·Clinical Research·

Correlation between visual function and refractive, topographic, pachymetric and aberrometric data in eyes with keratoconus

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Abstract

• **AIM: To analyze the relationship between two visual functions and refractive, topographic, pachymetric and aberrometric indicators in eyes with keratoconus.**

• **METHODS: Corrected distance visual acuity (CDVA), and letter contrast sensitivity (CS) were correlated with refraction, corneal topography, pachymetry, and total corneal wavefront data prospectively in 71 eyes with keratoconus. The topographic indices assessed were simulated keratometry for the flattest and steepest meridians (SimK1 and SimK2), posterior steeper K (Ks), elevation value in best−fit sphere (BFS) maps, squared eccentricity (e^2), aspheric asymmetric index (AAI), pachymetry, thickness progression index (TPI), the amount of pachymetric decentralization (APD), and GalileiTM−keratoconus indices.**

• **RESULTS: The mean CDVA (expressed as logMAR) were 0.25±0.21. The mean CS was 1.25±0.46. The spherical refraction correlated well with CDVA (r =−0.526, P < 0.001). From topographic indices, SRI correlated with CS (r =−0.695), and IAI with CS (r =−0.672) (P <0.001 for all). Root mean square (RMS) was 4.3±1.81 μm, spherical aberration (SA) was −0.4±0.67 μm, vertical and horizontal coma were −2.1 ±1.47 and −0.4 ±0.72 μm. All wavefront data (except horizontal coma), AAI, e^2 and maximum BFS correlated significantly with the visual function (P ≤0.001 for all).**

• **CONCLUSION: In this study, CS is more affected than CDVA as a visual function. The quantity and quality of vision is significantly correlated with well −known and new topographic indices. There is not a significant correlation between visual function and pachymetric parameters. The significantly correlated indices can be used in staging keratoconus and to follow the outcome of a treatment.**

• **KEYWORDS:** keratoconus; topographic index; contrast sensitivity; visual quality; corneal aberration

INTRODUCTION

Keratoconus is a progressive non-inflammatory dystrophy, characterized by corneal thinning and anterior protrusion of one or both corneal surfaces [1-2]. The progressive deformation of the keratoconic cornea causes changes in corneal shape that lead to impairment of visual acuity as a result of irregular astigmatism, higher-order aberrations HOAs, progressive myopia, and corneal thinning. Advances in the field of corneal imaging provide accurate and reliable measurement of corneal curvature, thickness and elevation. Scanning-slit elevation technology, scheimpflug imaging and optical coherence tomography (OCT) can provide anterior and posterior topography of the cornea [3]. Orbscan IIz (Bausch and Lomb, USA) incorporates scanning-slit technology and placido disc; Pentacam (Oculus, Germany) uses rotating Scheimpflug camera. Swept source OCT (Casia SS- 1000 Tomey Corp) is a developing technology and provides reliable values compared to Scheimpflug and Placido disk systems. Its advantages are having a better topographic quality and a shorter measurement time than the Scheimpflug system and enabling evaluation of the corneal structure [4-5] Galilei™ Dual Scheimpflug Analyzer combines placido imaging and dual-channel Scheimpflug rotating cameras to improve the accuracy of corneal curvature and pachymetry maps[4,6-7].

Table 1 The indices derived from corneal topographic and pachymetric maps

Indices (unit)	Description	Calculation method	Galilei reference map
C^2	Corneal surfaces may be spherical ($C^2=0$), prolate aspheric (C^2 positive, steeper at the center and flatter at the periphery), oblate aspheric (C^2 negative, flatter at the center and steeper at the periphery), elliptical ($0<C^2<+1.0$), parabolic ($C^2=+1.0$) or hyperbolic ($C^2>+1.0$).	Software	Instantaneous
BFS (μm)	These are anterior and posterior elevation values that match the thinnest pachymetric points found in the "Best Fit Sphere" elevation maps within the 5 mm central zone where the corneal shape is compared with a sphere as a reference surface. Normal anterior BFS is less than 10 μm and the posterior BFS is less than 15 μm.	Manual	BFS
AAI (μm)	It is the difference between the highest positive and lowest negative values within the 6 mm in BFTA elevation maps and defines the asymmetry of aspheric curvature changes on both corneal surfaces. Normal AAI values are below 20-25 μm.	Manual	BFTA
APD (mm)	It is the distance between the thinnest point and geometrical center of the cornea or the pupil. It is less than 1 mm in corneal pachymetry maps.	Manual	Pachymetry
TPI (μm/mm)	TPI was calculated by subtracting the thickness of the thinnest point from the thickness of any point of the cornea, dividing the result by the distance between them. While increased TPI seems to be related with ectasia and corneal distention, the dislocation of the thinnest point has been correlated with the asymmetry of surface and coma. It shows symmetries or real asymmetries in the distribution and progression of the pachymetry. The normal TPI value is less than 40 to 45 μm/mm.	Manual	Pachymetry

