Predictive model for early diagnosis of keratoconus

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Abstract

Background To describe the topographic, pachymetric and aberrometry characteristics in patients with keratoconus, subclinical keratoconus/forme fruste and normal corneas. Calculate a diagnostic model of subclinical keratoconus/forme fruste.

Methods The design was a cross-sectional study. It included 205 eyes from 188 patients distributed in 82 normal corneas, 40 subclinical keratoconus/forme fruste and 83 established keratoconus The topographic, pachymetric and aberrometry variables obtained by rotary Scheimpflug camera (Pentacam® type) were analyzed. A descriptive and bivariate analysis of the recorded data was performed. A diagnostic model of subclinical keratoconus/forme fruste was calculated.

Results Statistically significant differences were obtained when comparing normal corneas with subclinical keratoconus/forme fruste in variables of vertical asymmetry and corneal thickness.The regression model was calculated with the minimum corneal thickness and the anterior coma to 90º and posterior coma to 90º.

Conclusions The diagnosis of subclinical keratoconus/forme fruste depends on the central corneal thickness, and two aberrometric topographic parameters the anterior coma to 90º and posterior coma to 90º.

Background

Keratoconus is an asymmetrical bilateral eye disease[1] in which corneal thinning and protrusion occurs in the form of a generally lower temporal cone. This corneal deformation produces a significant decrease in visual quality.

It usually appears in adolescence, progressing into the third or fourth decade.[1]Although of unknown etiology, it has been related to genetic factors[2] such as environmental factors[3 − 4].

The incidence and prevalence of keratoconus are very variable. It has been seen that in Europe, the frequency would be between 5 and 23 per 100,000 people/year and the average prevalence would be 54 per 100,000[5]. In a recent study it was observed that the prevalence of keratoconus in southern Spain was 30 per 100,000.[6]

The diagnosis of keratoconus is clinical. Therefore, it is established when a patient presents progressive loss of vision that is not corrected with glasses and is accompanied by biomicroscopic findings in the exploration.

However, there are two entities known as Subclinical Keratoconus and Forme Fruste Keratoconus (SCKC/FFKC), which are included as early stages of the disease, where visual acuity is usually preserved.[5]

Throughout history, several classifications of clinical keratoconus have been used; the Amsler-Krumeich classification has been the most widely used.[24,28]. Alió-Shabayek modified it including coma-like corneal aberrations.[8]However, there is no adequate classification to determine the stage of this pathology at an early stage.

Corneal topography is a non-invasive diagnostic test that allows to know the surface of the cornea. It was established that this is the best method of diagnosis in incipient keratoconus.[9] The Oculus Pentacam® system provides the anterior and posterior topographic, pachymetric and aberrometry maps.

The anterior corneal surface is the most important refractive component of the eye, and it aberrations are very useful in the diagnosis of the corneal disease.[8,12,20,24,25]However, studies of aberrations of the posterior surface are discordant and inconclusive.[9,13,14,29,30]

The study of corneal aberrations in incipient stages has allowed us to affirm that the anterior coma to 90º is the one that most discriminates them from healthy corneas.[15,26].Parameters as minimum corneal thickness, posterior coma,[15,28]trefoil[17,27,31] and spherical aberration[14,24,27]would also have an influence.

It has been analyzed that corneal aberrations, especially the anterior coma to 90º and its influence in the visual quality of patients with keratoconus.[16,23]

The study of the wavefront has a great importance for the early diagnosis of keratoconus and the determination of variables that influence visual acuity. The main objective of this study is to establish a predictive model of early diagnosis in keratoconus with topographic variables obtained by

Pentacam®.

Methods

A cross-sectional study was carried out to analyses the topographic, pachymetric and aberrometry variables obtained by rotary Scheimpflug camera (Pentacam® type) from patients diagnosed with keratoconus, SCKC/FFKC and normal corneas in the Ophthalmology Service at the Torrecárdenas University Hospital (Almería, Spain) between February 2018 and February 2019. The data have been collected from the Pentacam® clinical database.

Participants have been previously informed of the data to be taken and have signed an informed consent authorizing the use of their data anonymously. The ethical principles for medical research on human beings of the Declaration of Helsinki have been followed.

Total of 188 patients was distributed in 3 groups.

