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1 Scleral shape and its correlation with corneal parameters in keratoconus

Abstract

Purpose:

To assess the correlation of the scleral shape and corneal tomographic parameters in keratoconus.

Methods:

Twenty eyes of 15 keratoconus patients with no previous specialty lens wear or ocular surgery were included in this study. Corneal imaging was obtained with the Pentacam HR and three-dimensional (3D) corneoscleral maps were acquired using the Eye Surface Profiler, ESP. Sagittal height was calculated at the central corneal level (annulus of 0–4 mm radius), peripheral cornea (annulus 4–6 mm radius) and sclera (annulus 6–8 mm radius) using ESP maps and Pentacam HR (exclusively for the central cornea). The flattest and steepest regions of each annulus and the circumferential scleral asymmetry were calculated based on custom-made software. The Pearson correlation coefficient (r) was used to evaluate the correlation between corneal parameters as measured by Pentacam HR and scleral asymmetry.

Results:

Anterior corneal parameters, such as flattest and steepest keratometry, were found to be correlated with scleral asymmetry in keratoconus (all $r > 0.5$, $p < 0.05$). In contrast, anterior astigmatism showed poor correlation with the level of scleral irregularity ($r = -0.11$; $p = 0.32$). Other disease-specific parameters pertaining to the posterior corneal curvature and corneal thickness were not correlated with scleral asymmetry. The steepest regions of the central cornea, peripheral cornea, and sclera tended to share a common angle ($r = 0.92$; $p < 0.001$ for central cornea compared to sclera).

Conclusion:

Anterior corneal parameters measured by corneal imaging are associated with the level of scleral asymmetry and the orientation of the steepest area of the sclera in eyes with keratoconus.

Keywords: Keratoconus; Scleral shape; Corneal imaging; ESP; Pentacam HR

Introduction

Over the past decade, the availability of scleral lenses has vastly increased worldwide. Most of the major manufacturers of corneal lenses now also fabricate scleral lenses of various designs, including lenses with quadrant-specific landing zones [1]. Scleral lenses rest on the conjunctival tissue overlying the sclera, whilst completely vaulting the cornea and limbus. It is generally accepted that the geometry of the landing zone of a scleral lens should align as closely as possible with the underlying ocular tissues [2]. Unequal weight-bearing of a scleral lens can induce sectorial impingement and excessive compression of the conjunctiva, thereby limiting wearing time and comfort [3]. Gaining insight into the shape of the anterior sclera is of particular relevance to eyes with keratoconus as it is the most common indication for scleral lens fitting worldwide [1].

Most research to date has focused on eyes with uncomplicated refractive error, demonstrating the rotationally asymmetric nature of the sclera and its correlation with axial length [4-6]. In keratoconus, significant changes to the anterior scleral shape have been found compared to healthy controls: the sclera appears to be more irregular and steeper in eyes with keratoconus [7-9]. In a large study including 227 ectasia eyes and 115 control eyes, DeNaeyer et al found higher levels of scleral irregularity in non-central ectasia (apex > 1.25 mm from the geometric centre of the cornea) compared to central ectasia, and a similar axis of scleral surface elevation as the ectatic region of the cornea [10]. Unfortunately, the number of eyes with keratoconus was not specified in this study, nor whether contact lens use was taken into consideration prior to imaging. In another recent report on 21 eyes with keratoconus and 88 healthy control eyes, a significant correlation was detected between the inner and outer best fit sphere (BFS) in keratoconus with a lack of correlation between the mean corneal and scleral radius [7]. In both studies, corneal tomographic data was not included, and eyes were not matched in terms of axial length, a correlate of scleral irregularity [11]. Corneal topography parameters in keratoconus have also been found to correlate poorly with scleral lens characteristics (sagittal height and landing zone toricity) in prior studies [12-13].

