

SCIENTIFIC REPORT

Keratoconus: an analysis of corneal asymmetry

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Background: Keratoconus, a non-inflammatory corneal ectasia, is reported to have bilateral involvement in over 90% of patients. The purpose of this study was to quantify the extent of asymmetry of disease at presentation to a regional corneal clinic.

Methods: Eighty three patients diagnosed at presentation, using a combination of videokeratography, slit lamp examination, and refractive findings were retrospectively selected. On this basis, 73 patients were designated as having evidence of keratoconus in both eyes. In order to quantify the degree of asymmetry between fellow eyes in these bilateral patients, intraclass correlation was calculated for best spectacle corrected visual acuity (BSCVA) and for 13 different topographical indices generated using videokeratography. In order to examine the link between each index and visual function, the inpatient differences in each index were compared to the inpatient differences in BSCVA using Pearson's correlation.

Results: BSCVA showed a high degree of asymmetry between fellow eyes with a correlation coefficient of $r=0.006$. With the exception of area analysed, all of the topographical indices also showed disparity between paired eyes ($r=0.01$ to $r=0.25$). Pearson's analysis found that the inpatient differences in the standard deviation of the power (SDP), average corneal power (ACP), central corneal power (K), as well as the composite keratoconus prediction index (KPI) inversely correlated with the inpatient differences in best spectacle corrected acuity ($r=-0.76$, -0.75 , -0.69 , and -0.73 respectively).

Conclusions: This study demonstrates, quantitatively, the asymmetry of disease found in patients at the point of initial diagnosis of keratoconus. It also suggests that increases in indices which reflect various aspects of corneal power as well as the composite index KPI correlate with a decrease in BSCVA.

Keratoconus is a non-inflammatory disease characterised by progressive corneal thinning and apical protrusion. Typically, it presents in early adulthood and visual symptoms result from irregular astigmatism and increasing myopia.^{1,2}

Early keratoconus is difficult to detect using clinical tests and videokeratography has proved invaluable when forming a definitive diagnosis.^{3–5} Computerised analysis has developed a range of quantitative indices assessing differing aspects of keratoconic corneal topography (table 1).^{6–9} In order to maximise the diagnostic potential of these descriptors, a multivariate keratoconus prediction index (KPI) was developed following discriminant analysis of SimK1, SimK2, OSI, CSI, DSI, SAI, IAI, and AA.⁹

Although many authors acknowledge the existence of asymmetric involvement,^{1,2,10,11} to date very few formal comparisons of the extent of asymmetric disease, between

fellow eyes, has been undertaken. The aims of this study were to use videokeratographic analysis to quantify the degree of inpatient asymmetry in bilateral keratoconus and to identify if any of the known indices could be used individually to quantify asymmetry. Secondly, the relation between these indices and the detrimental effect of keratoconus on visual function was investigated and correlated with asymmetry.

METHODS

Patient selection

A total of 83 consecutive keratoconus patients referred to the Regional Corneal Clinic, Royal Victoria Hospital between 1997 and 2000 were selected for investigation. Patients with a history of contact lens wear, previous eye surgery, or corneal disease were excluded from the study. Corneal maps had been performed on each patient at presentation using the Topographic Modelling System (TMS-1) (Computed Anatomy Inc, New York, USA). Uncorrected visions and best spectacle corrected visual acuities (BSCVA) had been measured using a conventional internally illuminated Snellen chart. Slit lamp biomicroscopic examination and refractive findings had also been recorded at initial assessment. A diagnosis of keratoconus for each eye had been determined at the time of initial diagnosis by experienced clinicians using the combined results from slit lamp biomicroscopy examination, refraction, and corneal mapping.

A total of 13 different corneal indices comprising K, I-S, SRI, SAI, ACP, CEI, SDP, DSI, OSI, CSI, IAI, AA, and KPI were generated for each corneal map.^{6,7,9,12}

Statistical analysis

A database containing all 13 quantitative indices, as well as BSCVA for each eye, was constructed for all keratoconus patients. In order to quantify the degree of asymmetry between fellow eyes, in the cases where evidence of bilateral disease had been identified, the intraclass correlation (one way random) coefficient between paired eyes was calculated for each quantitative descriptor. The BSCVA of the patients in the bilateral group, denoted as a Snellen decimal, was available for 57 patients. Inpatient disparity of this parameter was also quantified using intraclass correlation.