Group 1: Healthy patients without corneal pathology,

Group 2 Patients with SCKC/FFKC. This group included patients with any altered corneal topography but without clinical signs of disease and clinical keratoconus in the contralateral eye

Group 3 Patients with keratoconus. They must present at least one biomicroscopic alteration of the anterior segment (central thinning with Fleischer's ring and Vogt's striae) and the topography compatible with corneal ectasia. In patients with bilateral keratoconus, one of the eyes had been taken randomly.

The exclusion criteria were to have any systemic or ocular pathology and any ocular surgical intervention, including intrastromal rings and cross-linking.

A complete ophthalmological examination was performed in all cases.

Uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) were collected with Snellen's chart (decimal scale). Objective refraction obtained by an autorefractometer (KR8900, Topcon, Japan) biomicroscopy (Carl Zeiss Meditec AG, Jena, Germany) and fundus were examined.

A corneal topographic analysis was performed on all patients by the same trained physician, under the same dark conditions and a pupil diameter of 6 mm. Patients with soft contact lenses didn´t wear them for three weeks and the gas-permeable rigid lenses for at least five weeks before the test. The examination was performed with the rotary camera Scheimpflug (Pentacam® AXL, Oculus Optikgeräte, Wetzlar, Germany).

The following variables were collected:

Corneal topography of the anterior face: minor curvature (K1), major curvature (K2), mean curvature (Km), maximum curvature (KMAX), asphericity (Q), vertical asymmetry index (VAI); corneal topography of the posterior face: minor curvature (K1), major curvature (K2), mean curvature (Km) and asphericity (Q), central corneal thickness (CCT), minimum corneal thickness (MCT) with its coordinates (x,y) mean square root of total aberrations (Total RMS), mean square root of high order aberrations (HOA RMS), secondary corneal astigmatismto 0º ($Z2^{2}$) and to 45º ($Z2^{-2}$), anterior horizontal coma to 0º, posterior horizontal coma to 0º, total horizontal corneal coma to0º ($Z3^{1}$), anterior vertical coma to 90º, posterior vertical comato90º, total vertical corneal coma to 90º ($Z3^{-1}$), trefoil to 0º ($Z3^{-3}$), trefoil to 30º ($Z3^{3}$), tetrafoilto 0º ($Z4^{4}$), tetrafoilto 22.5º ($Z4^{-4}$) and spherical aberration ($Z4^{0}$).

Statistical analysis was performed using the software for Windows SPSS (version 25.0, SPSS, Chicago, Illinois, USA) and R (version 3.5.1).

Results

The study compared 205 eyes divided into three study groups, the distribution of which is shown in Table 1. There were no statistically significant differences in laterality or sex between the groups. There were statistically significant differences between the three groups ($p < 0.05$, Kruskal-Wallis) for the sphere, cylinder, spherical equivalent and BCVA (decimal scale). Also, there were statistically significant differences between group 1 and 2 for the sphere ($p = 0.012$, U Mann-Whitney), (Table 1). Means and standard deviations were calculated for the different variables. Those of more considerable clinical significance are presented in Table 2.

Table 1: Demographic characteristics

		Normal	KCSC/KCFF	KC	SCKC/FFKC Vs Controls P Value*	Controls Vs KC P Value*
Patients	n (%)	82 (39.8)	40 (19.4)	83 (40.3)		
Eye	Right	41 (50.0)	19 (47.5)	54 (65.1)		0.078
	Left	41 (50.0)	21 (52.5)	29 (34.9)		
Sex	Male	36 (43.9)	23 (57.5)	40 (48.2)		0.369
	Female	46 (56.1)	17 (42.5)	43 (51.8)		
Sphere (D)		-0.36 ± 3.02 [-8; 4.50]	-1.06 ± 1.71 [-5.50; 3]	-3.71 ± 4.71 [-16;6]	0.012	< 0.01
Cylinder (D)		-1.82 ± 2.15 [-6; 3.75]	-1.19 ± 0.99 [-2.50; 2.75]	-2.95±1.46 [-6;1]	0.059	< 0.01
Spherical equivalent (D)		-1.38 ± 3.23 [-10; 5.50]	-1.73 ± 1.62 [-5.50; 2.25]	-4.84 ± 4.61 [-18; 4.50]	0.251	< 0.01
BCVA (decimal scale)		0.97 ± 0.07 [0.7;1]	0.99 ± 0.06 [0.7;1]	0.6 ± 0.29 [0.05; 1]	0.219	< 0.01

