important challenge: this allows treating patients before the disease has an impact on vision. This is all the more important that they are often very young patients.

Determine more precise parameters of evolution would also eliminate problems too large of standard deviation of the current topo-tomography in our daily practice.

Throughout this study we therefore sought which could be the most predictive and earliest parameters of keratoconus evolution.

So for this we studied no less than 54 topo-tomographic parameters and watched their behavior over time in patients with keratoconus.

Two types of analyzes were performed: an observational analysis and a statistical one.

Among all the parameters, some appeared to be earlier and more predictive on observational analysis than Kmax ant. It was about Kmax post, coma V, coma tot and AAI post.

Then we tried to confirm these trends with statistical analysis. For each evolutionary group, three parameters were significant of precocity and predictability of keratoconus evolution before Kmax ant: Kmax post, Coma V and Coma tot.

Although AAI post seems to be more efficient than the Kmax ant on observational analysis, it is by no means emerged significant in statistical analysis.

Then for each of these three parameters we examined the thresholds beyond which we could talk about evolution and we expressed it in AUROC curves.

Then we found that for Kmax post, we can consider that there will have an evolution of Kmax ant> 1D if Kmax post increases of more than -0,04D at 6 months.

For Coma V, we can consider that there will have an evolution of Kmax ant>1D at 12 months if Coma V increases of more than 0,06D at 6 months

For Coma tot, we can consider that there will have an evolution of Kmax ant>1D if Coma tot increases of more than 0,11D at 6 months.

It is also important to note that no pachymetric parameter emerged in this study. Although some people (70)(71)(72) make it a determining factor in the diagnosis and severity(22) of keratoconus, we did not find any benefit to consider pachymetric clues to track patients in our study.

Another study by Reddy published in april 2014(73) on the parameters provided by the Galilei described that pachymetry showed promising results in differentiating keratoconus from normal eyes.

In a same way, some scoring systems(74) based on CCT are developed to differentiate diseased eyes from healthy one.

Similarly, eccentricity, whether anterior or posterior, showed no benefit over Kmax ant in the diagnosis of progressive keratoconus. Some studies (75) demonstrated that eccentricity can be helpful for the diagnosis of keratoconus at an early stage but in our work we found no interest to consider this parameter in monitoring patients.

Concerning anterior IS value, we also found no interest for this parameter in monitoring keratoconus. Some authors(76)(55) suggested that IS value was statistically the most significant in separating the keratoconus group from normal eyes.

Some publications(77) described that some quantitative indices (I-S and KISA values) might predict the progression of keratoconus.

Others(78) on the contrary consider that asymmetry nasal / temporal is more specific for keratoconus than vertical curvature asymmetry.

To our knowledge, this study is the first to evaluate new criteria of keratoconus evolution and no publication has yet described our three parameters (Kmax post, Coma V and Coma tot) as earlier and more predictive of keratoconus evolution.

However, a lot of publications describe that those parameters are already used to diagnose the pathology.

1. CONCERNING KMAX POST

In our study, we show that the variation of Kmax post is higher and earlier than Kmax ant. Some studies describe the same phenomenon to diagnose keratoconus that goes in the direction of an earlier event. For Fukuda and al(57), posterior elevation is the best discrimination parameter

for forme fruste keratoconus whatever the topography used. In a same way, a new parameter based on data of the posterior corneal surface was developed by C. Roberts and her team(66) : the Cone Location Magnitude Index is a combination of topographic information from the anterior and posterior surfaces and is a new robust index to detect the presence or absence of keratoconic index.

Others publications(70) agree that we should no longer just look at the anterior face to diagnose keratoconus but also and especially the posterior one.

All these studies concur in the same direction, namely that the posterior face is the seat of changes well before an impact on the front (79). So it seems logical to extend these ideas to the keratoconus evolution and not just to his diagnosis.

So viewing Kmax post as a new factor of keratoconus evolution beyond a threshold of -0,04D at 6 months seems legitimate.

2. CONCERNING COMA V

In our study, we find that Coma V seems to be a good parameter to earlier diagnosis of keratoconus since for each of evolutionary group, it was statistically significant.

No study has already described this but many studies exist to describe the important role of CHOAs in the detection and diagnosis of keratoconus.

Feizi and *al.*(80), tried to compare corneal higher-order aberrations between normal and keratoconic eyes, and to investigate the association between elevation-based corneal topographic indices and corneal wavefront data. They showed that in the keratoconus group, the strongest association was observed between vertical coma. Moreover, vertical coma aberrations were significantly correlated with mean keratometry.