Pearson's correlation coefficient was used to determine the degree of correlation between the asymmetry in each index and the asymmetry in BSCVA. In every case, asymmetry was determined by subtracting data relating to the left eye from that for the right eye. Tests of whether coefficients differed significantly from zero were conducted at the 5% significance level (two tailed). As corneal opacification limits the ability of

Abbreviations: AA, area analysed; ACP, average corneal power; BSCVA, best spectacle corrected visual acuity; CEI, corneal eccentricity index; CSI, centre surround index; DSI, differential sector index; IAI, irregular astigmatism index; I-S, inferior-superior dioptric asymmetry; K, central corneal power; KPI, keratoconus prediction index; OSI, opposite sector index; SAI, surface asymmetry index; SDP, standard deviation of the power; SRI, surface regularity index.

Table 1 Summary of the quantitative indices generated by videokeratography^{5 8 13}

| Index | Description | Normal range |
|-------|---|-----------------------|
| K | Central K reading. Calculates the difference in steepness between the inferior and superior cornea at a distance of 3 mm from the apex | <47.2 D or >7.2 mm |
| I-S | The inferior-superior dioptric asymmetry | <1.4 |
| ACP | Average corneal power | 40.5 to 46.7 D |
| CEI | Corneal eccentricity index or global shape factor. Positive for a prolate surface and negative for an oblate surface | -0.114 to 0.806 |
| SDP | Standard deviation of the power. Increased when there is a wide range of dioptric power within the cornea | 0.37 to 1.33 |
| DSI | Differential sector index. Reports the greatest difference in average power between any two sectors | 0.21 to 3.51 |
| OSI | Opposite sector index. Represents the greatest difference of average power in opposite sectors | -0.55 to 2.09 |
| CSI | Centre surround index. The difference in the average area corrected corneal power between the central corneal zone 3 mm in diameter and a 3 mm annulus surrounding the central area | -0.28 to 0.80 |
| IAI | Irregular astigmatism index. Reports the average inter-ring variation in power along semi-meridians | 0.19 to 0.49 |
| AA | Area analysed. The ratio of the area used for calculation compared to that covered by image of the concentric rings | 0.70 to 0.94 |
| SAI | Surface asymmetry index. Detects alteration of corneal symmetry—for example, off centre keratoconus apices by comparing areas of the cornea 180° apart | 0.10 to 0.42 |
| SRI | Surface regularity index. Values can be used to predict the optical outcome that might be expected based on corneal topography | 0.0 to 0.56 |

the cornea to refract light irrespective of the corneal curvature and regularity, seven patients with apical corneal scarring in at least one eye were excluded from this analysis. All the statistical analysis was performed using SPSS version 9.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Of the 83 patients with keratoconus, 10 individuals were excluded on the grounds that no clinical or videokeratographic signs of keratoconus could be detected in the fellow eye. These patients were designated as having unilateral keratoconus and were excluded from the analysis of corneal asymmetry. The remaining 73 patients had a mean age of 27.3 (SD 10.6) years (range of 12–65 years). Appraisal of the topographical maps for the paired eyes found that 81% of patients had bilateral inferior oval cones. The remaining patients were designated as having mixed cone types, with seven patients having oval cones in both eyes but in different positions and seven patients having a nipple cone in one eye and an oval cone in the other eye.

The mean (SD) values for BSCVA and for each of the indices in patients with bilateral keratoconus are shown in table 2. All of the indices except ACP, I-S, and CEI show a mean value which is outside the normal range quoted by other workers (table 1).^{6–9} The figures calculated for the range and standard deviation of these indices illustrate the wide variation in these quantitative descriptors in keratoconus

patients at initial presentation. Comparison of the data, between right and left eyes shows very little divergence in terms of mean, range, or standard deviation.

The intraclass correlation between paired eyes for BSCVA and for each of the corneal indices in patients designated as having bilateral keratoconus is shown in table 2. The correlation coefficient of $r = 0.006$ for BSCVA between paired eyes indicates a high degree of disparity in paired eyes at presentation (fig 1A). With the exception of AA there is also a poor correlation, and therefore a high level of disparity, between paired eyes for all of the indices tested (table 2). Notably, the intraclass correlation coefficient for BSCVA was among the lowest observed. The composite index KPI was also a relatively good indicator of inpatient asymmetry (fig 1B) but it was not markedly better than any of the individual indices (CSI, OSI, DSI, SAI) which are used to calculate this composite indicator.

