Comparison of Pentacam data in patients with diagnostic criteria for keratoconus in only one eye

Comparação dos dados do Pentacam em pacientes com critérios diagnósticos de ceratocone em apenas um olho

Karolyna Andrade de Carvalho[1], Nayara Aparecida Engelender de Oliveira[1], Raquel Silas Melice[2], Rafael Henrique Martini Mariano da Rocha[1], Pablo Felipe Rodrigues[3], Bernardo Kaplan Moscovici[3]

[1] Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil.
[2] UPO Oftalmologia, São Paulo, SP, Brazil.
[3] Universidade Federal de São Paulo, São Paulo, SP, Brazil.

How to cite:
Carvalho KA, Oliveira NA, Melice RS, Rocha RH, Rodrigues PF, et al. Comparison of Pentacam data in patients with diagnostic criteria for keratoconus in only one eye Rev Bras Oftalmol. 2024;83:e0047.

doi:
https://doi.org/10.37039/1982.8551.20240047

Keywords:
Keratoconus; Topography; Tomography, optic coherence; Dilatation, pathologic

Descritores:
Ceratocone; Topografia; Tomografia de coerência óptica; Dilatação patológica

Received on:
Feb 7,2024

Accepted on:
June 8,2024

Corresponding author:
Karolyna Andrade de Carvalho.
Rua Dr. Cesário Mota Júnior, 112 – Vila Buarque
Zip code: 01221-010 – São Paulo, SP, Brasil
E-mail: drakarolynacarvalho@gmail.com

Institution:
Private Clinic, São Paulo, Brazil

Conflict of interest:
no conflict of interest.

Financial support:
no financial support for this work.

ABSTRACT

Purpose: To compare data extracted from the Pentacam exam in patients with keratoconus in one eye and form fruste keratoconus in the other eye.

Setting: Private clinic in São Paulo, Brazil.

Design: Retrospective review.

Methods: This study reviewed charts of patients with keratoconus in one eye and forme fruste keratoconus (FFKC) in the other, from January to December 2019. All subjects were evaluated with a rotating Scheimpflug imaging system. Twenty-two eyes of 11 patients were compared, and only one eye had established diagnostic criteria for keratoconus. Given this, 38 variables obtained through Pentacam were compared.

Results: In eyes with keratoconus, several parameters exhibit significant alterations compared to those with FFK eyes. Notably, Belin elevation and posterior and total densitometry remain consistently significant, indicating early changes in mild forms of the disease and progression over time. Additionally, indicators such as IVA, KI, IHD, posterior elevation of BFTA, and R min demonstrate notable changes in FFKC eyes. Among these, the index of height decentration (IHD) stands out, with the highest alteration rate of 81.8% in FFKC patients. Furthermore, parameters like the D index (total), EI posterior, and Maximum posterior elevation with BFS, IHD, Kmax, and Q value demonstrate high accuracy, sensitivity, and specificity in distinguishing FFKC from control eyes. Kmax, Belin Ambrósio Posterior Elevation, IHD, and posterior elevation of best-fit reference sphere (BFS Posterior Elevation) emerge as the most altered parameters in FFKC.

Conclusion: We considered the IHD, the BFS posterior elevation, Kmax, asphericity, Belin-Ambrósio display, and decentration of the thinnest point as sensitive indicators for initial keratoconus cases, IHD being the most accurate of them.

RESUMO

Objetivo: Comparar os dados extraídos do exame Pentacam em pacientes com ceratocone em um olho e ceratocone frusto no outro olho.

Local: Clínica privada em São Paulo, Brasil.

Desenho do estudo: Revisão retrospectiva.

Métodos: Este estudo revisou prontuários de pacientes com ceratocone em um olho e ceratocone forma frusta (FFKC) no outro, de janeiro a dezembro de 2019. Todos os indivíduos foram avaliados com um sistema de imagem Scheimpflug rotativo. Vinte e dois olhos de 11 pacientes foram comparados, e apenas um olho tinha critérios diagnósticos estabelecidos para ceratocone. Diante disso, 38 variáveis obtidas através do Pentacam foram comparadas.

Resultados: Em olhos com ceratocone, vários parâmetros apresentam alterações significativas em relação àqueles com olhos FFKC. Notavelmente, a elevação de Belin e a densitometria posterior e total permanecem consistentemente significativas, indicando mudanças precoces nas formas leves da doença e progressão ao longo do tempo. Além disso, indicadores como IVA, KI, IHD, elevação posterior do BFTA e R min demonstram alterações notáveis nos olhos do FFKC. Dentre estes, destaca-se o índice de descentração da altura (IHD), com maior taxa de alteração de 81,8% nos pacientes com FFKC. Além disso, parâmetros como o índice D (total), IE posterior e elevação máxima posterior com BFS, IHD, Kmáx e valor de Q demonstram alta acurácia, sensibilidade e especificidade na distinção entre o FFKC e o olho controle. Kmax, Belin Ambrósio Elevação Posterior, IHD e elevação posterior utilizando BFS (BFS Posterior Elevation) emergem como os parâmetros mais alterados no FFKC.

