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ORIGINAL ARTICLE

Comparative Evaluation of Elevation, Keratometric, Pachymetric and Wavefront Parameters in Normal Eyes, Subclinical Keratoconus and Keratoconus with a Dual Scheimpflug Analyzer

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ABSTRACT

Purpose: To compare the corneal parameters in normal corneas, forme fruste keratoconus (FFKC) and keratoconus measured with a dual Scheimpflug analyzer.

Materials and methods: A total of 372 eyes of 197 patients were prospectively enrolled in the study and divided into three groups: 148 eyes of 102 patients with keratoconus, 47 contralateral topographically normal eyes of clinically evident keratoconus in the fellow eye and 177 eyes of 95 refractive surgery candidates with normal corneas. All eyes were measured with a dual Scheimpflug analyzer and elevation, keratometric, pachymetric and wavefront data were analyzed. Mean and intergroup comparisons were performed for 43 parameters.

Results: Eighty-eight percent of the parameters analyzed (38/43) were significantly different between normal and keratoconus whereas it was less than 40% (17/43) between normal and FFKC. The majority of the elevation parameters were significantly different between normal eyes and FFKC (11/14) whereas the I-S value and the K_{max} were the only two parameters related to the anterior curvature that were significantly different between both groups. Corneal vertical coma was the only corneal aberrations significantly different between normal and FFKC ($p < 0.07$).

Conclusion: The dual Scheimpflug analyzer provides useful parameters for differentiating normal corneas, FFKC and keratoconus.

Keywords: GALILEI, Dual Scheimpflug, Keratoconus, Forme fruste keratoconus, Corneal elevation, Posterior surface, Pachymetry, Wavefront profile, Placido disk.

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INTRODUCTION

Identifying corneas with risk of developing iatrogenic ectasia after laser-assisted *in situ* keratomileusis (LASIK) remains the major concern of the preoperative refractive surgery screening. Recent technological advances in anterior segment imaging enabled to sensitively detect keratoconus, however, the detection of subclinical keratoconus and its differentiation from normal eyes still remains a challenge with the current keratoconus detection programs. While corneal topography has been found sensitive for detecting keratoconus prior to clinical biomicroscopic findings, recent studies have pointed out the significant role of corneal epithelium in reducing corneal topographic irregularities[1] and in masking the presence of an underlying cone on the anterior surface in early keratoconus.[2,3] In contrast, several corneal indices derived from corneal tomography technology, which allows for a more extensive analysis of the corneal properties, have been recently reported for improving the sensitivity of the subclinical keratoconus detection. Various corneal indices and cutoff values derived from elevation,[4] thickness profile[5,6] or wavefront[7] have been extensively studied and reported with different imaging technologies, such as the Orbscan IIz system,[4] the Pentacam[8] and the Sirius system.[9] However, to our knowledge, there is to date, no report comparing the corneal features of normal, keratoconic and subclinical keratoconic corneas using the dual Scheimpflug analyzer. The GALILEI analyzer (Ziemer Ophthalmic Systems AG; Port, Switzerland) is a relatively new dual Scheimpflug imaging system combined with Placido disk technology, which allows for a large evaluation of the corneal features. Therefore, the aim of this study was first to compare elevation, keratometric, pachymetric and wavefront parameters in normal corneas, subclinical keratoconus and keratoconus and attempting to highlight the most relevant parameters for differentiating these corneas.

MATERIALS AND METHODS

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

Subjects

A total of 372 eyes of 197 patients were prospectively enrolled in the study and imaged with the GALILEI Dual Scheimpflug Analyzer System. Corneas were then classified into three groups based on eyes conditions: Normal (group 1) included 177 eyes of 95 subjects, forme fruste of keratoconus (FFKC, group 2) included 47 eyes of 47 patients and keratoconus (group 3), included 148 eyes of 102 patients. Groups were defined as follow:

Group 1: Normal eyes were enrolled among suitable candidates undergoing a screening examination for refractive surgery and among general population undergoing a routine ophthalmological examination. All patients had discontinued daily-wear soft contact lens use at least 1 week before evaluation. Eyes were considered normal when no clinical signs of keratoconus and no suggestive topographic or tomographic patterns of suspect keratoconus were found, such as asymmetric bow tie (AB) with a skewed radial axis (SRAX), focal or inferior steepening, central keratometry greater than 47.0 D or corneas thinner than 500 µm. Exclusion criteria for this group were: Previous ocular surgery, ocular pathology, familial history of keratoconus and contact lens wearing in the past week.

