TITLE: **THE VARIABILITY OF CORNEAL AND ANTERIOR SEGMENT PARAMETERS IN KERATOCONUS**

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ABSTRACT

Purpose: To analyse, describe and test diverse corneal and anterior segment parameters in normal and keratoconic eyes to better understand the geometry of the keratoconic cornea.

Method: 44 eyes from 44 keratoconic patients and 44 eyes from 44 healthy patients were included in the study. The Pentacam System was used for the analysis of the anterior segment parameters. New *ad-hoc* parameters were defined by measuring the distances on the Scheimpflug image at the horizontal diameter, with chamber depth now comprising of two distinctive distances: corneal sagittal depth and the distance from the endpoint of this segment to the anterior surface of the lens (DL).

Results: Statistically significant differences ($p<0.05$) between normal and keratoconic eyes were found in all of the analysed corneal parameters. Anterior chamber depth presented statistical differences between normal and keratoconic eyes (3.06 ± 0.43 mm versus 3.34 ± 0.45 mm, respectively; $p = 0.004$). This difference was found to originate in an increase of the DL distance (0.40 ± 0.33 mm in normal eyes against 0.61 ± 0.45 mm in keratoconic eyes; $p = 0.014$), rather than in the changes in corneal sagittal depth.

Conclusion: These findings indicate that keratoconus results in central and peripheral corneal manifestations, as well as changes in the shape of the scleral limbus. The DL parameter was useful in describing the forward elongation and advance of the scleral tissue in keratoconic eyes. This finding may help in the monitoring of disease progression and contact lens design and fitting.

KEYWORDS: Anterior chamber depth; Corneal sagittal depth; Corneal shape; Keratoconus; Scheimpflug imaging; Scleral shape

INTRODUCTION

Keratoconus is an ectatic corneal disorder, characterized by progressive thinning of the stroma and cone-like protrusion, which may lead to irregular astigmatism, myopia and severe visual impairments [1]. Several topographical descriptors have been introduced to characterize the anterior corneal shape in keratoconus, thus aiding in the detection of this condition [2]. However, early keratoconus detection has been found to require the combined analysis of anterior and posterior topographic parameters, as well as, several specific indices and descriptors, usually software or hardware dependent [2, 3]. Tools, such as the Scheimpflug Imaging System, have been used in several studies to measure corneal curvature parameters [4-6], corneal thickness in healthy [7, 8] and keratoconic eyes [9] and other anterior segment parameters in keratoconic eyes, including the depth of the anterior chamber [6].

The anterior corneal surface sagittal concept has been traditionally used to describe the relationship between the change in corneal power and the ablation depth in refractive surgery techniques, as well as the changes in corneal thickness associated with orthokeratology [10]. Although corneal sagittal assessment has been introduced in the fitting of soft contact lens of healthy corneas [11], many contact lens fitting guides still rely on corneal radii as the parameter to be considered for the selection of the first trial lens, even in keratoconic eyes [12]. In searching for better parameters, corneal sagittal depth, as measured by optical coherence tomography (OCT), has been used to fit scleral contact lenses [13] and to improve the description of the shape of the peripheral cornea in healthy [14] and keratoconic eyes [15].

The present study aimed at examining a selected range of corneal and anterior segment parameters in the keratoconus detection framework. Although many of these parameters are provided by the Pentacam software, additional anterior segment parameters were manually measured on Scheimpflug images or derived from others. To the best of our knowledge, some of these additional parameters have not been described as tools to differentiate between healthy and keratoconic eyes. The purpose of the present analysis was to gain a better understanding of the overall corneal geometry in keratoconus, in particular to explore whether structural changes are predominantly corneal, limbal/scleral, or a combination of both. This information should be useful when designing new contact lens fitting strategies for keratoconic eyes, either as an alternative or to complement the traditional approach based on the assessment of corneal radii.