Conclusão: Consideramos o IHD, a elevação posterior com BFS, Kmáx, a asfericidade, o Belin-Ambrósio e a descentração do ponto mais fino como indicadores sensíveis para os casos iniciais de ceratocone, sendo o IHD o mais preciso.

INTRODUCTION

Keratoconus is a chronic, non-inflammatory, bilateral corneal ectasia characterized by pathological progressive cornea thinning, causing a cone-shaped protrusion, irregular astigmatism, decreased vision, and potential blindness.[1,2]

Although a bilateral condition, the disease is usually asymmetrical, and only one eye may be initially affected. The ectasia can be diagnosed by the modified Rabinowitz-McDonnell criteria, considering a central corneal keratometry (K) value greater than 47.2 diopters (D), a difference in refractive power between an inferior region and superior (I-S) of the cornea in the same eye greater than 1.4 D and the difference in the central K value between the two eyes of the patient.[3-5]

However, the diagnosis of subclinical keratoconus is still a challenge. According to the 2015 Global Consensus on Keratoconus and Ectatic Diseases, subclinical keratoconus presents abnormalities on the posterior surface of the cornea, being best detected by the corneal Sheimpflug tomography method instead of the traditional topography. Although corneal tomographers provide several markers for the early detection of keratoconus,[6] there is still ongoing scientific search for the best early markers of the disease.[7-11]

Even with technologies such as corneal epithelial mapping, corneal tomography, and corneal biomechanics, diagnosing forme fruste keratoconus (FFKC) in refractive surgery screening is still challenging.[6] Thus, cases that can achieve a classic diagnosis using the Rabinowitz criteria in one eye and do not meet the criteria in the other eye are fundamental for the study and for understanding the indices from more advanced technologies in detecting FFKC.

We aimed to compare Pentacam (Oculus, Weitzlar, Germany) parameters of patients diagnosed with manifest keratoconus in one eye and subclinical disease in the contralateral eye to find early subclinical disease markers.

METHODS

Study design

This is a retrospective case-control study that adheres to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of *Santa Casa de Misericórdia de São Paulo*. All patients included provided informed consent. We used the database of Ophthalmological Private Clinic, REDEMO clinic (São Paulo, Brazil).

Study group

We used Rabinowitz's criteria to diagnose keratoconus. Patients whose keratoconus was diagnosed in one eye and whose contralateral eye did not meet classic diagnostic criteria were included in the study.

The eyes were divided into a keratoconus group (keratoconus itself [KC]) and a control group (forme fruste keratoconus or subclinical disease, contralateral eye [FFKC]). We analyzed another group without keratoconus in both eyes (to serve as a control).

Eleven patients were selected from a Scheimpflug Pentacam corneal tomography database.

Exclusion criteria were diagnostic criteria for keratoconus in both eyes, corneal opacity, previous surgeries, or other ocular diseases.

Data extraction

Only cases with acceptable-quality images and without extrapolated data were included in the study.

The following parameters were evaluated with the Scheimpflug system: corneal dioptric power on the flattest meridian in the central 3.0 mm zone (K), the value of I-S, dioptric asymmetry in the sagittal I-S, and tangential I-S curvature maps, the central keratoconus index (CKI), the best reference sphere (BFS), the minimum sagittal curve (Rmin), the maximum Ambrósio thickness ratio (ARTmax), the total deviation of the five parameters (D), deviation of ARTmax (Da), best fit toric and aspheric surface (BFTA), posterior map elevation deviation (Db), frontal map elevation deviation (Df), pachymetric progression deviation (Dp), minimum thickness deviation (Dt), index of height asymmetry (IHA), index of height decentration (IHD), index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), maximum keratometry (Kmax), lower difference I-S, the superior nasal-inferior temporal difference (SN-IT), and corneal asphericity (Q value).

Elevation was standardized compared to a best-fit reference sphere (BFS) calculated by a fixed optical zone of 9.0 mm.

The difference in posterior elevation values were extrapolated from the elevation maps by subtracting the highest and lowest elevation values.

The data was classified as altered, borderline, and not altered, according to the standard values established by the device.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 20 software, and a p-value of less than 0.05 was statistically significant. Due to the sample size, we used the Shapiro-Wilk

test to evaluate sample normality. Since the sample was normal, we used parametric tests: *t* student, Chi-squared, Fisher, and two proportion tests. We also used logistic regression and Receiver Operating Characteristic curves in our study.

RESULTS

We compared 22 eyes of 11 patients diagnosed with keratoconus to a control group without Rabinowitz Criteria for keratoconus (FFKC), consisting of 20 eyes of 10 patients classified as normal.

Qualitative and quantitative parameters from Pentacam, totaling 38 variables, were analyzed. The Chi-squared test was employed for quantitative analysis, categorizing corneal alteration - presence or absence (Table 1).