BFTA: Best fit toric aspheric.

Keratoconus often affects young individuals in their education years or active working age, therefore it is very important to evaluate their quality of vision and obtain their visual rehabilitation.

The purpose of this study is to evaluate the correlations between visual functions and refractive power, topographic indices, and corneal aberrations in keratoconic eyes. We assessed these relations using several new indices, as well as conventional keratoconus indices[8-10] available in the Galilei™ topography system. We found more significant correlations with some of the indices. The values which we recorded will contribute the sensitivity and specificity of old parameters and give new ideas to the clinicians about new parameters which can be used in diagnosis and follow up of keratoconus and might eventually help to improve visual function by minimizing the topographic irregularities of the cornea or wavefront aberrations[2,11-14].

SUBJECTS AND METHODS

This prospective, non-randomized, single-center study comprised keratoconic eyes. Informed consent was obtained from all participants and the study was reviewed by the local ethics committee.

Inclusion criteria were the presence of keratoconus showing an asymmetric bow-tie pattern with or without skewed axis and at least 1 keratoconus sign (*e.g* stromal thinning, conical protrusion of the cornea at apex, Fleischer ring, or Vogt striae). Eyes with corneal scarring, advanced keratoconus, cataract, ocular surgery, or any other ocular diseases were excluded from the study. One eye from each patient was examined in the study. Random selection was made in patients with bilateral keratoconus.

A comprehensive ophthalmologic examination was performed in all cases. The examination included a medical

and family history review, corrected distance visual acuity (CDVA), letter contrast sensitivity (CS) test, manifest refraction (sphere and cylinder), subjective refraction (sphere and cylinder), slit-lamp examination, and corneal topographic analysis. Subjects were all tested under identical lighting conditions.

Refractive values were obtained with an auto-refractometer (KR 8900, Topcon, Japan). CDVA was determined using a Snellen chart and expressed in logMAR. CS was evaluated with a Hamilton-Veale chart [15]. This test is modeled on the Pelli-Robson CS test and was conducted at 1 m from the subject, using a card with letters which were arranged in 16 pairs over 8 lines, where each line consisted of 2 sets of pairs all of with constant size. The contrast range was from 0 to 2.25 log units, with each pair of letter representing an increment of 0.15 log units. The last letter the patient could read was recorded as log CS [log (l/c)].

Topographic exams were performed with the GALILEI Dual Scheimpflug Analyzer System (software version 5.2.1; Ziemer Ophthalmic Systems, Port, Switzerland). Images with the highest possible data quality were recorded. The data and indices directly provided by the Galilei™ software or manually calculated were: simulated keratometry for the flattest and steepest meridians (SimK1 and SimK2), posterior steeper K (Ks), anterior and posterior thinnest elevation value in the respective best-fit sphere (BFS) map, anterior and posterior aspheric asymmetric index (AAI) (initially described as the Kranemann-Arce Index) [16] has been recently called aspheric asymmetric index[17-18], the squared eccentricity (C^2), thickness progression index (TPI), central average pachymetry value, and amount of pachymetric decentralization (APD) (Table 1).