Group 2: It was composed of 47 FFKC, which are defined as the contralateral eyes of clinically evident keratoconus in the fellow eye (n = 47). These eyes had no clinical signs of keratoconus and a normal topographical aspect with no AB and no focal or inferior steepening pattern. This condition is also known in the literature as 'subclinical keratoconus' since it has already been reported that approximately 50% of clinically normal fellow eyes of patients with a unilateral keratoconus progressed to keratoconus within 16 years with a greater risk during the first 6 years of onset.[10]

Group 3: Eyes with keratoconus were enrolled among patients that were referred to the NRCK for a regular control visit for moderate to advance keratoconus. Diagnosis of clinical keratoconus was previously defined and includes a combination of findings characteristics of keratoconus:[11,12] Corneal topography with AB 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 2 mm 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.

Dual Scheimpflug Analyzer System and Procedure

Measurements were performed with the GALILEI 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.

The GALILEI is a rotating Scheimpflug tomography based device combining dual-channel Scheimpflug cameras and a Placido disk. The system acquires between 15 and 60 Scheimpflug images per scan and two 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. This correction compensates for patient's eye motion during scanning by a tracker that locates and tracks a patch on the iris, matching its location on every scan.

Simultaneously, the system allows for a 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 recalculated recentered on the pupil center over a 6.0 mm optical zone. Individual Zernike coefficients for terms from 2nd to 6th order are displayed in microns as well as in diopters.

Analyzed Parameters and Description

All eyes were imaged with the GALILEI analyzer and patients had a detailed preoperative ophthalmic evaluation including uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA) using Early Treatment Diabetic Retinopathy Study charts, manifest refraction, slit-lamp evaluation, applanation tonometry and fundus examination. Forty-three variables were recorded and are listed in Table 1. Briefly, the analyzed parameters can be described as follow:

Curvature Derived Parameters

Simulated keratometries (SimK) are calculated with the so-called keratometric index, which is 1.3375, to compensate for the effect of the posterior corneal surface and are derived from the axial curvature map. 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. The magnitude of the astigmatism results from the difference between the steepest K and the flattest K, and the axis value was the direction of the meridian of the steepest axis.

K_{max} has been directly recorded from the curvature map and represents the maximal keratometric value, which is

Table 1: List of parameters analyzed

Curvature-derived parameters	*Elevation-derived parameters*	*Wavefront-derived parameters*	*Pachymetric-derived parameters*	*Other parameter age*
Anterior data:	*Anterior data:*			
K_{max}		RMS total corneal HOA	Thinnest point	
Axial SimKs, Kf, Cyl	With BFTA:	RMS corneal SA	Corneal volume	
Axial MeanK (0-4 mm)	Max elevation TP	RMS corneal vertical coma		
Tang MeanK (4-7 mm)	Max elevation K_{max}	RMS corneal horizontal coma	Biometric-derived parameters	
Tang MeanK (7-10 mm)	Max elevation	RMS total corneal coma		
Eccentricity (ε^2)				
I-S value	With BFS:	*Corneal power (CP)*	Anterior chamber depth	
	Max elevation TP	Total corneal power (0-4 mm)	Anterior chamber volume	
	Max elevation K_{max}	Total corneal power (4-7 mm)		
	Max elevation	Total corneal power (7-10 mm)		
	AAI			
Posterior data:	*Posterior data:*			
Axial Ks, Kf, Cyl				
Axial MeanK (0-4 mm)	With BFTA:			
Tang MeanK (4-7 mm)	Max elevation TP			
Tang MeanK (7-10 mm)	Max elevation K_{max}			
Eccentricity (ε^2)	Max elevation			
ISPS				
	With BFS:			
	Max elevation TP			
	Max elevation K_{max}			
	Max elevation AAI			