p<0.05

Table 2. Main Pentacam indices and bivariate analysis

	Controls	SCKC/FFKC	KC	SCKC/FKC Vs Controls p Value	KC Vs p Value
Anterior surface topography					
Km	43.55±1.43	43.37±1.55	48.26±4.644	0.616	
KMAX	45.49±1.92	45.91±1.97	55.14±7.657	0.285	<0.01
VAI	0.16±0.08	0.28±0.14	0.79±0.509	<0.01	<0.01
Posterior surface topography					
Km	-6.246±0.220	-6.148±0.343	-7.15±0.947	0.067	<0.01
Pachymetry					
CCT	543.76±36.42	515.20±27.59	466.92±55.94	<0.01	<0.01
MCT	538.52±37.03	503.67±26.62	456.93±50.65	<0.01	<0.01
Corneal Aberrometry					
RMS HOA	0.52±0.23	0.69±0.31	1.74±1.02	<0.01	<0.01
Ant Coma 90º	0.01±0.20	0.49±0.43	-2.06±1.51	<0.01	<0.01
Post Coma 90º	-0.01±0.05	0.11±0.10	0.53±0.386	<0.01	<0.01
Coma 90º	0.01±0.21	-0.40±0.32	-1.88±1.413	<0.01	<0.01
Trefoil 0º	0.03±0.18	0.08±0.22	0.09±0.34	0.396	<0.01
Spherical aberration	0.20±0.14	0.18±0.16	-0.279±0.75	0.204	<0.01

Early diagnosis of Keratoconus:

Our main objective in the study would be to be able to differentiate between healthy patients (group 1) and patients with SCKC/FFKC (group 2). Therefore, we consider normal corneas and SCKC/FFKC as a dichotomous dependent variable. Independent variables included MCT, anterior coma to 90º and posterior coma to 90º

Table 3 presents the equation variables accompanied by their statistical significance and their OR (Exp (B)) with the 95% confidence interval and the variance inflation factor to evaluate the collinearity between the variables

Table 3: Regression model coefficients for the diagnosis of subclinical keratoconus

	Estimate β	Exp β (OR)	Std. Error	P value	VIF
(Intercept)	19.25789	2.31E+08	6.20707	0.001918	
MCT	-0.04001	9.61E-01	0.01198	0.000838	1.25
COMA.POST.90	19.92046	4.48E+08	6.90491	0.003915	1.82
COMA.ANT.90	-2.62811	7.22E-02	1.53268	0.086397	1.53

The Hosmer and Lemeshow goodness of fit test (GOT) (p=0.566) indicated that the proposed model was correctly calibrated.

Table 4 shows a contingency table of observed cases versus predicted cases.

Table 4: Contingency table of observed cases versus predicted cases

	predicted	
outcome	low	high
0	79	3
1	9	31

The AUC (Area Under Curve) of the ROC (Receiver Operating Characteristics) curve for the binary logistic regression model was 0.92 (IC 95% 0.86 – 0.98) in the diagnosis of subclinical keratoconus/forme fruste (Figure 1)

Discussion

Detection of SCKC/FFKC has always been a challenge for ophthalmologists, especially when there are no clinical signs or symptoms in the patient.

The rotary camera Scheimpflug (Pentacam®) [13, 14, 20, 23, 25, 26, 30], has been used to diagnose keratoconus in daily clinical practice. The topographic parameters of clinical keratoconus are recognizable. However, it is not easy to diagnose subclinical keratoconus based on topographic variables. This study calculates a diagnostic model based on the aberrometry data of the anterior and posterior corneal surface provided by the Pentacam

The selection of the sample was made that there were no differences between the age groups[12 − 15, 17, 19, 21, 24, 29], sex[14, 21, 22, 29], and laterality[21, 22]. In Koçamis et al. study[22], there were significant differences for age between keratoconus (26.19 ± 7.90) and healthy (30.88 ± 7.57).

Pupillary dilatation is a parameter modifying aberrometry results[27]. In this study, it was prefixed in 6 mm. In previous studies[8, 12−14, 20, 23, 29]. Hondur et al[27] established it in 5 mm.

Many studies have been made between healthy patients with Keratoconus[8, 10, 12−14, 20, 22, 24, 27] or healthy patients with SCKC/FFKC[15, 17, 19, 21, 23, 26, 28−31]. The purpose in most of them was to analyze the topographic parameters to find differences between a healthy patient and an incipient corneal ectasia without symptoms.

Different classification methods have been used: Amsler-Krumeich[24, 27, 28], Alió and Shabayek[13, 20], KISA % index[21] or KSS[29].