Using Pearson's correlation, the link between index asymmetry and asymmetry of visual acuity was evaluated (table 3). If abnormal or raised values of an individual index predicted a fall in visual function then a strong inverse correlation would be found. The SDP, ACP, and K indices, which are various descriptors of corneal power, all show a strong inverse correlation with BSCVA with correlation coefficients of $r = -0.76$ ($p = 0.01$), $r = -0.75$ ($p = 0.01$), and $r = -0.69$ ($p = 0.01$) respectively. Figure 2A shows the inverse relation between SDP and BSCVA differences in the paired eyes. The composite index KPI is also a good predictor of BSCVA ($r = -0.73$, $p = 0.01$; fig 2B). Notably, CSI and SRI proved to be poor predictors of BSCVA despite being good measures of asymmetry.

DISCUSSION

In this study, we have used the precision and sensitivity of videokeratography to measure the degree of asymmetry of the disease in paired eyes of patients at first presentation to a hospital based specialist corneal clinic.

The quantification of asymmetry has important patient management implications. Successful RGP contact lens fitting requires good patient motivation, which is much less likely in asymmetric disease with good spectacle corrected visual acuity in the least affected eye.¹³ Similarly, decisions regarding penetrating keratoplasty will be influenced by good corrected visual acuity in the fellow eye.

The inpatient asymmetry of keratoconus at presentation is confirmed in our study by the poor intraclass correlation between paired eyes for spectacle corrected visual acuity ($r = 0.006$). All of the corneal indices assessed, except AA, confirmed the presence of asymmetry. SRI ($r = 0.001$), CSI ($r = 0.03$), and SDP ($r = 0.03$) proved to be the best markers for inpatient asymmetry.

The variable ability of these topographical indices to predict asymmetry between paired eyes is likely to be due to the fact that each assesses different corneal characteristics. A maximally increased CSI reading will be found with steep central cones and a moderately raised value with large decentred cones, whereas the DSI, OSI, and I-S indices produce maximum values with decentred cones and reduced measurements with central cones.^{6–9} In this and other studies, the majority of cones were of the inferior oval type.^{11–14} The reason that CSI proved to be a better measure of asymmetry between paired eyes than DSI, OSI, and I-S is unclear at present. Maguire and Bourne, (1989) found that the apex of inferiorly displaced cones were found 1.3 and 2.5 mm from the visual axis.³ This is within the central 3 mm annulus used for calculating the CSI index and would cause a higher value. However, we did not specifically quantify the magnitude and direction of cone apex displacement in our study.

Table 2 Intraclass correlation coefficient between paired eyes calculated for best corrected visual acuity (Snellen decimal equivalent) and for each topographical index

| Index | Right eye | | Left eye | | Intraclass correlation coefficient |
|---|---------------|----------------|---------------|----------------|------------------------------------|
| | Mean (SD) | Range | Mean (SD) | Range | |
| Best spectacle corrected VA (Snellen decimal) | 0.69 (0.34) | 0.00 to 1.20 | 0.63 (0.37) | 0.001 to 1.20 | 0.006 |
| Surface regularity index (SRI) | 1.24 (0.83) | 0.10 to 4.59 | 1.24 (0.82) | 0.02 to 4.02 | 0.01 |
| Standard deviation of power (SDP) | 3.80 (2.34) | 0.66 to 10.45 | 4.17 (2.59) | 0.84 to 11.45 | 0.03 |
| Centre surround index (CSI) | 1.51 (2.26) | -1.66 to 7.84 | 1.55 (2.81) | -5.56 to 10.30 | 0.03 |
| Surface asymmetry index (SAI) | 2.26 (1.84) | 0.25 to 9.45 | 2.45 (1.67) | 0.18 to 7.10 | 0.05 |
| Differential sector index (DSI) | 8.30 (4.69) | 1.01 to 21.08 | 9.21 (5.51) | 1.84 to 22.94 | 0.13 |
| Irregular astigmatism index (IAI) | 0.45 (0.19) | 0.20 to 1.26 | 0.47 (0.22) | 0.23 to 1.38 | 0.14 |
| Central corneal power (K) | 46.79 (4.54) | 40.00 to 57.31 | 46.94 (4.96) | 38.69 to 58.84 | 0.16 |
| Keratoconus predictor index (KPI) | 49.63 (41.20) | 0 to 100.00 | 53.24 (41.31) | 0.00 to 100.00 | 0.18 |
| Average corneal power (ACP) | 45.86 (3.76) | 33.39 to 54.73 | 46.18 (4.26) | 39.95 to 57.50 | 0.18 |
| Inferior minus superior power (I-S) | 5.74 (5.04) | -9.03 to 17.05 | 6.39 (4.83) | -4.12 to 18.17 | 0.18 |
| Opposite sector index (OSI) | 7.11 (4.96) | 0.15 to 21.08 | 7.80 (5.52) | 0.10 to 22.94 | 0.22 |
| Corneal eccentricity index (CEI) | -0.34 (0.63) | -0.96 to 0.95 | -0.28 (0.69) | -0.96 to 0.96 | 0.25 |
| Area analysed (AA) | 0.66 (0.14) | 0.24 to 0.86 | 0.66 (0.15) | 0.23 to 0.89 | 0.38 |