Ks: Steepest K; Kf: Flattest K; Cyl: Cylinder (D); MeanK: Average keratometry (D); I-S: Inferior-superior; ISPS: I-S posterior score; DSI: Differential sector index; SAI: Surface asymmetry index; OSI: Opposite sector index; SRI: Surface regularity index; CSI: Central/surround index; IAI: Irregular astigmatism index; ACP: Average central power; AA: Area analyzed; SDP: Standard deviation power; BFTA: Best fit toric aspheric sphere; BFS: Best fit sphere; TP: Thinnest point; KAI: Kranneman arce index; HOA: Higher order aberrations; SA: Spherical aberrations

often located in paracentral or peripheral cornea, at the top of the cone in keratoconic corneas, and therefore underestimated by the simulated steepest keratometry value, which is calculated only over the central cornea (0-4 mm).

Mean keratometry (MeanK) is the average keratometry calculated over the analyzed area, central (0-4 mm), paracentral (4-7 mm) or peripheral (7-10 mm) cornea. These values are derived from the axial curvature maps for the central cornea and from the tangential curvature maps for the paracentral and peripheral cornea. Since the axial curvature is highly dependent on the position of the reference axis, the use of axial radius of curvature could lead to underestimate areas of relative high curvature (keratoconus) and overestimate areas of relative lower curvature, especially in paracentral and peripheral cornea. However, tangential curvature is calculated using the real radius of curvature in a precise point of the map. Therefore, we decided to use the values derived from the tangential curvature map, for the areas between 4 and 10 mm in order to minimize bias in the measurement of the peripheral corneal curvature, which is well known to be the most critical area for detecting a keratoconus.

Eccentricity (ε^2) is one of the 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: $\varepsilon^2 = E = 1\ p = -Q$. It is calculated within a central diameter of 8 mm averaged over all meridians of the anterior corneal surface. A positive value refers to a prolate shape of the corneal surface whereas a negative value refers to an oblate shape.

I-S value is the amount of steepening of the inferior cornea compared with that of the superior cornea. It is calculated by subtracting the superior value from the inferior value. The inferior value was calculated by averaging 5 data points along the inferior cornea 3.0 mm from the center of the cornea at 30° intervals (i.e. at 210, 240, 270, 300 and 330°). The superior value was derived from averaging 5 points on the superior cornea 3.0 mm from the center of the cornea (i.e. at 30, 60, 90, 120 and 150°).

Posterior curvature data (Ks, Kf, Cylinder, MeanK, ε^2) are basically the same as for the anterior surface, the only difference is that the keratometries values (Ks, Kf) are not simulated since they are calculated with the real indices of refraction of the cornea (1,376) and the aqueous humor (1,336).

I-S Posterior Score (ISPS) has been designed over the course of the study for evaluating the asymmetry of the posterior surface. It is calculated by first calculating the I-S value of the posterior surface along with the superior and inferior cornea 3.0 mm from the center. The absolute value of the following formula corresponds to the ISPS:

$$\text{ISPS} = (\text{Posterior I-S ratio} - 1) \times 1000$$

Elevation-derived Parameters

Elevation values were measured with two different reference bodies over an 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 three locations by manually guiding the cursor over the anterior and posterior elevation maps: Highest elevation value within the 8 mm diameter zone (MAE and MPE), elevation value at the thinnest point (MAETP and MPETP) and elevation value at the K_{max} location (MAEKm and MPEKm).

The quantification of asymmetry of asphericity of a corneal surface, the asphericity asymmetry index (AAI) has been proposed and described by Arce.[13] It is calculated over the BFTA map display as the absolute value of the difference between the maximum negative elevation value and maximum positive elevation value within the central 6 mm diameter data zone. This index has been recorded for the anterior and posterior surfaces.

Corneal Wavefront-derived Parameters

Total corneal HOAs root mean square (RMS) from the 3rd to the 6th 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 6 mm 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:

$$\text{For all } C_n^m \text{ if n is even and } m < 0: C_n^m = -(C_n^m)$$
$$\text{For all } C_n^m \text{ if n is odd and } m > 0: C_n^m = -(C_n^m)$$

Corneal Power-derived Parameters

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

Pachymetric and Biometric-derived 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 along normals to the line between the outer iris endpoints.