Notable differences between keratoconus and FFKC were observed. Parameters such as Belin elevation and posterior and total densitometry remained consistently significant in keratoconus eyes, indicating early changes and disease progression. The analysis shows factors distinguishing an advanced keratoconus from FFKC, such as ISV,

Table 1. Comparing normal and studied groups

		Average	Median	Standard-deviation	Minimum	Maximum	n	p-value
ISV	Normal	18.80	16.5	9.01	9	49	20	- x -
	KC	64.58	6.5	27.44	28	114	12	<0.001
	FFKC	22.17	21.0	6.59	14	34	12	0.270
IVA	Normal	0.123	0.095	0.060	0.060	0.230	20	- x -
	KC	0.553	0.500	0.286	0.260	1.180	12	<0.001
	FFKC	0.171	0.180	0.055	0.090	0.260	12	0.030
KI	Normal	1.000	1.000	0.019	0.960	1.030	20	- x -
	KC	1.152	1.145	0.072	1.070	1.250	12	<0.001
	FFKC	1.042	1.045	0.015	1.020	1.060	12	<0.001
CKI	Normal	1.002	1.000	0.007	0.980	1.010	20	- x -
	KC	1.048	1.040	0.034	1.000	1.110	12	<0.001
	FFKC	1.012	1.010	0.009	1.000	1.030	12	0.002
IHA	Normal	4.45	2.3	5.59	0.1	21	20	- x -
	KC	24.07	22.0	16.54	2.8	66.4	12	<0.001
	FFKC	10.98	10.0	7.92	2.9	29.7	12	0.010
IHD	Normal	0.010	0.009	0.007	0.002	0.026	20	- x -
	KC	0.075	0.070	0.040	0.029	0.150	12	<0.001
	FFKC	0.020	0.020	0.007	0.007	0.035	12	<0.001
Rmin	Normal	7.889	7.915	0.259	7.320	8.320	20	- x -
	KC	6.297	6.285	0.818	4.320	7.400	12	<0.001
	FFKC	7.484	7.575	0.344	6.910	7.900	12	0.001
Corneal volume	Normal	60.71	60.4	3.48	56.3	67.5	20	- x -
	KC	58.75	57.7	3.87	54.5	65.1	12	0.151
	FFKC	58.69	57.0	3.91	53.3	65.2	12	0.141
Delta posterior curve	Normal	6.939	6.955	0.266	6.510	7.490	20	- x -
	KC	2.392	2.450	1.147	0.500	5.100	12	<0.001
	FFKC	0.817	0.650	0.565	0.400	2.400	12	<0.001
Q value	Normal	0.052	-0.005	0.405	-0.420	1.330	20	- x -
	KC	0.768	0.685	0.336	0.290	1.270	12	<0.001
	FFKC	0.406	0.370	0.179	0.200	0.860	12	0.008
Posterior elevation BFS	Normal	0.58	0.6	0.41	-0.97	1.01	20	- x -
	KC	52.92	51.0	20.53	28	88	12	<0.001
	FFKC	18.67	18.0	5.93	11	31	12	<0.001
Delta posterior elevation BFS	Normal	44.95	47.0	13.38	15	79	20	- x -
	KC	129.75	128.0	55.48	60	252	12	<0.001
	FFKC	46.00	40.0	15.29	32	79	12	0.840
BFTA posterior elevation	Normal	12.55	12.5	7.30	0	25	20	- x -
	KC	33.92	33.0	12.66	16	54	12	<0.001
	FFKC	14.67	13.0	6.72	7	28	12	0.420
Delta BFTA posterior elevation	Normal	16.15	15.5	4.82	10	25	20	- x -
	KC	78.83	81.0	33.59	34	157	12	<0.001
	FFKC	28.00	30.5	9.16	11	40	12	<0.001
Thinnest relative pachymetry	Normal	-6.41	-7.0	5.15	-19.7	1.9	20	- x -
	KC	10.95	8.3	8.28	3.4	34.55	12	<0.001
	FFKC	4.07	3.4	1.56	2.7	7.7	12	<0.001
CHORD μ	Normal	0.211	0.200	0.118	0.040	0.440	20	- x -
	KC	0.302	0.290	0.139	0.070	0.560	12	0.057
	FFKC	0.190	0.180	0.123	<0.001	0.420	12	0.643

Continue...

Continuation.