Galilei™ indices for keratoconus screening were derived from

anterior curvature maps [8-10]. Inferior-superior value (I-SV) also called Rabinowitz index [8,19-20], average central power (ACP), central/surround index (CSI), differential sector index (DSI), opposite sector index (OSI), irregular astigmatism index (IAI), surface asymmetry index (SAI), surface regularity index (SRI), keratoconus prediction index (KPI), and keratoconus probability index (KProb). Post Ks, anterior and posterior BFS, anterior and posterior AAI, anterior and posterior $\mathbb{C}^2$, TPI and APD are new indices; I-SV, ACP, CSI, DSI, OSI, IAI, SAI, SRI, KPI, KProb are conventional (well known) keratoconus indices. The description and calculation methods for all studied indices are summarized in Table 1. In addition to numeric topographic data, we categorized the cone location according to the axial curvature map as central or peripheral. Cones with a maximum K (K-max) in the axial map located beyond 0.85 mm from the map center were defined as peripheral.

Corneal Wavefront Analysis Wavefront analysis was performed with the Galilei™, which is aligned to the pupil from the 6 mm diameter central zone. This displays the wavefront maps of the total cornea (front and back surfaces). The device's software automatically converts the corneal elevation profile into corneal wavefront data and HOAs which are calculated up to the eighth order in terms of Zernike polynomials.

We recorded 3rd order vertical and horizontal coma (μm) and 4th order spherical aberration (SA) (μm) as HOAs and total root mean square (RMS) value respectively. Total RMS is the sum of corneal HOAs. Because coma is side oriented, the signs of the coefficients for horizontal coma in left eyes were reversed. The difference between the steeper axis of astigmatism and coma meridian was also assessed.

Statistical Analysis Statistical analysis was performed using SPSS software for Windows (version 11.5, SPSS, Inc.). The Spearman correlation (r value) test was used to assess the correlation between the visual quantity indicator (CDVA), visual quality indicator (CS) and refractive power (sphere and cylinder), topographic and pachymetric indices, and corneal aberrations. Descriptive statistical results were expressed as the mean, standard deviation (SD), median, minimum, and maximum.

RESULTS

This study comprised 71 eyes (36 right eyes and 35 left) of 71 patients with early to moderate keratoconus. Thirty-one patients (43.7%) were women and 40 patients (56.3%) were men. The mean age was 28.3±8.3y (ranging from 14 to 54y). Seventeen patients had a history of vernal keratoconjunctivitis. Fourteen eyes had Fleischer ring, 35 had Munson sign, and 20 had Vogt's striae.

Analysis of Visual and Refractive Value The mean logMAR CDVA was 0.25±0.21, and the mean log CS value was 1.25±0.46, as shown in Table 2.

Table 2 Descriptive statistics for the quality of vision

Variabl	Mean	SD	Median	Min	Max
CDVA	0.25	0.21	0.22	1	0
CS	1.25	0.46	1.35	0	1.8

CDVA: Corrected distance visual acuity; CS: Contrast sensitivity.

The mean sphere was -3.82±4.54 D, and the mean cylinder was -4.04 ±2.53 D. Manifest spherical and cylindrical refractions and their relations with the visual parameters are shown in Table 3.

There were significant relationships between refractive and visual parameters (P <0.001 for all except between CS and subjective cylindrical refraction). CS and distance vision were all significantly related with the refraction. It was found that when the refraction measurements were increased in the minus or myopic direction, visual function was reduced.

The most significant correlation was found between spherical refraction and CDVA (r =-0.526; P <0.001) (Table 3).

Analysis of Topographic and Pachymetric Value CS was the most affected parameter of visual function with regard to topographic data. A significant correlation was found between CS and SRI (r =-0.695), IAI (r =-0.672), posterior Ks (r =0.599), anterior AAI (r =-0.598), posterior BFS (r=-0.580) respectively (P <0.001 for all).

The next rankings of topographic indices correlated with CDVA were SRI (r=0.670), IAI (r=0.660), anterior BFS (r=0.586), the steepest keratometric value (K2) (r=0.563) and posterior BFS (r =0.551), respectively (P <0.001 for all). Of all indices directly provided by Galilei™, the I-SV had the weakest associations with visual parameters.

Regarding the relationship between the topographic indices and vision (Table 4), in general, an inverse relationship was seen.

That is, as the topographic indices increased, the vision decreased. However, the direction of the relationship was negative in only two parameters, which were pachymetry and Posterior Ks value. As the pachymetry and Posterior K value increased, logMAR visual acuity decreased.