STATISTICAL ANALYSIS

All calculations were performed with STATA/SE (StataCorp 2005, version 9.0, Texas, USA). In principle, p-values less than 0.05 were considered statistically significant. To correct for multiples testing, p-values were adjusted according to the Bonferroni-Holm procedure.

Part of the statistical analyses concerned the question of dependence between observations. Since for most patients the data included both eyes, it seemed plausible that there will be intraclass correlation within patient, so that the whole database cannot be considered as independent observations. Therefore, we initially used the mixed model rather than ANOVA for comparing group since mixed model takes account of the dependence among observations. However, results of this analysis indicated that there was no dependence so that the independence assumption was valid.

RESULTS

This study included 372 eyes of 197 subjects divided into three groups (normal, FFKC and keratoconus). Baseline clinical and demographic characteristics of the subjects by groups are summarized in Tables 2 to 5.

Normal *vs* Keratoconus

Normal and keratoconic corneas were significantly different in nearly all of the 43 parameters ($p < 0.001$), except in the biometric parameters, anterior chamber depth ($p = 0.07$) and anterior chamber volume ($p = 0.4$) as well as in peripheral mean keratometry ($p = 0.2$), horizontal coma ($p = 0.8$) and age ($p = 0.8$) that was similar in both groups, with 28.8 ± 8.6 years old and 28.9 ± 10 years old, respectively in the normal group and keratoconic group. The intergroup comparisons and means are shown in Tables 3 to 5.

Normal *vs* FFKC

There was no statistically significant difference between normal corneas and FFKC for 26 of the 43 analyzed parameters. Among the 17 variables that were statistically different between both groups, elevation parameters were

Table 2: Demographic characteristics of the subjects by groups

Characteristics	*Normal*	*FFKCN*	*KCN*
Eyes, n	177	47	148
Subjects, n	95	47	102
Age ± SD	28.9 ± 8.6	31.8 ± 9.8	28.9 ± 10.0
Female sex (%)	105 (59.3%)	12 (25.5%)	48 (32.4%)

FFKCN: Forme fruste keratoconus; KCN: Keratoconus; SD: Standard deviation

Table 3: Curvature-derived parameters and corneal power: Means and intergroup comparison