		Average	Median	Standard-deviation	Minimum	Maximum	n	p-value
Kmax	Normal	42.83	42.7	1.45	40.5	46.1	20	- x -
	KC	52.17	50.5	9.31	43.5	78.2	12	<0.001
	FFKC	47.09	44.6	4.85	42.7	57.5	12	0.001
Thinnest pachymetry	Normal	524.75	521.5	52.34	411	621	20	- x -
	KC	468.83	471.0	65.53	292	527	12	0.012
	FFKC	510.92	513.0	33.45	454	553	12	0.420
ARTmax	Normal	389.45	355.5	149.66	157	656	20	- x -
	KC	200.00	190.5	97.95	18	442	12	0.001
	FFKC	358.75	365.0	65.50	218	457	12	0.508
Minimum progression	Normal	1.012	1.060	0.390	0.590	2.180	20	- x -
	KC	1.233	1.130	0.464	0.650	2.440	12	0.160
	FFKC	0.839	0.810	0.158	0.650	1.200	12	0.155
Medium progression	Normal	1.308	1.340	0.429	0.760	2.490	19	- x -
	KC	2.161	1.670	1.636	0.870	7.150	12	0.038
	FFKC	1.116	1.080	0.179	0.880	1.600	12	0.152
Maximum progression	Normal	1.512	1.620	0.449	0.880	2.620	19	- x -
	KC	3.584	2.455	4.033	1.190	16.250	12	0.033
	FFKC	1.465	1.420	0.250	1.140	2.090	12	0.743
Belin-Ambrósio posterior elevation	Normal	1.20	1.0	2.33	-2	8	20	- x -
	KC	29.42	26.0	19.01	1	79	12	<0.001
	FFKC	7.08	5.0	5.84	1	19	12	<0.001
Df	Normal	0.664	0.505	2.086	-1.680	8.300	20	- x -
	KC	6.633	6.225	4.402	-1.240	13.890	12	<0.001
	FFKC	1.386	1.460	1.342	-0.550	3.610	12	0.293
Db	Normal	-0.208	-0.325	0.791	-1.420	1.660	20	- x -
	KC	5.874	5.235	4.411	-1.120	16.860	12	<0.001
	FFKC	0.541	0.200	1.349	-0.900	3.180	12	0.056
Dp	Normal	2.591	2.780	2.808	-0.970	10.320	20	- x -
	KC	8.495	5.155	11.121	-0.260	42.410	12	0.030
	FFKC	1.430	1.195	1.218	-0.200	4.700	12	0.187
Dt	Normal	0.535	0.480	1.644	-2.060	4.770	20	- x -
	KC	2.703	2.195	3.480	0.310	13.030	12	0.023
	FFKC	0.934	0.745	1.045	-0.430	2.830	12	0.458
Da	Normal	0.900	1.210	1.366	-1.530	3.020	20	- x -
	KC	2.631	2.715	0.896	0.420	4.300	12	0.001
	FFKC	1.186	1.125	0.596	0.280	2.460	12	0.500
D	Normal	1.332	1.205	1.134	-0.410	4.620	20	- x -
	KC	7.039	6.420	4.406	-0.030	17.620	12	<0.001
	FFKC	1.861	1.480	1.076	0.500	4.380	12	0.203
Anterior densitometry	Normal	21.05	20.2	2.77	17.3	28.1	20	- x -
	KC	21.77	21.5	1.45	20	24.9	12	0.411
	FFKC	21.56	21.2	2.69	17.8	27.9	12	0.612
Posterior densitometry	Normal	11.54	11.1	1.18	10	13.7	20	- x -
	KC	14.03	14.1	1.43	12.4	17.2	12	<0.001
	FFKC	14.05	13.6	2.29	12.3	20.6	12	<0.001
Total densitometry	Normal	15.23	14.7	1.78	13.3	19.6	20	- x -
	KC	17.55	17.7	1.39	15.8	21	12	0.001
	FFKC	17.47	17.4	2.48	15.2	24.2	12	0.006

ISV: index of surface variance; KC: keratoconus; FFKC: forme fruste keratoconus; IVA: index of vertical asymmetry; KI: keratoconus index; CKI: central keratoconus index; IHA: index of height asymmetry; IHD: index of height decentration; Rmin: minimum sagittal curve; BFS: best-fit sphere; BFTA: best-fit toric aspheric; Kmax: maximum keratometry; ARTmax: maximum Ambrósio thickness relation; Df: frontal map elevation deviation; Db: posterior map elevation deviation; Dp: pachymetric progression deviation; Dt: minimum thickness deviation; Da: maximum Ambrósio thickness relation deviation; D: total deviation.

greater posterior delta elevation BFS and BFTA, thinner pachymetry, ARTmax, and group D parameters (Df, Db, Dp, Dt, Da, D), which are more suitable for severity stratification, factors that were not sensible for severity or presence of disease, such as corneal volume or anterior densitometry, and factors that are already shown to be altered in subclinical cases, that is, that can be used for early detection.

In table 2, we performed a univariate logistic model to predict the odds ratio of each variable being altered in manifest or subclinical eyes concerning the control group of entirely normal eyes.

We observed that the CHORD μ, the minimum, average, and maximum pachymetry progressions, and the Dp presented an odds ratio of less than 1 in patients with FFKC and greater than 1 in patients with KC, suggesting that they are more altered in patients with KC.

Other indicators, such as IVA, KI, IHD, posterior elevation of BFTA and R min, showed changes in FFKC.

Table 2. Logistic regression to understand the relationship of each variable in the prediction of being keratoconus or Forme Fruste Keratoconus (FFKC) in reference to normal population