Table 4 summarizes other findings with regard to topography. The flattest keratometric value (K1) and K2 values in order were 46.3±3.80 D, 50.4±4.13 D. Any increase in K1 and K2 measurements resulted in a decrease in both visual parameters. K2 had stronger association with CS (r =-0.593; P <0.001) while K1 had stronger association with CDVA (r =0.466; P <0.001).

Anterior and posterior AAI had a significant correlation with visual parameters. Both showed the strongest relationships with CS (r =-0.598, r =-0.516 respectively). An increased anterior AAI or posterior AAI resulted in a reduction of vision.

Posterior $\mathbb{C}^2$ values were larger than anterior $\mathbb{C}^2$ values (1.4±0.63 vs 1.2±0.59). Both had a strong correlation with

Table 3 Descriptive statistics for refraction and correlation between spheric and cylindric refraction and quality of vision (Spearman correlation and their *P* values)

Variables (D)	Mean±SD	Range	Median	CDVA		CS	
				R	*P*	*r*	*P*
Objective spherical refraction	-3.82±4.54	-18.00±5.25	-2.50	-0.526	<0.001	0.407	<0.001
Objective cylindrical refraction	-4.04±2.53	-10.00±2.25	-3.75	-0.380	<0.001	0.471	<0.001
Subjective spherical refraction	-2.76±3.55	-13.00±4.75	-1.75	-0.481	<0.001	0.381	<0.001
Subjective cylindrical refraction	-2.24±1.88	-6.50±2.00	-1.75	-0.390	<0.001	0.336	<0.004

CDVA: Corrected distance visual acuity; CS: Contrast sensitivity.

Table 4 Descriptive statistics for topographic and pachymetric measurements and correlation with the quality of vision (Spearman correlation and their *P* values)

Variables	Mean±SD	Range	Median	CDVA		CS	
				r	*P*	*r*	*P*
Sim K1(D)	46.3±3.80	41.2 to 56.4	45.4	0.466	<0.001	-0.454	<0.001
Sim K2 (D)	50.4±4.13	43.3 to 59.7	49.7	0.563	<0.001	-0.593	<0.001
Posterior K_S (D)	-7.7±0.81	-9.5 to -6.3	-7.6	-0.534	<0.001	0.599	<0.001
Anterior BFS (μm)	17.6±8.13	1.0 to 44.0	17.0	0.586	<0.001	-0.554	<0.001
Posterior BFS (μm)	39.1±15.68	2.0 to 91.0	39.0	0.551	<0.001	-0.580	<0.001
Anterior AAI (μm)	54.9±26.9	15.0 to 158.0	47.0	0.479	<0.001	-0.598	<0.001
Posterior AAI (μm)	102±45.13	34.0 to 244.0	94.0	0.418	<0.001	-0.516	<0.001
Anterior $\in^2$	1.2±0.59	0.02 to 3.3	1.2	0.542	<0.001	-0.545	<0.001
Posterior $\in^2$	1.4±0.63	-0.4 to 3.4	1.4	0.493	<0.001	-0.556	<0.001
Pachymetry (μm)	488.9±34.61	384.0 to 560.0	491.0	-0.156	0.193	0.291	0.014
TPI (μm/mm)	55.4±12.76	33.0 to 94.0	54.0	0.383	<0.001	-0.395	<0.001
APD (mm)	1.0±0.26	0.3 to 1.8	0.9	0.109	0.364	-0.113	0.347
I-SV (D)	8.3±5.05	0.1 to 23.1	7.3	0.285	0.016	-0.403	<0.001
SAI (D)	4.3±2.40	0.8 to 14.0	3.7	0.360	0.002	-0.427	<0.001
SRI (D)	1.8±0.38	0.7 to 3.0	1.8	0.670	<0.001	-0.695	<0.001
IAI (D)	0.9±0.35	0.4 to 2.7	0.8	0.660	<0.001	-0.672	<0.001
DSI (D)	8.7±4.20	1.5 to 24.3	8.3	0.403	<0.001	-0.470	<0.001
OSI(D)	7.7±4.3	1.2 to 20.7	6.5	0.316	0.007	-0.393	<0.001
CSI(D)	2.7±2.11	-0.5 to 10.0	2.3	0.498	<0.001	-0.487	<0.001
ACP(D)	49.6±4.39	42.8 to 60.1	48.3	0.535	<0.001	-0.541	<0.001
KPI	80.5±25.57	4.8 to 100.0	99.1	0.497	<0.001	-0.573	<0.001
Kprob	94.6±17.44	4.2 to 100.0	100.0	0.502	<0.001	-0.510	<0.001

CDVA: Corrected distance visual acuity; CS: Contrast sensitivity.