METHOD

Study Sample

A group of patients with keratoconus was selected. The same corneal specialist diagnosed and classified all keratoconic eyes according to the Amsler-Krumeich classification [16]. For comparison purposes, an age and corneal diameter-matched control group of healthy patients was recruited. In order to match for age and corneal diameter, first a data base search was conducted to identify normal subjects with the same age (± 2 years) as each of the keratoconus subjects. Subsequently, within the same age, eyes with similar corneal diameter (± 0.2 mm) to the target keratoconus eyes were included in the control group. Eyes with a history of ocular or refractive surgery, ocular trauma, wearing contact lenses or suffering from a corneal pathology, other than keratoconus, were excluded from the study. All participants provided written informed consent after an explanation of the nature and possible risks and consequences of the study. The study was conducted in accordance with the Declaration of Helsinki tenets of 1975 (as revised in Tokyo in 2004).

Corneal and Anterior Segment Parameters

The Pentacam Scheimpflug system (software version 1:18, Optikgeräte Oculus GmbH, Wetzlar, Germany) was used to analyse anterior and posterior corneal, as well as anterior segment parameters. All Pentacam measurements were conducted following the guidelines of the manufacturer. An experienced optometrist, masked to the purpose of the study and of the status of the participants (keratoconus or normal) conducted all Scheimpflug measurements. Three consecutive measurements were obtained of each eye and the best captures were selected for data analysis.

Although most of the parameters that underwent evaluation were collected from the Pentacam output display, others required additional calculation, based on manual measurements conducted on the Scheimpflug images. **Table 1** displays a summary of the parameters that were under consideration.

The Scheimpflug image closest to the horizontal meridian (180º) was chosen for image analysis. Given the difficulties for data acquisition without manually retracting the upper eyelid, the vertical corneal meridian was not explored. Firstly, a line was drawn from limbus to limbus, approximately parallel to the lens. The limbus was identified by the loss of corneal transparency, that is, by the white tone in the Scheimpflug image that marks the start of the sclera. For this purpose, the Pentacam software option "Show Pixel Edge" was employed to mark the boundary of the structures in the Scheimpflug images, selecting as a reference the first pixel belonging to the cornea at both limbi. The length of this line was defined as the horizontal white to white diameter (Øww). Secondly, starting from the highest corneal point of the image, which is identified by the software with a white line, a second line was drawn perpendicularly to the previous one, defining the 180º meridian sagittal height (SAGT_180). Finally, a third line was drawn from the end point of this sagitta to the anterior surface of the lens (distance to the lens, DL). The "Show Fitted Curve" option was used to define the boundary of the anterior surface of the lens when the line of pixels was interrupted. This option displays the mathematic curve, which better describes the previously detected edges of the image. In addition, the sagittal distance from the corneal endothelium at the horizontal meridian (SAGI_180) was also calculated by subtracting the corneal central thickness, provided by the software, from the corresponding sagittal values measured from the epithelium (SAGT_180). Therefore, the distance from the lens to the corneal endothelium

(ACD_end_180) was defined as the sum of DL_180 and SAGI_180. These distances are illustrated in **Figure 1**.

Data Analysis

Statistical analysis of the data was conducted with the SPSS 19.0 software for Windows (IBM Spain SA, Madrid, Spain). Data were first examined to establish normality with the Kolmogorov-Smirnov test, which revealed conformity with a normal distribution. Data from all of the keratoconus eyes were pooled together and compared with that of healthy eyes with a paired Student's t-test (equal variances were assumed). It must be noted that the sample of healthy eyes were age and white to white diameter-matched to the characteristics of the keratoconus group, thus allowing for the assumption that any differences in saggital parameters between both groups would originate in the actual topographical changes associated with keratoconus. A p-value of 0.05 or less was defined as the cut-off point for statistical significance. Given the exploratory nature of the present research, no Bonferroni correction (which would require a p-value < 0.002) was applied to control for family-wise type I error in order to avoid missing a possible effect worthy of further investigation [17].