Saad and Gatinel(58) in 2012 described that indices generated from corneal and ocular wavefront can identify very mild forms of ectasia that may be undetected by Placido-based neural network programs and showed that vertical coma was significantly different in the FFKC as compared with the control group.

An other team in 2012(81) compared higher order aberrations of the cornea with inferior-superior (I-S) corneal topographic values in keratoconic eyes and tried to find the best indicator for the detection of keratoconic eyes.

They concluded that vertical coma represents a good means of identifying suspected keratoconus.

To conclude, Coma V is a very good parameter in the diagnosis but also in monitoring patients carriers keratoconus.

3. CONCERNING COMA TOT

In our study, we show that the variation of Coma tot is more significant than Kmax ant.

A lot of studies describe that corneal coma is a good indicator to detect keratoconus even at early stages.

Mesplié and al(82) tried to determine the value of wavefront analysis in the detection of keratoconus : they conducted a prospective study on keratoconic and control group with an analysis of total and corneal aberrations. Total and corneal comatic aberrations, corneal trefoil and secondary corneal astigmatism have significantly differentiated the groups.

Bühren in 2007(21) described corneal higher-order wavefront aberrations of clinically inconspicuous fellow eyes in patients with early keratoconus. They showed that clinically normal fellow eyes of eyes with early KC showed significant differences of RMS Coma compared to normal eyes and could therefore be considered as eyes with subclinical KC.

In a same way, Alio(19) used the anterior corneal surface higher order aberrations as a tool to detect and grade keratoconus using corneal map analysis videokeratoscopy. Corneal higher order aberrations, especially coma-like aberrations, are significantly higher in eyes with keratoconus than normal eyes. Coma-like aberrations, with the aid of a corneal aberrometry map, are also good indicators for early detection and grading of keratoconus.

Determine the earliest topographic criteria of evolution compared to the gold standard which is currently the Kmax and investigate the existence of predictive factors of evolution could also allow for more precise criteria, thus reducing the margin of error attributed to the standard deviation of the topo-tomographic examination.

4. PROBLEM OF STANDARD DEVIATION OF THE TOPO-TOMOGRAPHIC EXAMINATION

To diagnose progression of keratoconus, the topographic examinations must have excellent reliability and a very high inter-session repeatability for all the different parameters.

A lot of study found a high value for the standard deviation of the anterior steep keratometry.

Szalai(44) tried to evaluate the repeatability and reliability of anterior segment optical coherence tomography and a high-resolution Scheimpflug camera and to assess the agreement between the 2 instruments when measuring healthy eyes and eyes with keratoconus. They found in control group for the steep keratometry a SD closed to 1,7 for rotating Scheimpflug system imaging and this value increases with the severity of the keratoconus.

Savini chose to study(53) the repeatability of measurements performed by Galilei in unoperated and post-refractive surgery eyes. Concerning Sim K, they found in unoperated eyes a standard deviation of 1,44 D and after LASIK a standard deviation of 1,51 D. We are well beyond the values found in our study.

An article written in 2012 by Smadja(83) described parameters of the posterior corneal surface after myopic LASIK. All the measurements were performed with the Galilei. In the central 4mm, standard deviation was between 0,09 and 0,25 (depending on the thickness of tissue ablated). This value increases when it measures to the peripheral cornea. In our study we find similar results with an average standard deviation of 0,03.

An other study(54) found for the posterior keratometry a deviation standard of 0,24.

All of these studies have in terms of standard deviation similar or higher values than those of our study. This is why the different values that we found can be considered valid and not due to a measurement bias performed poorly.

Concerning the repeatability of wavefront aberrations, Wang(54) found a deviation standard of 0,08 for the Coma. Again, our results are the same of those found in the litterature.

5. LIMITS OF OUR STUDY AND PERSPECTIVES

We can consider that our study suffers from some bias.

However it is true that the number of subjects is still insufficient especially to extrapolate data to 1 year since we had lost many patients. It would be desirable to conduct a study on a larger number.

We also should further test our new settings on a large sample of patients to follow in the long term to fully validate our hypothesis.

6. CONCLUSION

So diagnosing an early progression remains an important challenge due to the clinical and therapeutic attitude in young patients who must maintain a certain visual acuity.

The main objective of our study was to determine the earliest topographic criteria of evolution compared to the gold standard which is currently the Kmax.