N (n subjects)	*Mean ± SD (min; max)*			*Intergroup comparisons mixed model (p-value)*		
	Normal	*FFKCN*	*KCN*	*N vs FFKC*	*N vs KCN*	*FFKC vs KCN*
	177 (n = 95)	*47 (n = 47)*	*148 (n = 102)*			
Anterior surface						
K_{max} (D)	44.2 ± 1.3 (41.2; 46.9)	45.4 ± 1.7 (41.7; 49.4)	54.7 ± 5.2 (47; 76.6)	**0.01**	**<0.001**	**<0.001**
Axial SimKs (D)	44.0 ± 1.3 (40; 46.9)	44.2 ± 1.7 (41.2; 48.9)	48.9 ± 4.3 (39.2; 64.3)	0.5	**<0.001**	**<0.001**
Axial SimKf (D)	43.0 ± 1.3 (39.6; 46.4)	42.9 ± 1.5 (38.4; 45.9)	45.3 ± 3.6 (37.8; 59.9)	0.63	**<0.001**	**<0.001**
Cylinder (D)	0.94 ± 0.6 (0.11; 1.4)	1.3 ± 1 (0.3; 5.5)	3.6 ± 2.2 (0.35; 10.7)	0.31	**<0.001**	**<0.001**
Axial MeanK (0-4 mm)	43.5 ± 1.3 (39.8; 46.9)	43.6 ± 1.5 (39.9; 46.6)	47.4 ± 4 (38.2; 63.2)	0.55	**<0.001**	**<0.001**
Tang MeanK (4-7 mm)	41.6 ± 1.4 (38.4; 44.7)	41.2 ± 1.8 (37.6; 44.8)	40.6 ± 2.7 (33.8; 48)	0.23	**<0.001**	**<0.001**
Tang MeanK (7-10 mm)	39.6 ± 1.8 (33.5; 43.8)	38.5 ± 2.1 (33; 43)	38.6 ± 3.6 (29.9; 49.9)	0.12	0.19	0.55
Eccentricity (ε^2)	0.22 ± 0.1 (–0.05; 0.5)	0.3 ± 0.3 (–0.6; 1.1)	0.92 ± 0.8 (–1.5; 2.81)	0.30	**<0.001**	**<0.001**
I-S value	0.58 ± 0.4 (0; 1.95)	1.41 ± 0.8 (0.13; 2.8)	8.44 ± 4.3 (0.9; 24.7)	**0.004**	**<0.001**	**<0.001**
Posterior surface						
Axial Ks (D)	–6.38 ± 0.2 (–7.2; –5.7)	–6.37 ± 0.3 (–7.2; –5.8)	–7.3 ± 0.8 (–10.1; –5.6)	0.89	**<0.001**	**<0.001**
Axial Kf (D)	–6.08 ± 0.2 (–6.7; –5.5)	–6.05 ± 0.2 (–6.7; –5.6)	–6.6 ± 0.7 (–9; –5.35)	0.80	**<0.001**	**<0.001**
Cylinder (D)	–0.3 ± 0.11 (–0.7; –0.1)	–0.3 ± 0.16 (–0.7; –0.1)	–0.7 ± 0.3 (–1.7; –0.1)	0.99	**<0.001**	**<0.001**
Axial MeanK (0-4 mm)	–6.23 ± 0.2 (–7; –5.66)	–6.2 ± 0.3 (–6.9; –5.7)	–7.05 ± 0.8 (–9.8; –5.5)	0.82	**<0.001**	**<0.001**
Tang MeanK (4-7 mm)	–5.86 ± 0.2 (–6.6; –5.2)	–5.7 ± 0.4 (–6.6; –4.9)	–5.2 ± 0.7 (–7; –3.2)	0.06	**<0.001**	**<0.001**
Tang MeanK (7-10 mm)	–5.25 ± 0.2 (–5.8; –4.5)	–5.1 ± 0.4 (–5.7; –4.2)	–4.5 ± 0.8 (–6; –1.6)	**0.03**	**<0.001**	**<0.001**
Eccentricity (ε^2)	0.19 ± 0.19 (–0.2; 0.8)	0.32 ± 0.3 (–0.4; 1.09)	1.3 ± 0.96 (–1.3; 3.6)	0.14	**<0.001**	**<0.001**
ISPS	27.8 ± 18.9 (0; 73.3)	94.0 ± 78 (0; 302.6)	524 ± 348 (9.2; 2173)	**<0.001**	**<0.001**	**<0.001**
Corneal power (CP)						
TCP (0-4 mm)	41.7 ± 1.2 (38; 44.8)	41.8 ± 1.5 (37.9; 44.9)	45.2 ± 3.7 (36; 60.2)	0.47	**<0.001**	**<0.001**
TCP (4-7 mm)	42.2 ± 1.3 (38.8; 45.6)	42.2 ± 1.5 (39.5; 44.9)	44.3 ± 2.2 (39.3; 51.5)	0.33	**<0.001**	**<0.001**
TCP (7-10 mm)	42.6 ± 1.5 (39.1; 45.9)	42.4 ± 1.7 (39; 45.3)	43.9 ± 2 (38.4; 51.5)	0.68	**<0.001**	**<0.001**

FFKCN: Forme fruste keratoconus; KCN: Keratoconus; SD: Standard deviation; Ks: Steepest K; Kf: Flattest K; Cyl: Cylinder (D); MeanK: Average keratometry (D); Tang: Tangential map; I-S: Inferior-superior ratio; ISPS: I-S posterior score; TCP: Total corneal power; OSI: Opposite sector index. *Note*—Bold: Statistically significant

the most discriminant with 11 variables out of the 14 that were significantly different. The maximum anterior elevation (MAE) and maximum posterior elevation (MPE) calculated relative to a BFS were not different between normal corneas and FFKC, whereas it was significantly different when calculated relative to a BFTA reference surface (Table 4). Curvature-derived parameters relative to the anterior surface were not significantly different between

Table 4: Elevation-derived parameters and pachymetric data: Means and intergroup comparison