RESULTS

Study sample demographics

Forty-four eyes from 44 patients suffering from keratoconus (aged 35.29 ± 13.21 years old, 23 females) were included in this study: 25 eyes were at stage I of the Amsler-Krumeich classification, 10 eyes at stage II, 2 eyes at stage III and 7 eyes at stage IV. The control group included 44 healthy eyes from 44 patients (aged 34.14 ± 8.49 years, 22 females).

Corneal parameters

Statistically significant differences were found between healthy and keratoconic eyes in all corneal parameters ($p \leq 0.05$), as shown in **Table 2**.

Anterior segment parameters at the horizontal meridian

Statistically significant differences were found between healthy and keratoconic eyes in anterior chamber depth from the corneal endothelium (ACD_end), as provided by the Pentacam software. Of the new parameters measured on the Scheimpflug image at 180°, statistically significant differences were uncovered between both samples in ACD_end_180 and DL_180. **Table 3** displays a summary of the results for the various anterior segment parameters under evaluation. **Figure 2** shows mean values and confidence intervals of ACD_end_180, SAGI_180 and DL_180 parameters. Interestingly, a similar increase was found in ACD_end_180 (0.28 mm) and DL_180 (0.21 mm) when comparing eyes with keratoconus to healthy eyes. Differences in the values of SAGI_180 between keratoconic and healthy eyes failed to reach statistical significance.

It may be noted that, although no Bonferroni correction was applied to control for family-wise type I error, statistical analyses revealed p-values < 0.002 in almost all pair-wise comparisons between normal and keratoconic eyes.

DISCUSSION

Although eye care practitioners commonly rely on topographical parameters and indices readily available from the results screen of many anterior segment assessment devices, such as the Pentacam or Orbscan imaging systems, not many of these parameters are useful to describe corneal periphery. However, some of these devices allow for *ad hoc* measurements to be conducted on the original image captures, thus encouraging researchers to define and to investigate the diagnostic validity of new parameters. In the present study, we examined corneal and anterior segment parameters in a group of keratoconus patients and compared them to a control group of normal eyes.

All corneal parameters that underwent evaluation showed significant differences between healthy and keratoconic eyes, therefore reflecting the significant anterior and posterior corneal involvement associated with keratoconus. Indeed, these findings were expected, as the same Amsler-Krumeich classification that was used in this study requires changes in corneal radii and corneal thickness at the thinnest point. In addition, the discriminative power of other corneal parameters (BFS, Elev_A, Elev_B and Ct_central) to differentiate between healthy and keratoconus eyes has been extensively investigated using Scheimpflug imaging [18-20], suggesting their possible use as indicators for the detection and follow up of this pathology. Our findings are in agreement with these previous research efforts. Our findings on corneal volume (CV) revealed a statistically significant reduction in eyes with keratoconus in comparison to normal eyes, as previously reported [21, 22]. Progressive corneal thinning in keratoconus was described as a probable cause of the reduction in CV [21]. In addition, our findings on the distance from the pupil centre to the corneal apex (C_A) denote that, with the progression of the disease, there is a shift in the position of the corneal apex.

This finding is in agreement with a previous study using the Pentacam systems [23], in which the displacement of the corneal apex from the pupil centre was found to be correlated with the severity of keratoconus, particularly in the vertical axis.

Keratoconic eyes were found to present statistically significant higher values of ACD_end. These findings are in agreement with published literature [21, 24] documenting deeper anterior chambers in keratoconus than in healthy eyes. Regarding the newly defined distances measured on the Scheimpflug image at the horizontal meridian, statistically significant differences were found between healthy and keratoconic eyes in DL_180 ($p = 0.014$) and ACD_end_180 ($p = 0.004$). It must be noted that, whereas the difference between healthy and keratoconic eyes in ACD_end_180 (0.28 mm) and DL_180 (0.21 mm) is very similar, no differences in SAGI_180 between both groups of patients were found (**Figure 2**). Thus, keratoconus is associated with an increase in the distance from the limbus plane to the lens.