The secondary objective was to investigate the existence of predictive factors of evolution.

Among all the parameters studied, some appeared to be earlier and more predictive on observational and statistical analysis than Kmax ant. It was about Kmax post, coma V, coma tot and AAI post.

Others studies should be performed in order to confirm those data and study those parameters in a prospective study in order to validate the thresholds found.

REFERENCES

1. Zadnik K, Barr JT, Edrington TB, Everett DF, Jameson M, McMahon TT, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Invest Ophthalmol Vis Sci.* 1998 Dec;39(13):2537–46.
2. Edwards M, McGhee CN, Dean S. The genetics of keratoconus. *Clin Experiment Ophthalmol.* 2001 Dec;29(6):345–51.
3. Nielsen K, Hjortdal J, Pihlmann M, Corydon TJ. Update on the keratoconus genetics. *Acta Ophthalmol (Copenh).* 2013 Mar;91(2):106–13.
4. Karimian F, Aramesh S, Rabei HM, Javadi MA, Rafati N. Topographic evaluation of relatives of patients with keratoconus. *Cornea.* 2008 Sep;27(8):874–8.
5. Cullen JF, Butler HG. MONGOLISM (DOWN'S SYNDROME) AND KERATOCONUS. *Br J Ophthalmol.* 1963 Jun;47:321–30.
6. Weed KH, MacEwen CJ, McGhee CNJ. The variable expression of keratoconus within monozygotic twins: dundee University Scottish Keratoconus Study (DUSKS). *Contact Lens Anterior Eye J Br Contact Lens Assoc.* 2006 Jul;29(3):123–6.
7. Bawazeer AM, Hodge WG, Lorimer B. Atopy and keratoconus: a multivariate analysis. *Br J Ophthalmol.* 2000 Aug;84(8):834–6.
8. Harrison RJ, Klouda PT, Easty DL, Manku M, Charles J, Stewart CM. Association between keratoconus and atopy. *Br J Ophthalmol.* 1989 Oct;73(10):816–22.
9. Downie LE. The necessity for ocular assessment in atopic children: bilateral corneal hydrops in an 8 year old. *Pediatrics.* 2014 Aug;134(2):e596–601.
10. Krachmer JH. Eye rubbing can cause keratoconus. *Cornea.* 2004 Aug;23(6):539–40.
11. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. *Invest Ophthalmol Vis Sci.* 2010 Nov;51(11):5546–55.
12. 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 Nov;33(11):1860–5.
13. Schlegel Z, Hoang-Xuan T, Gatinel D. Comparison of and correlation between anterior and posterior corneal elevation maps in normal eyes and keratoconus-suspect eyes. *J Cataract Refract Surg.* 2008 May;34(5):789–95.
14. Thibos LN. Principles of Hartmann-Shack aberrometry. *J Refract Surg Thorofare NJ* 1995. 2000 Oct;16(5):S563–565.
15. Cheng X, Himebaugh NL, Kollbaum PS, Thibos LN, Bradley A. Validation of a clinical Shack-Hartmann aberrometer. *Optom Vis Sci Off Publ Am Acad Optom.* 2003 Aug;80(8):587–95.
16. Cheng X, Thibos LN, Bradley A. Estimating visual quality from wavefront aberration