Coefficients were calculated using data collected from patients designated as having signs of bilateral keratoconus (n=73 for all indices except for best corrected spectacle visual acuity where n=57 and I-S were n=72).

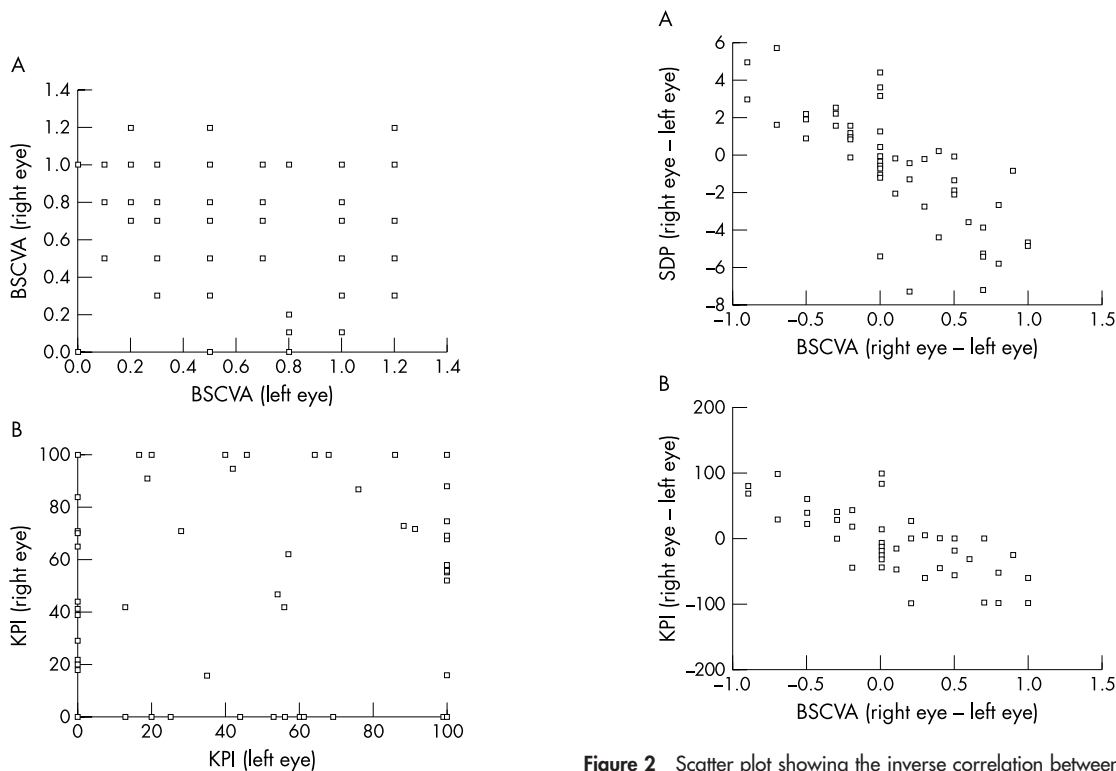


Figure 1 Scatter plot showing the variation between paired eyes in patients with bilateral keratoconus. (A) Best spectacle corrected visual acuity. Intraclass correlation $r=0.006$ (n=57). Data points represent the Snellen decimal equivalent recorded for each eye at presentation. (B) Composite index KPI. Intraclass correlation $r=0.18$ (n=73). Data points represent the indices generated by computerised analysis of corneal mapping performed at presentation.