N (n subjects)	*Means ± SD (min; max)*			*Intergroup comparisons mixed model (p-value)*		
	Normal *177 (n = 95)*	*FFKCN* *47 (n = 47)*	*KCN* *148 (n = 102)*	*N vs FFKCN*	*N vs KCN*	*FFKCN vs KCN*
Anterior surface						
BFTA MAETP	0.44 ± 1.4 (–4; 5)	2.21 ± 2.8 (–4; 13)	17.5 ± 12 (–7; 58)	0.06	**<0.001**	**<0.001**
BFTA MAEKm	2.4 ± 2.2 (–2; 10)	4.9 ± 4.1 (–2; 16)	23.8 ± 15.1 (–1; 69)	**0.03**	**<0.001**	**<0.001**
BFTA MAE	4.8 ± 1.7 (1; 9)	8.4 ± 3.9 (1; 19)	31.9 ± 15.8 (6; 87)	**0.03**	**<0.001**	**<0.001**
BFS MAETP	1.55 ± 1.4 (–2; 8)	3.3 ± 2.5 (–1; 11)	17.9 ± 10.8 (–2; 56)	**0.04**	**<0.001**	**<0.001**
BFS MAEKm	1.36 ± 1.7 (–8; 7)	3.2 ± 2.9 (–2; 12)	18.1 ± 11.8 (2; 60)	**0.04**	**<0.001**	**<0.001**
BFS MAE	5.4 ± 3.15 (0; 15)	7.2 ± 4.3 (2; 20)	25.2 ± 12.5 (6; 64)	0.2	**<0.001**	**<0.001**
AAI anterior	9.2 ± 3.6 (0; 27)	15.8 ± 6.9 (3; 33)	54.4 ± 26.2 (13; 150)	**0.01**	**<0.001**	**<0.001**
Posterior surface						
BFTA MPETP	–0.84 ± 2.4 (–9; 5)	3.55 ± 6.6 (–9; 32)	35.9 ± 24.9 (–11; 107)	**0.02**	**<0.001**	**<0.001**
BFTA MPEKm	3.3 ± 4 (–9; 14)	9.7 ± 8.4 (–10; 27)	43.1 ± 27.3 (1; 135)	**0.005**	**<0.001**	**<0.001**
BFTA MPE	8.6 ± 2.8 (4; 17)	16.9 ± 6.9 (4; 39)	57.8 ± 28.4 (10; 135)	**0.004**	**<0.001**	**<0.001**
BFS MPETP	2.3 ± 2.4 (–3; 11)	7.4 ± 6.7 (–3; 32)	38.2 ± 21.5 (3; 109)	**0.01**	**<0.001**	**<0.001**
BFS MPEKm	0.9 ± 4.2 (–25; 10)	6.8 ± 6.7 (–5; 24)	33.7 ± 20.5 (–9; 103)	**0.002**	**<0.001**	**<0.001**
BFS MPE	13.1 ± 5.2 (3; 30)	15.4 ± 6.5 (3; 34)	46 ± 20.6 (6; 109)	0.2	**<0.001**	**<0.001**
AAI posterior	16.76 ± 5 (0; 36)	31.1 ± 12.3 (7; 66)	99.8 ± 49.2 (20; 250)	**0.002**	**<0.001**	**<0.001**
Pachymetric data						
Thinnest point	550 ± 25 (505; 630)	520 ± 29.4 (450; 575)	478.3 ± 39 (313; 565)	**<0.001**	**<0.001**	**<0.001**
Corneal volume	33.6 ± 1.5 (30.9; 38.5)	31.9 ± 1.7 (28.3; 35.9)	31.2 ± 1.7 (25.2; 35.4)	**<0.001**	**<0.001**	**<0.001**

FFKCN: Forme fruste keratoconus; KCN: Keratoconus; SD: Standard deviation; BFTA: Best-fit toric aspheric surface; BFS: Best-fit sphere; MAETP: Maximum anterior elevation at the thinnest point; MAEKm: Maximum anterior elevation at the K_{max}; MAE: Maximum anterior elevation; MPETP: Maximum posterior elevation at the thinnest point; MPEKm: Maximum posterior elevation at the K_{max}; MPE: Maximum posterior elevation; AAI: Asphericity asymmetry index. *Note*—Bold: Statistically significant

the two groups, except for the I-S value (p = 0.004) and K_{max} (p = 0.01). At the posterior surface, the ISPS was significantly greater in FFKC than in normal eyes, with 94.0 ± 78 and 27.8 ±18.9 respectively in the FFKC group and in the normal group. The RMS vertical coma was the only corneal aberration significantly different between the two groups, with a mean of –0.35 µm in the FFKC group and 0.01 µm in the normal group. Pachymetric derived parameters (thinnest point and corneal volume) were significantly different between the two groups with thinner corneas and a lower corneal volume in the FFKC group. All the intergroup comparisons are shown in Tables 3 to 5.