- measurements. *J Refract Surg Thorofare NJ* 1995. 2003 Oct;19(5):S579–584.
17. Maeda N, Fujikado T, Kuroda T, Mihashi T, Hirohara Y, Nishida K, et al. Wavefront aberrations measured with Hartmann-Shack sensor in patients with keratoconus. *Ophthalmology*. 2002 Nov;109(11):1996–2003.
 18. Barbero S, Marcos S, Merayo-Lloves J, Moreno-Barriuso E. Validation of the estimation of corneal aberrations from videokeratography in keratoconus. *J Refract Surg Thorofare NJ* 1995. 2002 Jun;18(3):263–70.
 19. Alió JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg Thorofare NJ* 1995. 2006 Jun;22(6):539–45.
 20. Gobbe M, Guillon M. Corneal wavefront aberration measurements to detect keratoconus patients. *Contact Lens Anterior Eye J Br Contact Lens Assoc*. 2005 Jun;28(2):57–66.
 21. Bühren J, Kühne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. *Am J Ophthalmol*. 2007 Mar;143(3):381–9.
 22. Kamiya K, Ishii R, Shimizu K, Igarashi A. Evaluation of corneal elevation, pachymetry and keratometry in keratoconic eyes with respect to the stage of Amsler-Krumeich classification. *Br J Ophthalmol*. 2014 Apr;98(4):459–63.
 23. Rabinowitz YS, Yang H, Brickman Y, Akkina J, Riley C, Rotter JI, et al. Videokeratography database of normal human corneas. *Br J Ophthalmol*. 1996 Jul;80(7):610–6.
 24. Asri D, Touboul D, Fournié P, Malet F, Garra C, Gallois A, et al. Corneal collagen crosslinking in progressive keratoconus: multicenter results from the French National Reference Center for Keratoconus. *J Cataract Refract Surg*. 2011 Dec;37(12):2137–43.
 25. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003 May;135(5):620–7.
 26. Wollensak G, Spörl E, Mazzotta C, Kalinski T, Sel S. Interlamellar cohesion after corneal crosslinking using riboflavin and ultraviolet A light. *Br J Ophthalmol*. 2011 Jun;95(6):876–80.
 27. Koller T, Pajic B, Vinciguerra P, Seiler T. Flattening of the cornea after collagen crosslinking for keratoconus. *J Cataract Refract Surg*. 2011 Aug;37(8):1488–92.
 28. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008 May;34(5):796–801.
 29. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *J Cataract Refract Surg*. 2011 Jan;37(1):149–60.
 30. Erdurmus M, Yildiz EH, Abdalla YF, Hammersmith KM, Rapuano CJ, Cohen EJ. Contact lens related quality of life in patients with keratoconus. *Eye Contact Lens*. 2009 May;35(3):123–7.
 31. Jinabhai A, Radhakrishnan H, O'Donnell C. Visual acuity and ocular aberrations with different rigid gas permeable lens fittings in keratoconus. *Eye Contact Lens*. 2010 Jul;36(4):233–7.

32. Touboul D, Pinsard L, Mesplier N, Smadja D, Colin J. [Correction of irregular astigmatism with intracorneal ring segments]. *J Fr Ophtalmol*. 2012 Mar;35(3):212–9.
33. Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. *J Cataract Refract Surg*. 2000 Aug;26(8):1117–22.
34. Pesudovs K, Schoneveld P, Seto RJ, Coster DJ. Contrast and glare testing in keratoconus and after penetrating keratoplasty. *Br J Ophthalmol*. 2004 May;88(5):653–7.
35. Reinhart WJ, Musch DC, Jacobs DS, Lee WB, Kaufman SC, Shtein RM. Deep anterior lamellar keratoplasty as an alternative to penetrating keratoplasty a report by the american academy of ophthalmology. *Ophthalmology*. 2011 Jan;118(1):209–18.
36. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998 Feb;42(4):297–319.
37. D'Souza S, Ganesh S, Shetty R, Ramachandran S, Kurian M. Intrastromal corneal ring segments for management of keratoconus. *Indian J Ophthalmol*. 2013;61(8):451.
38. Raikup F, Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A. I. Principles. *Ocul Surf*. 2013 Apr;11(2):65–74.
39. Raikup F, Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A. Part II. Clinical indications and results. *Ocul Surf*. 2013 Apr;11(2):93–108.
40. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. *Ophthalmology*. 1994 Mar;101(3):439–47.
41. Choi JA, Kim M-S. Progression of keratoconus by longitudinal assessment with corneal topography. *Invest Ophthalmol Vis Sci*. 2012 Feb;53(2):927–35.
42. Vinciguerra P, Albè E, Trazza S, Rosetta P, Vinciguerra R, Seiler T, et al. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. *Ophthalmology*. 2009 Mar;116(3):369–78.
43. McMahon TT, Anderson RJ, Joslin CE, Rosas GA, Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Topography Analysis Group. Precision of three topography instruments in keratoconus subjects. *Optom Vis Sci Off Publ Am Acad Optom*. 2001 Aug;78(8):599–604.
44. Szalai E, Berta A, Hassan Z, Módis L Jr. Reliability and repeatability of swept-source Fourier-domain optical coherence tomography and Scheimpflug imaging in keratoconus. *J Cataract Refract Surg*. 2012 Mar;38(3):485–94.
45. Chen D, Lam AKC. Reliability and repeatability of the Pentacam on corneal curvatures. *Clin Exp Optom J Aust Optom Assoc*. 2009 Mar;92(2):110–8.
46. Shankar H, Taranath D, Santhirathelagan CT, Pesudovs K. Anterior segment biometry with the Pentacam: comprehensive assessment of repeatability of automated measurements. *J Cataract Refract Surg*. 2008 Jan;34(1):103–13.
47. Chen W, McAlinden C, Pesudovs K, Wang Q, Lu F, Feng Y, et al. Scheimpflug-Placido topographer and optical low-coherence reflectometry biometer: repeatability and agreement. *J Cataract Refract Surg*. 2012 Sep;38(9):1626–32.
48. De Sanctis U, Missolungi A, Mutani B, Richiardi L, Grignolo FM. Reproducibility and