Scleral lens practice has been expanding over the past decade beyond tertiary care centres, whereas specialised imaging devices such as corneoscleral topographers remain less widespread [1]. Hence, scleral lens fitting still mostly depends on a diagnostic fitting approach. It is therefore useful to study how corneal parameters, as measured by corneal imaging devices such as Pentacam HR, relate to the scleral shape in keratoconus. Topographic analysis of the anterior cornea has long been the main tool to characterize keratoconus. Full characterization of the corneal structure, including analysis of anterior and posterior corneal curvature, as well as pachymetry, is necessary for a comprehensive understanding of the association between corneal and scleral shape in keratoconus. To complement the previous

studies on corneoscleral geometry, this study aimed to determine how various tomographic parameters of disease severity relate to scleral morphometry in keratoconus.

Methods

Participants

A prospective, cross-sectional study was performed at the Department of Ophthalmology of Ghent University Hospital, Belgium. The study was approved by the Ethics Committee of Ghent University Hospital and adhered to the tenets of the Declaration of Helsinki. Patients with keratoconus, 18 years of age or older, attending the contact lens clinic between September 2018 and August 2019 were asked to participate in the study. Exclusion criteria included axial length >25 mm, a history of corneal crosslinking, contact lens wear or refractive or intraocular surgery (such as corneal grafting, cataract surgery, pars plana vitrectomy, etc.) as these procedures may all affect corneal and/or scleral characteristics. Patients meeting the criteria (n=17) gave written informed consent to participate after the nature, and the possible consequences of the study were explained. Both eyes were considered eligible as keratoconus is an asymmetric disease with limited intrasubject correlation [14]. The required sample size was calculated based on previously published data of scleral topography in eyes with keratoconus [9]. A sample size of at least 10 participants would yield 90% power to detect significant differences in elevation between different corneoscleral sectors in eyes with keratoconus at the 0.05 significance level.

Data collection

The study protocol included corneal tomography (Pentacam HR, Oculus, Wetzlar, Germany) and subsequently, corneoscleral topography (Eye Surface Profiler (ESP), Eaglet Eye BV, Houten, Netherlands). Pentacam HR measurements were performed prior to ESP imaging, as the instillation of fluorescein is necessary for the ESP imaging procedure. The Pentacam HR uses a monochromatic blue light-emitting diode (LED) with a wavelength of 475 nm and a Scheimpflug camera that rotates around the corneal axis. Participants were asked to blink before each scan was taken, open both eyes and fixate on the central light. One good-quality Pentacam HR measurement was acquired per eye. When needed, measurements were repeated until a good quality score ("OK" on Pentacam HR software) was obtained. The ESP is a sequential double fringe projection system based on Fourier transform profilometry. Its accuracy has been found to be similar to Placido disc-based videokeratoscopes [15]. A BioGlo (HUB Pharmaceuticals, LLC, Plymouth, MI, USA) ophthalmic strip was moistened with one drop of eye lubricant (Hylo-Comod, 1 mg/ml of unpreserved sodium hyaluronate URSAPHARM Arzneimittel GmbH Saarbrücken, Germany) and subsequently used to touch the upper temporal

ocular surface gently. Eyelids were manually retracted, but special care was taken not to compress the globe. Three subsequent ESP measurements were taken, and the one with the largest scleral area coverage was included for data analysis.

Data analysis

Scleral asymmetry was assessed using the three-dimensional (3D) corneoscleral maps acquired with ESP, using a methodology described elsewhere [16]. In brief, the cornea and the sclera were separated at the level of the limbus [17]. Further, the root mean square error (RMSE) of the difference between the 3D scleral annulus data and a fixed reference surface, built using a conic quadratic function, was calculated as an estimate of corneoscleral asymmetry [13]. This low-variance, automated method grades scleral asymmetry in micrometres. Low values indicate a fairly regular anterior sclera, whereas high values correspond with an irregular surface. Consequently, scleral asymmetry in the current work reflects scleral irregularity and is not interchangeable with scleral toricity as defined by DeNaeyer et al. [10]. The corneal apex, which refers to the geometric centre of the cornea, is the reference level for corneoscleral sagittal height analysis. The ESP device incorporates an internal procedure, based on 3D data, to estimate the position of the corneal apex and to ensure that corneal data are not tilted or rotated (for details, see [18].) In addition, clinical built-in parameters, including cone position (the distance from the corneal apex to the thinnest corneal location) were exported from Pentacam HR to investigate the correlation of those parameters with scleral asymmetry.