	KC		FFKC	
	p-value	Odds ratio OR	p-value	Odds ratio OR
ISV	0.018	1.18	0.275	1.05
IVA	0.987	*	0.039	*
KI	0.995	*	0.030	*
CKI	0.009	*	0.011	*
IHA	0.002	1.23	0.026	1.16
IHD	0.984	*	0.005	*
Rmin	0.117	0.00	0.009	0.01
Corneal volume	0.154	0.85	0.146	0.85
Delta posterior curve	0.996	0.00	0.997	0.00
Q value	0.004	84.63	0.025	29.30
BFS posterior elevation	0.996	40.02	0.997	4.02
Delta BFS posterior elevation	0.038	1.16	0.834	1.01
BFTA posterior elevation	0.027	1.38	0.408	1.05
Delta BFTA posterior elevation	0.992	30.10	0.005	1.26
Thinnest relative pachymetry	0.989	*	0.986	*
CHORD μ	0.068	327.17	0.631	0.22
Kmax	0.012	3.14	0.024	1.91
Thinnest pachymetry	0.034	0.98	0.409	0.99
ARTmax	0.010	0.98	0.496	1.00
Minimum progression	0.175	3.64	0.163	0.12
Medium progression	0.050	8.29	0.159	0.15
Maximum progression	0.005	35.69	0.733	0.71
Belin-Ambrósio posterior elevation	0.020	1.45	0.015	1.65
Df	0.005	1.76	0.305	1.25
Db	0.008	3.81	0.076	2.04
Dp	0.039	1.40	0.191	0.78
Dt	0.051	1.72	0.447	1.22
Da	0.010	6.37	0.488	1.27
D	0.003	2.82	0.209	1.56
Anterior densitometry	0.402	1.14	0.600	1.07
Posterior densitometry	0.004	4.64	0.005	3.94
Densitometry total	0.005	2.24	0.018	1.78

KC: keratoconus; FFKC: forme fruste keratoconus; OR: odds ratio; ISV: index of surface variance; IVA: index of vertical asymmetry; KI: keratoconus index; CKI: central keratoconus index; IHA: index of height asymmetry; IHD: index of height decentration; Rmin: minimum sagittal curve; BFS: best-fit sphere; BFTA: best-fit toric aspheric; Kmax: maximum keratometry; ARTmax: maximum Ambrósio thickness relation; Df: frontal map elevation deviation; Db: posterior map elevation deviation; Dp: pachymetric progression deviation; Dt: minimum thickness deviation; Da: maximum Ambrósio thickness relation deviation; D: total deviation.

Table 3. Comparing alteration rate between keratoconus and Forme Fruste Keratoconus groups

	KC		FFKC	
	n (%)	p-value	n (%)	p-value
IHD	11 (100)	<0.05	9 (81.8)	<0.05
BFS posterior elevation	11 (100)	<0.05	5 (45.5)	0.076
KI	10 (90.9)	0.306	0	<0.001
Delta posterior curve	10 (90.9)	0.306	2 (18.2)	0.003
BFTA posterior elevation	10 (90.9)	0.306	2 (18.2)	0.003
Df	10 (90.9)	0.306	2 (18.2)	0.003
Dp	10 (90.9)	0.306	1 (9.1)	<0.001
D	10 (90.9)	0.306	2 (18.2)	0.003
Posterior elevation (Belin-Ambrósio)	10 (90.9)	0.306	4 (36.4)	0.030
Medium progression	9 (81.8)	0.138	1 (9.1)	<0.001
Db	9 (81.8)	0.138	2 (18.2)	0.003
IVA	8 (72.7)	0.062	0	<0.001
Q value	8 (72.7)	0.062	3 (27.3)	0.010
Belin elevation	8 (72.7)	0.062	2 (18.2)	<0.003
CKI	7 (63.6)	0.027	0	<0.001
IHA	7 (63.6)	0.027	1 (9.1)	<0.001
Rmin	7 (63.6)	0.027	2 (18.2)	<0.003
Delta BFS posterior elevation	7 (63.6)	0.027	0	<0.001
ISV	6 (54.5)	0.011	0	<0.001
ARTmax	6 (54.5)	0.011	0	<0.001
Da	6 (54.5)	0.011	0	<0.001
Kmax	5 (45.5)	0.004	4 (36.4)	0.030
Dt	4 (36.4)	0.001	2 (18.2)	0.003
Thinnest pachymetry	3 (27.3)	<0.001	1 (9.1)	<0.001
Delta BFTA posterior elevation	0	<0.001	0	<0.001
CHORD μ	0	<0.001	0	<0.001

KC: keratoconus; FFKC: forme fruste keratoconus; IHD: index of height decentration; BFS: best-fit sphere; KI: keratoconus index; BFTA: best-fit toric aspheric; Df: frontal map elevation deviation; Dp: pachymetric progression deviation; D: total deviation; Db: posterior map elevation deviation; CKI: central keratoconus index; IHA: index of height asymmetry; Rmin: minimum sagittal curve; ISV: index of surface variance; ARTmax: maximum Ambrósio thickness relation; Da: maximum Ambrósio thickness relation deviation; Kmax: maximum keratometry; Dt: minimum thickness deviation.

Finally, other parameters, such as BAD-D, were mainly altered in manifest forms and could be used as markers of KC; the most altered index was the total BAD-D index, and Db was altered in both KC and FFKC.

In table 3, comparing the alteration rates in the groups with KC and FFKC, we observe that the test with the highest alteration rate in patients with FFKC is the IHD (81.8%). However, it is not considered statistically different from the greater BFS posterior elevation (45.5%, p-value <0,05), which is different from the other indices. The most altered parameters in FFKC were Kmax, Belin-Ambrósio Posterior Elevation, IHD, and BFS Posterior Elevation.

Among patients with KC, the tests with the highest discrimination rate are also IHD and the maximum posterior BFS elevation, both 100%, thus being more altered in the group with keratoconus. However, they were only statistically higher than the ISV, ART MAX, Da, Kmax, Dt, thinner pachymetry, Delta posterior elevation BFTA, and CHORD μ in this group.