Our findings may be approached with caution, as the vertical meridian of the cornea was not used for image analysis. Should further studies show that our results at 180° are also extendable to the other corneal meridians/quadrants, these findings would suggest that the increment in chamber depth associated with keratoconus originates in a stretching of scleral tissue adjacent to the limbus, that is, keratoconus results in changes of the anterior eye as a whole, and not only of the cornea. Previous research has hypothesised that the anterior central protrusion of the cornea associated with keratoconus may lead to an increase in the depth of the anterior chamber [21]. The present findings highlighted that these changes are more evident in the scleral portion of the anterior chamber (DL_180 distance), rather than in the corneal portion (SAGI_180), that is, there is an anterior displacement of the area of transition between cornea and sclera, with reference to the plane of the iris. This finding is in agreement with previous observations reported by Sorbara et al [15]. These authors measured scleral angles along particular chord diameters (horizontal visible iris diameter and at 15 mm), and described statistically significant differences in scleral angles between normal and keratoconic eyes, only at the 15 mm chord, thus also suggesting a change in the scleral shape adjacent to the limbus in keratoconus.

In conclusion, the present findings suggest that keratoconus is accompanied by central and peripheral corneal involvement and by changes in the scleral shape adjacent to the limbus. The evaluation of corneal and anterior segment parameters may be useful for the characterization of the peripheral cornea and the scleral zone, which may lead to a better understanding of the morphological changes in keratoconus. In addition, this information may assist both practitioners and manufacturers in designing and fitting large diameter contact lenses, which repose in this area for stability, for the keratoconus patient. In effect, one of the main difficulties in designing rigid gas permeable contact lenses for keratoconus resides in providing both sufficient clearance at the apex of the cone and good peripheral alignment for comfort and stability. The present findings, together with on-going research exploring the rotational symmetry of the corneoscleral junction, may prove to be useful when designing the periphery of these contact lenses.

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TABLES

Table 1. Corneal and anterior segment parameters assessed in keratoconus and healthy eyes. Parameters were provided by the Pentacam software, manually measured on the Scheimpflug images or derived from other parameters.

Parameter	Abbreviation
Corneal parameters (provided by the Pentacam software)	
Anterior flat keratometry (D)	Kmin_A
Anterior steep keratometry (D)	Kmax_A
Posterior flat keratometry (D)	Kmin_P
Posterior steep keratometry (D)	Kmax_P
Anterior central astigmatism (D)	Ant Ast
Anterior best-fit-sphere (mm)	BFS
Maximum anterior corneal elevation (µm)	Elev_A
Maximum posterior corneal elevation (µm)	Elev_P
Maximum anterior refractive power (D)	RP
Eccentricity	Ecc
Central corneal thickness (mm)	Ct_central
Corneal thickness at the thinnest point (mm)	Ct_min
Corneal volume (mm^3)	CV
Distance from the pupil centre to the corneal apex (mm)	C_A
Anterior segment parameters (provided by the Pentacam software)	
Anterior chamber angle (degrees)	ACA
Anterior chamber volume (mm^3)	ACV
Anterior chamber depth from corneal endothelium (mm)	ACD_end
Anterior segment parameters (derived from the Scheimpflug image)	
White-to-white horizontal diameter (mm)	Øww
Sagitta (180º meridian) from corneal endothelium (mm)	SAGI_180
Distance to the lens[a] (mm)	DL_180
Distance from corneal endothelium to the lens (180º meridian) (mm)	ACD_end_180

[a] Distance from the endpoint of the sagitta measurement (180º meridian) to the lens.

Table 2. Comparison of corneal parameters between healthy eyes and keratoconic eyes. Results are shown as mean ± standard deviation.