DISCUSSION

While discriminating between normal corneas and keratoconus is no longer a problem with the current corneal imaging technologies, identifying subclinical keratoconus remains the most challenging situation faced by the ophthalmologist when considering a refractive surgery procedure. In the present study, our results obtained with the GALILEI analyzer corroborate this finding, with nearly 90% (38/43) of the parameters analyzed that were significantly different between normal corneas and keratoconus compared to only 39% (17/43) between normal and FFKC. According to our results, the variables that were the most differents between normal corneas from FFKC were related to corneal elevation, with 11 variables out of 14 that were significantly different. Interestingly, the MAE and MPE calculated relative with a BFS were not different between both groups whereas it was significantly different when calculated relative to a BFTA. In a previous work of our group, we demonstrated that the use of a BFTA reference

Table 5: Wavefront and biometric parameters: Means and intergroup comparison

N (n subjects)	*Mean ± SD (min; max)*			*Intergroup comparisons mixed model (p-value)*		
	Normal *177 (n = 95)*	*FFKCN* *47 (n = 47)*	*KCN* *148 (n = 102)*	*N vs FFKCN*	*N vs KCN*	*FFKCN vs KCN*
Corneal wavefront (μ)						
RMS total HOA	0.53 ± 0.16 (0.2; 1)	0.76 ± 0.26 (0.3; 1.52)	2.71 ± 1.3 (0.66; 8.2)	0.08	**<0.001**	**<0.001**
RMS SA	0.22 ± 0.1 (0.03; 0.4)	0.18 ± 0.17 (–0.2, 0.6)	–0.1 ± 0.57 (–1.8, 1.2)	0.46	**<0.001**	**<0.001**
RMS vertical coma	0.01 ± 0.2 (–0.5; 0.68)	–0.35 ± 0.4 (–1.2; 0.32)	–2.1 ± 1.3 (–7.66; 0.9)	**0.006**	**<0.001**	**<0.001**
RMS horizontal coma	–0.01 ± 0.3 (–0.8; 0.8)	–0.04 ± 0.34 (–0.7; 0.8)	0.01 ± 0.94 (–4.4; 3.2)	0.84	0.81	0.71
RMS total coma	0.35 ± 0.2 (0.02; 0.9)	0.55 ± 0.28 (0.07; 1.3)	2.27 ± 1.26 (0.45; 7.7)	0.07	**<0.001**	**<0.001**
Biometric data						
AC depth	3.2 ± 0.3 (2.4; 3.8)	3.2 ± 0.3 (2.4; 3.8)	3.3 ± 0.3 (2.6; 3.9)	0.98	0.07	**< 0.001**
AC volume	120.6 ± 23.4 (44; 268)	116.8 ± 22.1 (65; 164)	118.3 ± 15.6 (84; 151)	0.27	0.42	0.60

FFKCN: Forme fruste keratoconus; KCN: Keratoconus; SD: Standard deviation; HOA: Higher order aberrations; SA: Spherical aberrations; AC: Anterior chamber. *Note* 1—Bold: Statistically significant. *Note* 2—Corneal aberrations for 6 mm pupil diameter.

surface for calculating elevation improved the sensitivity of subclinical keratoconus detection compared to that with a BFS.[14] The optimized cutoff value for best differentiating normal corneas from FFKC was set at 13 µm of posterior elevation in the BFTA display. By matching closer to the natural toric and aspherical shape of the cornea, the BFTA allows to neutralize the ridge pattern commonly seen in elevation maps calculated relative to BFS and due to the effect of corneal toricity[15,16] and therefore might help revealing more sensitively the first signs of asymmetry in elevation. This difference between the BFS and BFTA displays becomes particularly relevant when tracking subtle abnormalities in elevation maps for detecting subclinical keratoconus.