Table 4 compares the altered indexes between FFKC and normal patients. The values were statistically significant, except for Rmin (p-value 0,118), Thinnest Pachymetry (p-value 0,355), ISV (p-value 1,000), VAT (p-value 1,000), KI p-value 1,000), IHA (p-value 0,355), Dt (p-value 0,118), Da (p-value 0,118), CKI (p-value 1,000), Chord μ (p-value 1,000), Delta posterior elevation BFS (p-value 1,000), and BFTA (p-value 1,000). The indexes with greater accuracy, sensitivity, and specificity were the D index (total), EI posterior, and Maximum posterior elevation with BFS, IHD, Kmax, and Q value.

Receiver Operating Characteristic curves were utilized to establish an early marker for FFKC, with statistical significance found in various parameters when comparing FFKC with keratoconus and normal eyes. Parameters meeting the criteria of statistical significance, sensitivity, and specificity greater than 80% included KI (sensitivity 83.30% and specificity 95%), IHD (sensitivity 83.3% and specificity 85%), LRP (sensitivity and SP 100%), and Delta posterior curvature (sensitivity and specificity 100%).

Table 4. Comparing alteration rate between Forme Fruste Keratoconus and normal groups

		Altered	Normal	p-value	Accuracy %	Sensitivity %	Specificity %	VP + %	VP- %
ARTmax	FFKC	3	8	0.037	74.2	1000	71.4	27.3	100
	Normal	0	20						
CHORD μ	FFKC	0	11	1.000	64.5	- x -	64.5	0.0	100
	Normal	0	20						
CKI	FFKC	0	11	1.000	64.5	- x -	64.5	0.0	100
	Normal	0	20						
D	FFKC	6	5	0.001	83.9	100,0	80.0	54.5	100
	Normal	0	20						
Da	FFKC	2	9	0.118	71.0	100,0	69.0	18.2	100
	Normal	0	20						
Db	FFKC	3	8	0.037	74.2	100,0	71.4	27.3	100
	Normal	0	20						
Delta posterior curve	FFKC	3	8	0.037	74.2	100,0	71.4	27.3	100
	Normal	0	20						
Delta posterior elevation BFS	FFKC	0	11	1.000	64.5	- x -	64.5	0.0	100
	Normal	0	20						
Delta posterior elevation BFTA	FFKC	0	11	1.000	64.5	- x -	64.5	0.0	100
	Normal	0	20						
Df	FFKC	4	7	0.010	77.4	100,0	74.1	36.4	100
	Normal	0	20						
Dp	FFKC	3	8	0.037	74.2	100,0	71.4	27.3	100
	Normal	0	20						
Dt	FFKC	2	9	0.118	71.0	100,0	69.0	18.2	100
	Normal	0	20						
EI posterior	FFKC	6	5	0.001	83.9	100,0	80.0	54.5	100
	Normal	0	20						
Belin-Ambrósio elevation	FFKC	3	8	0.037	74.2	100,0	71.4	27.3	100
	Normal	0	20						
Posterior elevation BFS maximum	FFKC	8	3	<0.001	90.3	100,0	87.0	73	100
	Normal	0	20						
Posterior elevation BFTA maximum	FFKC	3	8	0.037	74.2	100,0	71.0	27	100
	Normal	0	20						
IHA	FFKC	1	10	0.355	67.7	100,0	66.7	9.1	100
	Normal	0	20						
IHD	FFKC	10	1	<0.001	96.8	100,0	95.0	91%	100
	Normal	0	20						
ISV	FFKC	0	11	1.000	64.5	- x -	64.5	0.0	100
	Normal	0	20						
IVA	FFKC	0	11	1.000	64.5	- x -	64.5	0.0	100
	Normal	0	20						
KI	FFKC	0	11	1.000	65.0	- x -	65.0	0.0	100
	Normal	0	20						
Kmax	FFKC	6	5	0.001	83.9	100,0	80.0	54.5	100
	Normal	0	20						
Thinnest pachymetry	FFKC	1	10	0.355	67.7	100,0	66.7	9.1	100
	Normal	0	20						
Medium progression	FFKC	4	7	0.010	77.4	100,0	74.1	36.4	100
	Normal	0	20						
Q value	FFKC	6	5	0.001	83.9	100,0	80.0	54.5	100
	Normal	0	20						
Rmin	FFKC	2	9	0.118	71.0	100,0	69.0	18.2	100
	Normal	0	20						

VP: Predictive value; ARTmax: maximum Ambrosio thickness relation; FFKC: forme fruste keratoconus; CKI: central keratoconus index; D: total deviation; Da: maximum Ambrosio thickness relation deviation; Db: posterior map elevation deviation; BFS: best-fit sphere; Df: frontal map elevation deviation; Dp: pachymetric progression deviation; Dt: minimum thickness deviation; BFTA: best-fit toric aspheric; IHA: index of height asymmetry; IHD: index of height decentration; ISV: index of surface variance; IVA: Index of Vertical Asymmetry; CKI: Central keratoconus Index; Kmax: maximum keratometry; Rmin: minimum sagittal curve.