Sagittal height was calculated using custom-made software from corneal maps (acquired with Pentacam HR) in all directions at the central corneal level (0 – 4 mm radius) and from corneoscleral maps (acquired with ESP) in all directions for the central cornea (0 – 4 mm radius), peripheral cornea (annulus 4 – 6 mm radius) and sclera (annulus 6 – 8 mm radius). Each of these annuli was divided into 10° sectors, and the mean sagittal height in each sector was calculated. The sectors with the highest and lowest sagittal height were considered the steepest and flattest sector, respectively. The corresponding angular position of the steepest and flattest sectors with respect to the corneal apex was also recorded and used to calculate the relative angle between the steepest and flattest regions of the sclera.

Statistical analysis

The statistical analysis was performed using Microsoft Office Excel (Microsoft Office Professional Plus 2016; Microsoft; Redmond, WA, USA). The normality of all sets of data was not rejected (Shapiro-Wilk test, $p > 0.05$). The level of significance was set to 0.05. To assess

whether the level of scleral asymmetry can be inferred from corneal tomography data, Pearson correlation coefficient (PCC, denoted by ' r '), along with the corresponding p-value was calculated. The goodness of fit was calculated by the coefficient of determination (R^2). In addition, a paired t-test and a Bland-Altman analysis was performed to determine the agreement between the sagittal height data calculated from ESP and Pentacam HR maps.

Results

Measurements were taken in 24 eyes of 17 keratoconus patients who had not worn any type of contact lens in the past three months. The other ten eyes of these patients had undergone intraocular surgery and were therefore excluded. Due to insufficient coverage of the superior area (related to blinking) and suboptimal fixation, four eyes were excluded from analysis. Consequently, twenty eyes of 15 keratoconus patients were included in this study. The mean age was 40.7 ± 15.6 years. Scleral asymmetry was, on average, $72 \pm 28 \mu\text{m}$ (range 37 – 129 μm).

Relationship between scleral asymmetry with Pentacam HR corneal parameters

Corneal parameters relevant to keratoconus diagnosis and follow-up were assessed in terms of their correlation with scleral asymmetry. Statistically significant results were found for several parameters, as shown in Table 1.

Table 1. Built-in Pentacam HR parameters and their correlation with scleral asymmetry, calculated with the Pearson correlation coefficient (r).

Parameter	Mean $\pm$ SD	r	p-value
K1 (D)	45.4 ± 3.47	0.66	0.001*
K2 (D)	48.1 ± 3.52	0.60	0.003*
Anterior Astigmatism (D)	2.7 ± 1.8	- 0.11	0.32
K_{max} (D)	51.6 ± 4.4	0.53	0.008*
BFS anterior (mm)	7.42 ± 0.44	- 0.64	0.001*
Ele F BFS (μm)	17 ± 10	0.04	0.43
ARC (mm)	7.02 ± 0.51	- 0.47	0.01*
PRC (mm)	5.40 ± 0.48	- 0.33	0.07
BFS posterior (mm)	6.14 ± 0.46	- 0.50	0.01*
Ele B BFS (μm)	38 ± 19	0.08	0.36
TCT (μm)	471 ± 30	0.13	0.29

PPI _{Avg}	1.69 ± 0.43	0.06	0.39
BAD-D	5.63 ± 2.24	0.16	0.25

K1: flattest keratometry; K2: steepest keratometry; K_{max}: maximal keratometry; BFS: Best-fit sphere; Ele F BFS: anterior elevation: maximal point of elevation in the 4 mm zone surrounding the thinnest point relative to BFS; ARC: anterior radius of curvature; PRC: posterior radius of curvature; Ele B BFS: posterior elevation: maximal point of elevation in the 4 mm zone surrounding the thinnest point relative to BFS; TCT: thinnest corneal thickness; PPI_{Avg}: Average value of Pachymetric Progression Index; BAD-D index: Belin/Ambrosio Total Deviation Index).