- repeatability of central corneal thickness measurement in keratoconus using the rotating Scheimpflug camera and ultrasound pachymetry. *Am J Ophthalmol.* 2007 Nov;144(5):712–8.
49. Sideroudi H, Labiris G, Giarmoulakis A, Bougatsou N, Mikropoulos D, Kozobolis V. Repeatability, reliability and reproducibility of posterior curvature and wavefront aberrations in keratoconic and cross-linked corneas. *Clin Exp Optom J Aust Optom Assoc.* 2013 Nov;96(6):547–56.
 50. Shetty R, Arora V, Jayadev C, Nuijts RMMA, Kumar M, Puttaiah NK, et al. Repeatability and Agreement of Three Scheimpflug-Based Imaging Systems for Measuring Anterior Segment Parameters in Keratoconus. *Invest Ophthalmol Vis Sci.* 2014;55(8):5263–8.
 51. Al-Mohtaseb ZN, Wang L, Weikert MP. Repeatability and comparability of corneal thickness measurements obtained from Dual Scheimpflug Analyzer and from ultrasonic pachymetry. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Für Klin Exp Ophthalmol.* 2013 Jul;251(7):1855–60.
 52. Güler E, Yağcı R, Akyol M, Arslanyilmaz Z, Balcı M, Hepşen IF. Repeatability and reproducibility of Galilei measurements in normal keratoconic and postrefractive corneas. *Contact Lens Anterior Eye J Br Contact Lens Assoc.* 2014 Oct;37(5):331–6.
 53. Savini G, Carbonelli M, Barboni P, Hoffer KJ. Repeatability of automatic measurements performed by a dual Scheimpflug analyzer in unoperated and post-refractive surgery eyes. *J Cataract Refract Surg.* 2011 Feb;37(2):302–9.
 54. Wang L, Shirayama M, Koch DD. Repeatability of corneal power and wavefront aberration measurements with a dual-Scheimpflug Placido corneal topographer. *J Cataract Refract Surg.* 2010 Mar;36(3):425–30.
 55. Tomidokoro A, Oshika T, Amano S, Higaki S, Maeda N, Miyata K. Changes in anterior and posterior corneal curvatures in keratoconus. *Ophthalmology.* 2000 Jul;107(7):1328–32.
 56. Ishii R, Kamiya K, Igarashi A, Shimizu K, Utsumi Y, Kumanomido T. Correlation of corneal elevation with severity of keratoconus by means of anterior and posterior topographic analysis. *Cornea.* 2012 Mar;31(3):253–8.
 57. Fukuda S, Beheregaray S, Hoshi S, Yamanari M, Lim Y, Hiraoka T, et al. Comparison of three-dimensional optical coherence tomography and combining a rotating Scheimpflug camera with a Placido topography system for forme fruste keratoconus diagnosis. *Br J Ophthalmol.* 2013 Dec;97(12):1554–9.
 58. Saad A, Gatinel D. Evaluation of total and corneal wavefront high order aberrations for the detection of forme fruste keratoconus. *Invest Ophthalmol Vis Sci.* 2012;53(6):2978–92.
 59. Smadja D, Santhiago MR, Mello GR, Krueger RR, Colin J, Touboul D. Influence of the reference surface shape for discriminating between normal corneas, subclinical keratoconus, and keratoconus. *J Refract Surg Thorofare NJ 1995.* 2013 Apr;29(4):274–81.
 60. Smadja D, Touboul D, Cohen A, Doveh E, Santhiago MR, Mello GR, et al. Detection of Subclinical Keratoconus Using an Automated Decision Tree Classification. *Am J Ophthalmol.* 2013 août;156(2):237–246.e1.
 61. Arbelaez MC, Versaci F, Vestri G, Barboni P, Savini G. Use of a support vector machine for