Cut-off values were determined as 1.025 (KI), 0.0155 (IHD), 2.3 (LRP), and 4.455 (Delta posterior curvature).

DISCUSSION

Our study aimed to explore subclinical keratoconus (FFKC) and to compare it with manifest keratoconus, primarily focusing on identifying key parameters for early detection and improving prognosis. Our thorough analysis of Pentacam-derived tomographic indices uncovered several crucial factors for distinguishing eyes with FFKC.

Certain parameters, such as Kmax and Delta posterior BFTA elevation, demonstrated mild specificity in

differentiating between KC and FFKC.[12-26] In contrast to our findings, Smadja et al.[26] reported significant sensitivity and specificity for posterior elevation in FFKC. Additionally, Uçakhan et al. and Ozkan et al. [2,24] highlighted the significance of combining corneal power, thickness, and elevation data in detecting keratoconus and subclinical keratoconus, further emphasizing the importance of posterior elevation in subclinical cases.[27]

Studies by Awad et al. and Tian et al. underscored the effectiveness of indices like IHD in distinguishing FFKC from normal eyes.[22,27] Our findings align with these studies, with IHD demonstrating sensitivity as a topometric index for FFKC. Nicula et al. and Di Sanctis et al. also emphasized the significance of IVA, thinnest point (TP), and BAD-D in differentiating FFKC from normal eyes, highlighting the potential of these parameters in early diagnosis.[12,25-29]

Our study particularly emphasizes IHD as a crucial parameter for early detection, potentially preceding changes observed in other indices.[22,27] The BAD-D index also exhibited high sensitivity in slightly more progressed subclinical cases, consistent with studies emphasizing its utility in detecting corneal ectasia.[10,11,16-18]

While some parameters like corneal volume did not show relevance in our study, posterior and total densitometry emerged as crucial indicators for early diagnosis.[19-21,30] Although significant in diagnosing keratoconus, the maximum Ambrósio thickness ratio showed a divergence between FFKC and manifest cones, suggesting its limited utility in subclinical cases.[22]

Our findings underscore the importance of vigilance towards IHD as a sensitive indicator for early keratoconus cases. Integration with other measures could enhance the detection of eyes predisposed to the disease, enabling early intervention and curbing disease progression. Further studies with larger samples are warranted to validate the effectiveness of our tools for diagnosing early keratoconus.

Receiver Operating Characteristic curve and area under the curve analyses yielded results consistent with the literature, except for corneal densitometry, posterior curvature, relative pachymetry, and delta elevation values.[30,31] These variables warrant further investigation in newer studies, especially densitometry, which has shown promise in recent research as a marker for keratoconus progression.

In summary, detecting FFKC remains challenging and requires the identification of optimal indices for early detection. Our study highlights the potential of IHD, the posterior elevation of BFS, Kmax, asphericity, BAD-D, and decentration of the TP as sensitive indicators for initial keratoconus cases. Additionally, variables such as relative pachymetry, posterior curvature, delta posterior elevation and curvature, and densitometry may prove useful in early detection and require further exploration in future studies.

CONCLUSION

Our study highlights the importance of early detection of keratoconus and fruste keratoconus through analysis of Pentacam parameters. We identified several sensitive markers for early disease detection, including index of height decentration, best-fit sphere posterior elevation, maximum keratometry, asphericity, Belin-Ambrósio display, and decentration of the thinnest point as sensitive indicators for initial keratoconus cases, the index of height decentration being the most accurate.

These results offer valuable insights to improve clinical diagnosis and can guide future research in the area. Early detection of these conditions can lead to early interventions and improve clinical outcomes for patients.

REFERENCES

1. Cao K, Verspoor K, Sahebjada S, Baird PN. Evaluating the performance of various machine learning algorithms to detect subclinical keratoconus. Transl Vis Sci Technol. 2020;9(2):24.
2. 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;37(6):1116-24.
3. Zhang X, Munir SZ, Sami Karim SA, Munir WM. A review of imaging modalities for detecting early keratoconus. Eye (Lond). 2021;35(1):173-87.
4. Heidari Z, Hashemi H, Mohammadpour M, Amanzadeh K, Fotouhi A. Evaluation of corneal topographic, tomographic and biomechanical indices for detecting clinical and subclinical keratoconus: a comprehensive three-device study. Int J Ophthalmol. 2021;14(2):228-39.
5. Henriquez MA, Hadid M, Izquierdo L Jr. A systematic review of subclinical keratoconus and forme fruste keratoconus. J Refract Surg. 2020 Apr 1;36(4):270-279.
6. Ambrósio R Jr, Salomão MQ, Barros L, da Fonseca Filho JBR, Guedes J, Neto A, et al. Multimodal diagnostics for keratoconus and ectatic corneal diseases: a paradigm shift. Eye Vis (Lond). 2023;10(1):45.
7. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, et al.; Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34(4):359-69.
8. Cao K, Verspoor K, Chan E, Daniell M, Sahebjada S, Baird PN. Machine learning with a reduced dimensionality representation of comprehensive Pentacam tomography parameters to identify subclinical keratoconus. Comput Biol Med. 2021;138:104884.
9. Thulasidas M, Teotia P. Evaluation of corneal topography and tomography in fellow eyes of unilateral keratoconus patients for early detection of subclinical keratoconus. Indian J Ophthalmol. 2020;68(11):2415-20.
10. Hashemi H, Beiranvand A, Yekta A, Maleki A, Yazdani N, Khabazkhoob M. Pentacam top indices for diagnosing subclinical and definite keratoconus. J Curr Ophthalmol. 2016;28(1):21-6.
11. Liu Y, Zhang Y, Chen Y. Application of a scheimpflug-based biomechanical analyser and tomography in the early detection of subclinical keratoconus in chinese patients. BMC Ophthalmol. 2021;21(1):339.