CS and CDVA (r=-0.556, r=0.493 respectively and P<0.001 for posterior $\in^2$; r=-0.545, r=0.542 respectively and P<0.001 for anterior $\in^2$).

Anterior and posterior BFS value increased as visual acuity decreased. KPI and Kprob indices were also in a negative relationship with visual parameters. KPI correlated better than Kprob with CS.

Central average thickness was 488.9±34.61 μm. Pachymetry had no significant correlation with any visual parameter. TPI had a weak correlation with CS (r=-0.395), CDVA (r=0.383) (P<0.001 for all).

The APD measurement had no significant correlation with any visual parameter. The cone location was central in 31 eyes, and decentralized in 40 eyes. There were also no significant correlations found between visual acuity and the topographical centralization and decentralization of keratoconus.

Analysis of Aberrometric Value The total RMS was 4.3±1.81 μm, SA was -0.4±0.67 μm, vertical coma was -2.1±1.47 μm, and horizontal coma was -0.4±0.72 μm. CS was the most affected visual function in the relationship between vision and wavefront data. RMS and vertical coma correlated better with loss of vision (Table 5).

There was a good correlation between RMS and CS (r=-0.608; P<0.001), and between vertical coma and CS (r=0.613; P<0.001) (Table 5). The difference between the steeper axis of the astigmatism and the axis of the coma was less than 30 degrees in 29 eyes, and more than 30 degrees in 42 eyes. No significant correlation was found between the visual function and the axis difference between astigmatism and coma.

Table 5 Descriptive statistics for corneal aberrometry data and correlation between higher-order aberrations and quality of vision (Spearman correlation and their *P* values)

Variables	Mean±SD	Range	Median	CDVA		CS	
				r	*P*	*r*	*P*
RMS (μm)	4.3±1.81	0.8 to 10.4	4.1	0.475	<0.001	-0.608	<0.001
SA (μm)	-0.4±0.67	-2.9 to 1.1	-0.2	-0.451	<0.001	0.368	0.002
Vertical coma (μm)	-2.1±1.47	-7.1 to 2.4	-1.9	-0.503	<0.001	0.613	<0.001
Horizontal coma (μm)	-0.4±0.72	-2.4 to 2.0	-0.4	-0.185	0.122	0.039	0.749

CDVA: Corrected distance visual acuity; CS: Contrast sensitivity.

DISCUSSION

Evolution in corneal topography increased the sensitivity and specifity of keratoconus diagnosis and follow up [19]. Corneal tomography is used for early diagnosis of subclinical keratoconus, patients' suitability for refractive surgery and post-laser assisted *in situ* keratomileusis [21-23]. Since collagen-cross-linking is a treatment option to slow the progression of ectatic disease, accurate and earlier diagnosis of ectatic disease before severe visual deterioration becomes more important [24]. Topographic indices are used in keratokonus diagnosis; visual, refractive, topographic data, corneal aberrations and corneal biomechanical properties are used in keratoconus grading[25-26].

This study showed that refraction and several topographic, pachymetric, and wavefront indices derived from Galilei™ were significantly correlated with the visual function assessed by the CS and CDVA, in that order. CS was affected more than CDVA in its correlation with refractive, topographic, pachymetric, and aberrometric changes. This finding is in accordance with the literature [27-28] showing that the CS is a more sensitive indicator of visual function in keratoconus follow-up than CDVA.

Maeda *et al* [27], found a significantly greater loss in CS in a keratoconus group than a normal control group and there were statistically a significant negative correlation between the number of correct letters and SRI and SAI, as in our study. They concluded that subtle visual deteriorations, which are detected by CS testing, can be predicted objectively by corneal topographic indices.