Scleral asymmetry was also found to be moderately correlated with the level of decentration of the cone ($r=0.42$, $p=0.03$) (Figure 1), and well correlated with the mean elevation of the central cornea (central 4 mm radius) calculated from Pentacam HR maps ($r=0.71$, $p<0.001$).

Figure 1. Scleral asymmetry in relation to cone position (distance in mm from the corneal apex to the thinnest point of the cornea as generated by Pentacam HR software).

Relationship between corneal and scleral elevation patterns

The location of the steepest area in the central and peripheral corneal annulus was strongly correlated ($r=0.91$; $p<0.001$). Similarly, the position of the steepest area in the sclera was also highly correlated with both the central ($r=0.92$; $p<0.001$) (Figure 2) and peripheral cornea ($r=0.93$; $p<0.001$). Weaker correlations were found regarding the flattest regions in the three annuli. A low correlation was found between the position (angle) of the flattest area in the central and peripheral cornea ($r=0.41$; $p=0.03$). In addition, the flattest area in the sclera was not correlated with the central cornea ($r=0.12$; $p=0.30$), but showed a moderate correlation with the peripheral cornea ($r=0.57$; $p=0.004$). The relative angle between the steepest and flattest regions in the sclera was $140 \pm 35^\circ$, ranging from 50° to 180° . Figure 3 illustrates this phenomenon. No correlation was found between this relative angle and scleral asymmetry

($r=0.01$; $p=0.48$). Similarly, no correlation was found between scleral asymmetry and the deviation of the relative angle from 90° ($r=0.01$; $p=0.48$).

Figure 2. The angle of the steepest region of the central cornea in relation to that of the sclera, as calculated from corneoscleral maps acquired with the ESP.

Figure 3. Corneoscleral right map (16 mm chord) of a representative keratoconus participant (randomly selected). The steepest scleral sector (SSS) is separated by 130° from the flattest scleral sector (FSS). The steepest peripheral corneal and central corneal sectors are aligned with the SSS, as indicated by solid black lines. This is not the case for the flattest peripheral and central corneal sectors, as indicated by dotted black lines. Steepest and flattest corneal regions are separated 90° from each other. Dashed circumferences demarcate central cornea (0–4 mm radius), peripheral cornea (annulus 4–6 mm radius), and sclera (6–8 mm radius).

The white cross indicates the position of the cone, estimated using automatic Pentacam HR parameters, including distance of the thinnest corneal point from the corneal apex and corresponding polar coordinate. N: nasal; I: inferior, T: temporal, S: superior.

Notably, at the level of the central cornea (0–4 mm radius), the mean sagittal height (elevation) calculated with ESP data was not significantly different from that calculated with Pentacam HR data (paired t-test, $p=0.39$). In addition, Bland-Altman analysis showed a mean difference of -0.0014 mm between the two devices (95% limits of agreement -0.014 to +0.011 mm) indicating good agreement.

Figure 4. Bland-Altman plot showing differences in sagittal height (SH) of the central cornea (0–4 mm radius) between ESP and Pentacam HR measurements. The red line indicates the mean difference and the blue lines indicate the 95% limits of agreement.

Discussion

Both the anterior and posterior corneal surfaces are affected in keratoconus but detected changes do not necessarily follow the same course [19]. The present study aimed at investigating how a selected range of corneal tomography parameters in keratoconus correlate with scleral geometry. Primarily corneal parameters reflecting central/generalized steepening of the anterior corneal surface (K1, K2 and anterior BFS) were associated with scleral irregularity, and to a greater extent than parameters centered on the cone itself (K_{max} and ARC). Pinero et al. have previously demonstrated a significant correlation between BFS of the corneal and scleral area in eyes with keratoconus, indicating that when the cornea steepens in keratoconus, the sclera also tends to steepen [7]. The current study additionally demonstrates that the sclera not only tends to steepen, it also becomes more irregular when the anterior corneal surface steepens. Despite the significant correlation found for K1 and K2,