All this methodological variability leads to an outstanding selection and classification bias that it must be taken into account when making comparisons between studies.

If we analyze the refractive parameters of our study, statistically significant differences were obtained between the three groups analyzed for the sphere, the cylinder and the spherical equivalent ($p < 0.05$, Kruskal-Wallis), as in other studies[19, 30]. However, when comparing normal corneas with SCKC/FFKC, we obtained statistically significant differences only for the sphere ($p = 0.012$, U Mann-Whitney).

Saadand Gatinel[17]obtained that the mean of the sphere was significantly higher in their normal group than in their SCKC/FFKC group ($p < 0.001$). Reddy et al[19]obtained statistically significant differences for the cylinder ($p < 0.001$) not obtaining these differences for the sphere ($p = 0.08$). However, Naderanet al[29]found no statistically significant differences for sphere ($p = 0.136$) or cylinder ($p = 0.108$).

Statistically significant differences were observed between the visual acuity of the three groups, not existing between normal corneas and SCKC/FFKC. These values are consistent with previous studies[8, 20, 22, 27, 30, 31].

A bivariate analysis has been performed between normal corneas and SCKC/FFKC. Statistically significant differences were only obtained for variables of vertical asymmetry, coma to 90º and corneal thickness ($p < 0.05$).

According to Bührenet al[15], the anterior coma to 90º would be the most useful parameter to differentiate normal corneas from SCKC/FFKC. Other parameters such as the posterior coma to 90º and the minimum corneal thickness would not exceed the value of the anterior surface.

When the corneal coma to 90º was analyzed in absolute value, we found that it was higher in SCKC/FFKC (|-0.404| ± 0.319) than in normal (0.0123 ± 0.209), but lower than in keratoconus (|-1.877| ± 1.413). This value indicates that group 2 included those patients with a very early stage of keratoconus and that the parameter corneal coma to 90º had increased with the natural history of the disease[17]. The negative sign of the corneal coma to 90º refers to the lower decentration of the cone in the axis of ordinate[17].

More recently, Naderanet al[29] y Xu et al[30] indicated the importance of posterior surface aberrations to differentiate normal SCKC/FFKC corneas. In the first study, they obtained that the values for posterior coma to 90º of the healthy group were 0.032 ± 0.363 and for the SCKC/FFKC group were 0.193 ± 0.264 with statistically significant differences between groups ($p = 0.003$, U Mann-Whitney). In our database, the posterior coma to 90º for normal corneas were -0.008 ± 0.049 and for SCKC/FFKC were 0.112 ± 0.103, ($p < 0.05$, U Mann-Whitney).

The relationship between coma-like aberrations of the anterior surface and the degree of manifest keratoconus is well known.[8, 12, 22, 24−27] Piñero et al[13] were the first to attempt to characterize the posterior corneal surface and its aberrations in patients with normal corneas and keratoconus, finding results that were not concordant by the optical theory of the corneal surface.

In this study in the healthy patients were obtained values of anterior coma to 90º of 0.001 ± 0.225 and posterior coma to 90º of 0.319 ± 0.372 while in keratoconus were -1.754 ± 0.976 and -3.692 ± 1.81 respectively. If we analyze the results of our study, in healthy patients the anterior coma to 90º were 0.009 ± 0.200 and posterior coma to 90º were-0.008 ± 0.049, and in keratoconus, we obtained -2.073 ± 1.513 and 0.536 ± 0.386 respectively. In our case, the anterior parameters, in absolute value, were higher than the posterior ones, which is concordant with the corneal optical theory.

For Buhrenet al[15], the minimum corneal thickness was the most discriminating pachymetric parameter between normal corneas and SCKC/FFKC. However, he concluded that the posterior surface was not discriminate as to the anterior surface, and this surface was not sufficient for the diagnosis of the subclinical entity. Safarzadeh et al[28] reflected that minimum corneal thickness and posterior corneal elevation would be the best parameters for differentiating suspicious keratoconus from healthy eyes. Although other authors[17, 21, 30] have established binary logistic models, it is the first report of a simple diagnostic model to obtain the probability of having or not having subclinical keratoconus using parameters obtained from the Pentacam® topographer.

Conclusions

The diagnosis of subclinical keratoconus/forme fruste depends on the minimum corneal thickness, and two aberrometric topographic parameters the anterior coma to 90º and posterior coma to 90º.