12. de Sanctis U, Loiacono C, Richiardi L, Turco D, Mutani B, Grignolo FM. Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus. Ophthalmology. 2008;115(9):1534-9.
13. Nilforoushan MR, Speaker M, Marmor M, Abramson J, Tullo W, Morschauser D, et al. Comparative evaluation of refractive surgery candidates with Placido topography, Orbscan II, Pentacam, and wavefront analysis. J Cataract Refract Surg. 2008;34(4):623-31.
14. Chen D, Lam AK. Intrasession and intersession repeatability of the Pentacam system on posterior corneal assessment in the normal human eye. J Cataract Refract Surg. 2007;33(3):448-54.
15. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. J Refract Surg. 1995;11(5):371-9.
16. Shajari M, Jaffary I, Herrmann K, Grunwald C, Steinwender G, Mayer WJ, et al. Early tomographic changes in the eyes of patients with keratoconus. J Refract Surg. 2018;34(4):254-9.
17. Muftuoglu O, Ayar O, Hurmeric V, Orucoglu F, Kılıc I. Comparison of multimetric D index with keratometric, pachymetric, and posterior elevation parameters in diagnosing subclinical keratoconus in fellow eyes of asymmetric keratoconus patients. J Cataract Refract Surg. 2015;41(3):557-65.
18. Kanellopoulos AJ, Asimellis G. Revisiting keratoconus diagnosis and progression classification based on evaluation of corneal asymmetry indices, derived from Scheimpflug imaging in keratoconic and suspect cases. Clin Ophthalmol. 2013;7:1539-48.
19. Cavas-Martínez F, Bataille L, Fernández-Pacheco DG, Cañavate FJ, Alio JL. Keratoconus detection based on a new corneal volumetric analysis. Sci Rep. 2017;7(1):15837.
20. Shen Y, Han T, Jhanji V, Shang J, Zhao J, Li M, et al. Correlation between corneal topographic, densitometry, and biomechanical parameters in keratoconus eyes. Transl Vis Sci Technol. 2019;8(3):12.
21. Ahsounah M, Abou-Samra W, Khalaf M, Farag R. Corneal densitometry in different stages of keratoconus. Egyptian Journal of Ophthalmology (MOC) 2021;2:91-102.
22. Awad EA, Abou Samra WA, Torky MA, El-Kannishy AM. Objective and subjective diagnostic parameters in the fellow eye of unilateral keratoconus. BMC Ophthalmol. 2017;17(1):186.
23. Piñero DP, Alio JL, Barraquer RI, Michael R, Jiménez R. Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated study. Invest Ophthalmol Vis Sci. 2010;51(4):1948-55.
24. Ozkan HH, Koc M, Kiziltoprak H, Tekin K, Aydemir E. Evaluation of topographic, tomographic, topometric, densitometric, and aberrometric features of cornea with Pentacam HR system in subclinical keratoconus. Int Ophthalmol. 2021;41(5):1729-41.
25. Koc M, Tekin K, Kiziltoprak H, Inanc M, Kosekahya P, Ozulken K, et al. Topometric and Tomographic Evaluation of Subclinical Keratoconus. Ophthalmic Epidemiol. 2020;27(4):289-97.
26. 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. 2013;29(4):274-81.
27. Tian L, Zhang D, Guo L, Qin X, Zhang H, Zhang H, et al. Comparisons of corneal biomechanical and tomographic parameters among thin, normal cornea, forme fruste keratoconus, and mild keratoconus. Eye Vis (Lond). 2021;8(1):44.
28. Koc M, Aydemir E, Tekin K, Inanc M, Kosekahya P, Kiziltoprak H. Biomechanical analysis of subclinical keratoconus with normal topographic, topometric, and tomographic findings. J Refract Surg. 2019;35(4):247-52.
29. Nicula CA, Bulboacă AE, Nicula D, Nicula AP, Horvath KU, Bolboacă SD. Performances of corneal topography and tomography in the diagnosis of subclinical and clinical keratoconus. Front Med (Lausanne). 2022;9:904604.
30. Rodrigues PF, Moscovici BK, Ferrara G, Lamazales L, Freitas MM, Torquetti L, et al. Corneal densitometry in patients with keratoconus undergoing intrastromal Ferrara ring implantation. Eur J Ophthalmol. 2021;31(6):3505-10.
31. Cui J, Zhang X, Hu Q, Zhou WY, Yang F. Evaluation of corneal thickness and volume parameters of subclinical keratoconus using a Pentacam scheimflug system. Curr Eye Res. 2016;41(7):923-6.