Figure 2 Scatter plot showing the inverse correlation between (A) the intrapatient differences in SDP and the intrapatient differences in best spectacle corrected visual acuity (BSCVA) (Snellen decimal equivalent) in patients with bilateral keratoconus $r=-0.76$ $p=0.01$ (n=50), and (B) the intrapatient differences in KPI and the intrapatient differences in (BSCVA) (Snellen decimal equivalent) in patients with bilateral keratoconus $r=-0.73$; $p=0.01$ (n=50). Patients with apical corneal scarring in either eye were excluded from the analysis. Coefficients were evaluated using data collected from patients at presentation.

Table 3 Pearson's correlation coefficient between the inpatient differences for each index with the inpatient differences in spectacle corrected visual acuity (n = 50)

| Index | Pearson's correlation |
|-------------------------------------|-----------------------|
| Standard deviation of power (SDP) | -0.76** |
| Average corneal power (ACP) | -0.75** |
| Keratoconus prediction index (KPI) | -0.73** |
| Central corneal power (K) | -0.69** |
| Differential sector index (DSI) | -0.6** |
| Inferior minus superior power (I-S) | -0.67** |
| Opposite sector index (OSI) | -0.64** |
| Surface regularity index (SRI) | -0.57** |
| Surface asymmetry index (SAI) | -0.57** |
| Irregular astigmatism index (IAI) | -0.51** |
| Centre surround index (CSI) | -0.50** |
| Corneal eccentricity index (CEI) | -0.36* |
| Area analysed (AA) | 0.21 |

Coefficients were calculated using data collected from patients designated as having bilateral keratoconus. Patients with apical corneal scarring in either eye were excluded from the analysis. Significance is denoted by *p=0.05 and **p=0.01.

The SDP index reflects the variation in area corrected corneal power.¹² It is not influenced by the apical location and appears to be a sensitive measure of corneal asymmetry. The SRI and IAI both reflect local fluctuations in corneal power, which is reported to be a characteristic of moderate to severe keratoconus.^{9, 12} It is likely, therefore, that these two indices show poor inpatient correlation in asymmetric disease because they reflect keratoconus progression.⁸

The SAI will not be increased by regular astigmatism or centrally located cones but will detect irregular astigmatism and decentred cones.⁸ This value will increase as the irregular astigmatism increases or the decentred cone becomes steeper. Consequently, it should act as a disease progression marker, as confirmed by the poor SAI correlation between paired eyes in this study ($r = 0.05$).

The KPI value is a composite calculation and it might be expected to be a more sensitive indicator of corneal asymmetry. This was not the case in this study and several individual indices showed greater disparity between paired eyes. An explanation may lie in the purpose of the index, which is to give a measure of certainty of diagnosis.⁹ The KPI ranges from 0–100%, indicating the degree of certainty of detection of keratoconus⁹ with moderate to severe cones receiving a KPI score of 100%. Smolek and Klyce¹³ have noted the inability of KPI to distinguish between moderate and severe keratoconus, so its role in illustrating the degree of asymmetric disease may be limited.

Many KPI values were clustered around the 0% value suggesting an unaffected eye—that is, unilateral keratoconus. The criteria for bilaterality in our study, however, also considered clinical examination, refractive findings, and the topographical map. Thus, many corneas, which gave KPI indices of 0% exhibited other signs of keratoconus.

An inverse correlation between the inpatient difference for a particular index and the inpatient difference in corrected acuities would suggest that progressive visual loss in keratoconus is a direct result of specific changes in corneal

topography. The rank order of indices for which the inpatient difference predicted impaired visual acuity was different from the order with which they predicted asymmetry. The strongest predictor of visual impairment was the SDP descriptor ($r = -0.76$; $p = 0.01$), which provides a measure of the range in corneal power.⁹ Other measures of corneal power such as ACP ($r = -0.75$; $p = 0.01$) and K ($r = -0.69$; $p = 0.01$) also showed a strong inverse correlation. The I-S descriptor which depicts off centre cones⁷ also demonstrated a good inverse correlation ($r = -0.43$; $p = 0.01$). These results would suggest that the overall power and cone protrusion reduced the efficacy of the spectacle correction irrespective of cone location.

In conclusion, this study formally demonstrates the degree of asymmetry of disease at presentation of keratoconus patients, both for corneal shape and visual acuity. Quantitative topographical indices reflecting changes in corneal power correlated best with impaired acuity.

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