Abbreviations

SCKC/FFKC

Subclinical Keratoconus /Forme Frustre Keratoconus

MCT

Minimum Corneal Thickness

UCVA

Uncorrected Visual Acuity

BCVA

Best Corrected Visual Acuity

Km

Mean curvature (Km),

Kmax

maximum curvature (KMAX),

Q

asphericity

VAI

vertical asymmetry index

Total RMS

mean square root of total aberrations

HOA RMS

mean square root of high order aberrations

AUC

Area Under Curve

ROC curve

Receiver Operating Characteristics curve

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were by the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its comparable ethical standards. Ethical approval by Ethics Committee Torrecárdenas Universitary Hospital. The committee's reference number is 19/2019

Informed consent: Informed consent was obtained from all individual participants included in the study

Consent for publication

Not Applicable

Availability of data and material

The datasets generated and/or analysed during the current study are available in the KERATOCONUS repository, Castro de Luna, Gracia; Perez Rueda, Antonio (2020), "KERATOCONUS", Mendeley Data, V2, doi: 10.17632/t2yzmb4c7s.2

Competing interests

The authors declare no competing interests

Fundings

No funding was obtained for this study

Authors' contributions

GCL has contributed in the design of this study and has calculated the statistical data

APR has collected the data

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Not Applicable

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Figures

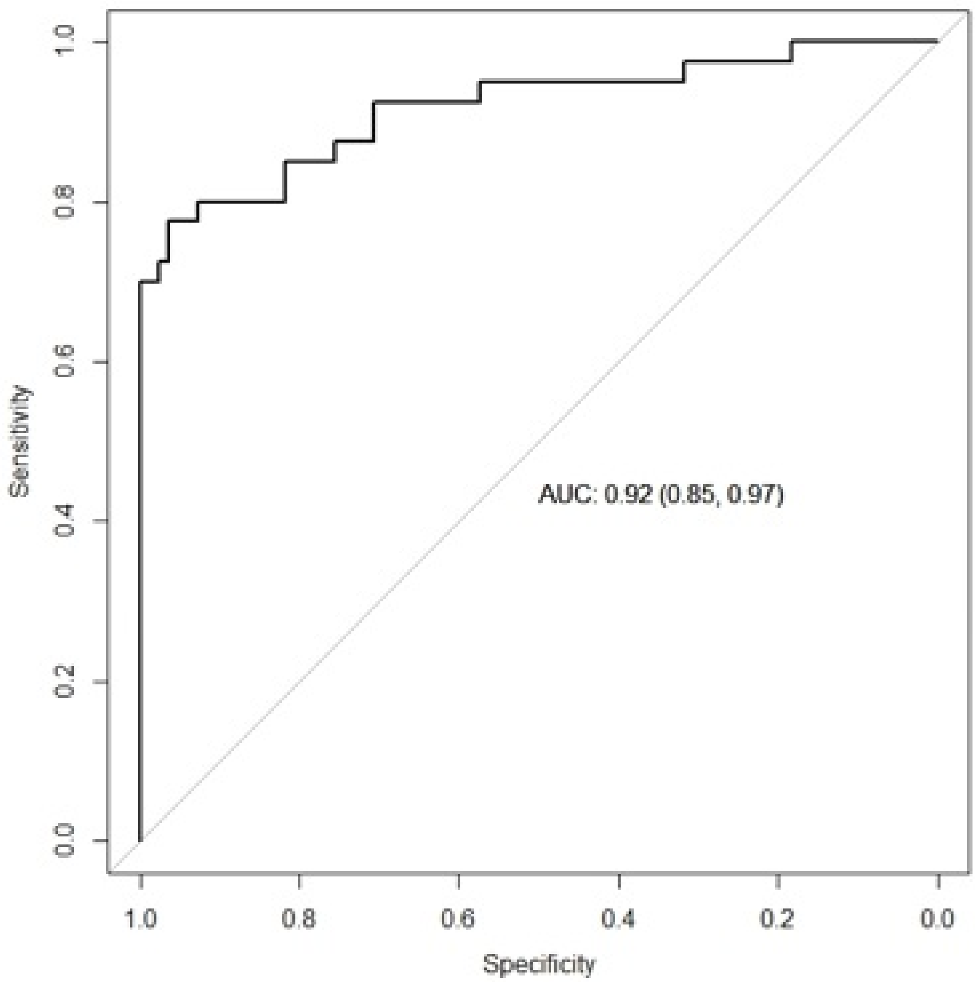

Figure 1

the ROC (Receiver Operating Characteristics) curve for the regression model