anterior corneal astigmatism was not correlated with scleral irregularity ($p=0.32$). A previous study in patients with irregular corneas (including a subset of eyes with keratoconus) similarly failed to detect a significant correlation between the asymmetry of central corneal sagittal height and the need for a toric sclera lens landing zone [12]. In contrast, in eyes with regular, with-the-rule astigmatism, corneal astigmatism is correlated with the level of scleral irregularity [20]. Interestingly, disease-specific markers of severity such as thinnest pachymetry, PRC and BAD-D index failed to show a significant correlation with scleral asymmetry.

Scleral lenses are of particular benefit in both advanced and more peripheral keratoconus, as corneal (and hybrid) lenses typically suffer from lens decentration and dislocation in these eyes [21]. Hypothetically, one could expect a more irregular sclera (and thus landing area for the lens) in displaced cones. In this study, a moderate correlation was found between scleral asymmetry and the level of decentration of the cone (Figure 1). In contrast, De Naeyer et al. observed a strong correlation between these parameters [10]. These authors assessed a large group of irregular/ectatic corneas (227 eyes of 166 ectasia subjects) and found higher levels of scleral asymmetry in eyes with an apex located >1.25 mm from the corneal centre. Unfortunately, the number of eyes with keratoconus was not specified, and both groups were not matched for severity of ectasia. To allow comparison with the findings from De Naeyer and colleagues, the same correlation as illustrated in Figure 1 was recalculated, including only those five eyes with an apex located >1.25 mm from the corneal centre. A higher correlation between scleral asymmetry and the level of decentration of the cone was then found ($r = 0.80$ vs. $r = 0.42$). The severity of keratoconus likely is a relevant confounding factor within this analysis. Mas-Aixala and associates have previously shown that the distance from the pupil centre to the corneal apex increases with progression of disease [22]. Further research with larger groups of eyes with keratoconus, matched for disease severity, is required to evaluate the influence of cone decentration as a predictor of scleral asymmetry.

Based on corneoscleral ESP maps, the position of the steepest area was angularly stable from the centre of the cornea towards the sclera, as seen in Figure 2. Similarly, De Naeyer et al. found that scleral surface elevation varies along the same axis of corneal ectasia in their study with the sMap3D ocular surface topographer [10]. In the current study, the orientation of the flattest region was also examined but no consistent pattern was detected in the central and peripheral cornea and sclera. The asymmetric, non-toric nature of the sclera in keratoconus is also reflected by the large range of angles found between the steepest area and the flattest area of the sclera (mean angle of 140° , ranging from 50 to 180°), as illustrated by the example shown in Figure 3. These findings provide an anatomical basis, next to the influence of gravity

and the blinking force exerted by the upper eyelid, to the frequently observed inferior-temporal decentration of scleral lenses in keratoconus [3,23]. Kowalski and associates have previously shown that higher levels of scleral irregularity are associated with greater decentration of scleral lenses and in particular, vertical lens decentration primarily was governed by the initial apical clearance [23].

ESP and Pentacam HR central (0–4 mm) sagittal height measurements were found to be in good agreement (Figure 4). However, further research should be conducted regarding instrument agreement across a range of parameters in a larger sample. In previous research, ESP was found to be in good agreement with Placido disc-based videokeratoscopes [15]. In the current study, predominantly eyes with mild to moderate keratoconus were included, mainly because of the exclusion of eyes with current specialty lens wear. Longitudinal data of patients with progression of corneal disease would be of particular value to investigate if and how scleral changes occur in progressive keratoconus.

Conclusion

Anterior corneal curvature parameters were moderately associated with the level of scleral asymmetry in keratoconus eyes: the steeper the anterior cornea, the more asymmetric the sclera. Corneal astigmatism, pachymetry, and posterior curvature were not correlated with scleral shape in keratoconus. The steepest point of the sclera was aligned with the thinnest corneal point (cone location).

Declaration of interest

None.

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