The Collaborative Longitudinal Evaluation of Keratokonus (CLEK) study, in which keratoconus was classified according to K2, found that more advanced keratoconic eyes have steeper and more toric corneas[29]. In our study, the steeper K2 had a more significant correlation with both visual parameters than the flatter K1. Our results support that using the steeper K2 rather than the mean keratometry value may be better for keratoconus classification.

SRI, IAI and KPI showed stronger correlations, while CSI showed a moderate correlation. The I-S index is related to a vertical asymmetry and it unexpectedly didn't show a significant correlation with visual parameters in our study. The results for CSI and I-S can be explained by the significant number of eyes (43%) having central cones.

This study also investigated the relationship between visual function, pachymetry and related indices (Tables 1, 4). The thinnest pachymetric value is used in keratoconus classification [30]. It seems to be an effective index in the diagnosis and follow-up of keratoconic patients [6]. The percentage of thickness increase from the thinnest corneal point toward the periphery in eyes with keratoconus is different or higher than in normal eyes [31-32]. The normal pachymetric difference between a thinnest point and the periphery at 9 mm diameter has been reported less than 200 μm in Galilei™ pachymetry maps [33]. A larger difference originates larger TPI. TPI further helps to understand if the thickness progression and distribution is symmetric or asymmetric. For that reason we consider that TPI is a more reliable pachymetric parameter to study the thickness progression than the simpler average (overall) thickness progression profile. However, in this study we found that average TPI had less significant correlations with visual functions than other topographic or aberrometric indices and pachymetry didn't show a significant correlation with visual parameters.

An increase in the distance between the thinnest corneal point and the geometrical center of the cornea or the pupil (named as amount of pachymetric desantralisation) supports the possibility of keratoconus [34]. Dislocation of the thinnest point use to correlate well with the axis of the corneal coma (José Alfonso MD, personal communication). In our study group, despite the expected possible relation with coma, this distance, did not correlate significantly with any of the visual parameters. Further studies could perform investigations on this relationship.

Therefore, in our keratoconus population with almost 43% of central cones, pachymetric parameters affect visual functions less than the other topographic or wavefront indices. This result is parallel with the literature[35].

The increase of total eye HOAs in keratoconic eyes results from the increase of corneal HOAs[36]. Negative vertical coma was the most dominant of the HOAs in the keratoconus group [36-39]. As in our study, vertical coma is usually negative, meaning that there is inferior steepening.

It is known that visual acuity decreases with increasing RMS error of the corneal first surface or within any single mode of the normalized Zernike expansion [40-41]. Corneal irregularities

originating from ectatic disease cause a decrease in optical quality and visual performance by increasing a combination of ocular aberrations [42-43]. Alio *et al* [26] found significant correlations between some corneal aberrometric parameters and CDVA. In our study, total RMS and vertical coma had significant and strong correlations with the visual function (P<0.001 for all) (Table 5).

Okamoto *et al* [44] demonstrated that there was a more significant correlation between CS and third-order aberrations than fourth-order aberrations. In our study, we also demonstrated a more significant correlation between CS and coma aberration than with SA.

Changes in curvature, shape, and wavefront representing the progressive deformation of the cornea, seem to be more important than changes in pachymetry for determining the worsening of visual acuity in keratoconus. In conclusion, conventional indices such as SRI (r=-0.695, P<0.001), IAI (r=-0.672, P<0.001) and KPI (r=-0.573, P<0.001), new indices such as anterior AAI (r=-0.598, P<0.001), posterior BFS (r=-0.580, P<0.001), and anterior $\mathcal{C}^2$ (r=-0.545, P<0.001) and some aberrometric indices such as total corneal RMS (r=-0.608, P<0.001) and vertical coma (r=0.613, P<0.001) are well correlated with visual function in eyes with keratoconus. Despite keratoconus is characterized by surface ectasia, indices of asymmetry of surface shape (like SRI, IAI, AAI and vertical coma) have greater correlations than indices of protrusion (like BFS, $\mathcal{C}^2$ and SA). Decreases in visual acuity is associated with decreasing vision-related quality of life in keratoconus [45]. To gain more visual acuity increase in keratoconic patients, correcting indices of asymmetry with new techniques may be introduced; but more other studies should be performed.

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