- keratoconus and subclinical keratoconus detection by topographic and tomographic data. *Ophthalmology*. 2012 Nov;119(11):2231–8.
62. Uçakhan ÖÖ, Cetinkor V, Özkan M, Kanpolat A. Evaluation of Scheimpflug imaging parameters in subclinical keratoconus, keratoconus, and normal eyes. *J Cataract Refract Surg*. 2011 Jun;37(6):1116–24.
 63. Wagner H, Barr JT, Zadnik K, the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: Methods and findings to date. *Contact Lens Anterior Eye*. 2007 Sep;30(4):223–32.
 64. Maeda N, Klyce SD, Smolek MK, Thompson HW. Automated keratoconus screening with corneal topography analysis. *Invest Ophthalmol Vis Sci*. 1994 May;35(6):2749–57.
 65. Mahmoud AM, Nuñez MX, Blanco C, Koch DD, Wang L, Weikert MP, et al. Expanding the cone location and magnitude index to include corneal thickness and posterior surface information for the detection of keratoconus. *Am J Ophthalmol*. 2013 Dec;156(6):1102–11.
 66. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982 Apr;143(1):29–36.
 67. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988 Sep;44(3):837–45.
 68. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983 Sep;148(3):839–43.
 69. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. *J Cataract Refract Surg*. 2012 Dec;38(12):2167–83.
 70. Luz A, Ursilio M, Castañeda D, Ambrósio R. [Corneal thickness progression from the thinnest point to the limbus: study based on a normal and a keratoconus population to create reference values]. *Arq Bras Oftalmol*. 2006 Aug;69(4):579–83.
 71. Ruiseñor Vázquez PR, Galletti JD, Minguez N, Delrivo M, Fuentes Bonthoux F, Pförtner T, et al. Pentacam Scheimpflug Tomography Findings in Topographically Normal Patients and Subclinical Keratoconus Cases. *Am J Ophthalmol*. 2014 Apr 5;
 72. Reddy JC, Rapuano CJ, Cater JR, Suri K, Nagra PK, Hammersmith KM. Comparative evaluation of dual Scheimpflug imaging parameters in keratoconus, early keratoconus, and normal eyes. *J Cataract Refract Surg*. 2014 Apr;40(4):582–92.
 73. Qin B, Chen S, Brass R, Li Y, Tang M, Zhang X, et al. Keratoconus diagnosis with optical coherence tomography-based pachymetric scoring system. *J Cataract Refract Surg*. 2013 Dec;39(12):1864–71.
 74. Dao CL, Kok JH, Brinkman CJ, van Mil CJ. Corneal eccentricity as a tool for the diagnosis of keratoconus. *Cornea*. 1994 Jul;13(4):339–44.
 75. Rabinowitz YS, Li X, Canedo ALC, Ambrósio R, Bykhovskaya Y. Optical coherence tomography combined with videokeratography to differentiate mild keratoconus subtypes. *J Refract Surg Thorofare NJ* 1995. 2014 Feb;30(2):80–7.
 76. Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes in unilateral

- keratoconus patients. *Ophthalmology*. 2004 Mar;111(3):440–6.
- 77. Abad JC, Rubinfeld RS, Del Valle M, Belin MW, Kurstin JM. Vertical D: a novel topographic pattern in some keratoconus suspects. *Ophthalmology*. 2007 May;114(5):1020–6.
 - 78. Belin MW, Ambrósio R. Scheimpflug imaging for keratoconus and ectatic disease. *Indian J Ophthalmol*. 2013 Aug;61(8):401–6.
 - 79. Feizi S, Einollahi B, Raminkhoo A, Salehirad S. Correlation between Corneal Topographic Indices and Higher-Order Aberrations in Keratoconus. *J Ophthalmic Vis Res*. 2013 Apr;8(2):113–8.
 - 80. Gordon-Shaag A, Millodot M, Ifrah R, Shneor E. Aberrations and topography in normal, keratoconus-suspect, and keratoconic eyes. *Optom Vis Sci Off Publ Am Acad Optom*. 2012 Apr;89(4):411–8.
 - 81. Mesplié N, Léoni-Mesplié S, Gallois A, Colin J, Touboul D. [Detection of keratoconus using wavefront analysis]. *J Fr Ophtalmol*. 2011 Oct;34(8):547–56.
 - 82. Smadja D, Santhiago MR, Mello GR, Roberts CJ, Dupps WJ, Krueger RR. Response of the posterior corneal surface to myopic laser in situ keratomileusis with different ablation depths. *J Cataract Refract Surg*. 2012 Jul;38(7):1222–31.