	Healthy	**Keratoconus**	**p value***
Corneal parameters			
Kmin_A (D)	41.86 ± 5.45	46.40 ± 4.93	<0.001
Kmax_A (D)	42.79 ± 5.57	50.26 ± 5.85	<0.001
Kmin_P (D)	-6.07 ± 0.26	-6.63 ± 1.07	0.001
Kmax_P (D)	-6.40 ± 0.31	-7.46 ± 1.10	<0.001
Ant Ast (D)	0.94 ± 0.59	3.56 ± 2.85	<0.001
BFS (mm)	7.95 ± 0.27	7.44 ± 0.48	<0.001
Elev_A (µm)	4.05 ± 3.11	39.93 ± 20.78	<0.001
Elev_P (µm)	5.54 ± 4.66	70.98 ± 31.06	<0.001
RP (D)	42.88 ± 1.52	52.81 ± 7.51	<0.001
Ecc	0.46 ± 0.14	0.63 ± 0.43	0.019
Ct_apex (mm)	0.56 ± 0.03	0.48 ± 0.05	<0.001
Ct_central (mm)	0.55 ± 0.03	0.47 ± 0.05	<0.001
CV (mm^3)	61.62 ± 4.07	58.06 ± 4.86	<0.001
C_A (mm)	0.19 ± 0.1	0.44 ± 0.30	<0.001

* Student's t-test. $p < 0.05$ denotes statistical significance.

Table 3. Comparison of anterior segment parameters between healthy eyes and keratoconic eyes. Results are shown as mean ± standard deviation.

	Healthy	Keratoconus	p value*
Pentacam software parameters			
ACA (º)	39.77 ± 6.60	37.38 ± 8.25	0.137
ACV (mm^3)	180.11 ± 43.62	196.57 ± 43.68	0.081
ACD_end (mm)	3.06 ± 0.43	3.34 ± 0.45	**0.004**
Parameters derived from the Scheimpflug image at the horizontal meridian			
Øww (mm)	12.01 ± 0.67	11.98 ± 0.55	0.835
SAGI_180 (mm)	2.70 ± 0.32	2.77 ± 0.30	0.332
DL_180 (mm)	0.40 ± 0.33	0.61 ± 0.45	**0.014**
ACD_end_180 (mm)	3.10 ± 0.42	3.38 ± 0.45	**0.004**

* Student's t-test. $p < 0.05$, in bold, denote statistical significance.

FIGURES

Figure 1. Measured parameters on the Scheimpflug image corresponding to the horizontal meridian at 180°. (Øww: white-to-white horizontal diameter; SAGT_180: corneal sagitta from the epithelium at 180º; SAGI_180: corneal sagitta from the endothelium at 180º; DL_180: distance from the endpoint of the sagitta measurements to the lens at 180º; ACD_end_180: distance from the corneal endothelium to the lens at 180º)

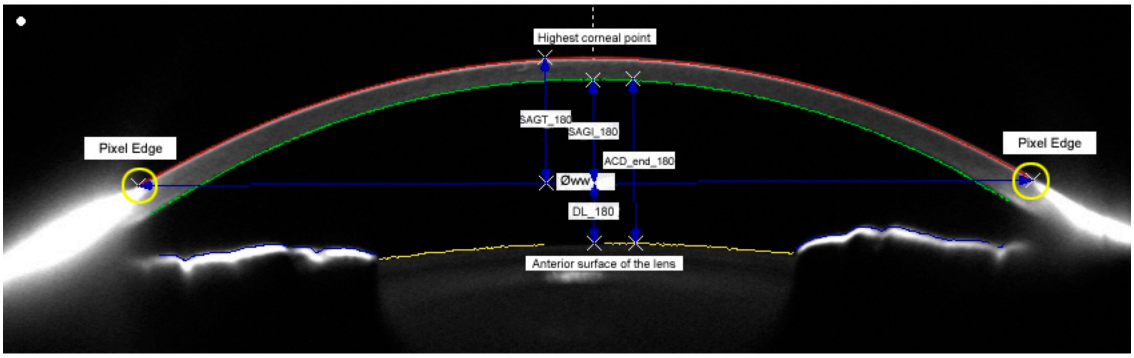

Figure 2. Mean values and confidence intervals of ACD_end_180, SAGI_180 and DL_180 for healthy and keratoconic eyes. (ACD_end_180: distance from the corneal endothelium to the lens at 180º; SAGI_180: corneal sagitta from the endothelium at 180º; DL_180: distance from the endpoint of the sagitta measurements to the lens at 180º)