Another interesting finding is that curvature-derived parameters related to the anterior corneal surface were mostly not significantly different between normal and FFKC with only two variables (I-S value and K_{max}) out of nine, which is not surprising given the exact definition of the FFKC that implies a topographically normal cornea. Although corneal topography has been found sensitive for detecting keratoconus prior to clinical biomicroscopic findings, it has reported evidences of subclinical keratoconus in corneas undergoing tomographic analysis while they were considered normal by the various topographic keratoconus detection indices.[4,17] This finding further feeds the debate on the location of the first detectable sign of subclinical keratoconus, whether it would be subtle changes in anterior surface curvature seen with Placido disk or posterior surface changes detected only by tomography. Placido disk technology is exclusively limited to the anterior surface analysis and several recent studies have pointed out the ability that has the epithelium to remodel itself to compensate for stromal surface abnormalities, which can mask the presence of an underlying cone on the anterior surface in early keratoconus.[2,3] In contrast, corneal tomography, which allows for a more complete analysis of the corneal properties, such as elevation-derived parameters, posterior surface analysis, pachymetric spatial profile or wavefront analysis has already been successfully used in multiples studies for improving the sensitivity of subclinical keratoconus detection. Schlegel et al have reported significant greater posterior astigmatism, posterior elevation and a more prolate posterior surface in keratoconus suspect eyes compared to normal eyes by using the Orbscan IIz system.[18] Pinero et al have later supported this finding with another system, the Pentacam (Oculus).[8] Nilforoushan et al performed a multiple regression analysis and have identified the larger difference between the highest and lowest points on the posterior elevation maps with both Pentacam and Orbsacn IIz system, as the strongest predictor of suspect keratoconus.[19] Similarly, in the present study, we found a strong statistical difference ($p < 0.001$) in the posterior AAI between normal corneas and FFKC, which is also calculated as the absolute difference between the highest and the lowest elevation value but in the posterior BFTA elevation map, which further supports the finding of Nilforoushan et al. These recent findings in the field of keratoconus detection have all contributed to point out the clinical significance of the posterior surface modifications and to consider it as a key variable in the subclinical keratoconus screening process.

Corneal thinning has also been shown to be a key pathologic feature of keratoconus.[19,20] In our study, the pachymetric indices were found significantly different between normal corneas, FFKC and keratoconus, with a progressive thinning along with the progression of the ectatic process. Previous studies have already reported thinner corneas in suspect keratoconus than in normal eyes[18,19] and a progressive thinning along with the progression of the disease.[8] To go even further, Saad and Gatinel have recently calculated with the Orbscan system, the percentage increase in thickness (PIT), that was described by Ambrosio et al with the Pentacam,[21] and reported a significantly higher PIT in the most incipient form of the keratoconus disease (FFKC) than in normal corneas.[4] This finding suggests that subclinical form of keratoconus might be characterized not only by thinner corneas but also by a quick modification of the corneal thickness from the thinnest point to the periphery.

In the present work, we found that vertical coma was the only corneal aberration that was significantly different ($p = 0.006$) between normal corneas and FFKC with a means of 0.01 μm and –0.35 μm, respectively. This finding is in agreement with recent reports showing that the anterior corneal vertical coma had a strong ability to discriminate between normal corneas and subclinical keratoconus.[22,23] Corneal vertical coma has even been incorporated recently in a new keratoconus classification for grading the disease.[24]

By providing precious information on corneal properties, such as anterior and posterior elevation data, pachymetric and wavefront profile, the GALILEI analyzer has shown to be a useful imaging system for differentiating between normal corneas, subclinical keratoconus and keratoconic corneas, similarly to other imaging systems. However, as previously shown in the literature,[25,26] although, differences in corneal features have been demonstrated between normal and FFKC, it remains that one parameter alone can hardly reach a high discriminative ability for differentiating normal eyes from subclinical keratoconus. Therefore, the most discriminant parameters provided by the Dual Scheimpflug Analyzer should be combined in a single discriminant function to provide a more sensitive detection program for identifying corneas at risk of ectasia.

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