Comparison of topographic indices and corneal higher order aberrations in eyes with an extreme asymmetry of keratoconus with control eyes

ABSTRACT

**Purpose:** To compare topographic indices and anterior corneal higher order aberrations (HOAs) of forme fruste keratoconus (KC) (fellow eyes) with clinical KC and control eyes. **Setting:** Tertiary Eye Hospital, India. **Materials and Methods:** This study retrospectively reviewed 298 patients with KC. Patients were evaluated with placido-based topographer. KC was diagnosed according to Rabinowitz and McDonnell criteria and clinical sign. Twenty-one patients with clinical KC in one eye (Group A), fellow eye (Group B) with normal topography with no clinical sign, and 21 control eyes (Group C) were included in the study. Topographic indices (keratometry, inferior superior ratio, irregularity, shape factor, and eccentricity) and HOAs (trefoil, coma, spherical aberration, total root mean square [RMS], HOAs RMS of third to seventh order for 6 mm diameter) were obtained. Group B was compared with Groups A and C. **Results:** The prevalence of an extreme asymmetry of KC in our study population is 7.04% with mean age of 21.98 ± 7.39 years. All topographic indices were higher in Group A compared to Group B \((P < 0.01)\) and no significant difference was found between Groups B and C. All HOAs were higher in Group A compared to Group B \((P < 0.05)\). HOAs RMS, oblique trefoil and spherical aberration were significantly higher in Group B compared to Group C \((P < 0.02)\). Of these 21 patients, four had severe to advanced KC in one eye. **Conclusions:** Corneal HOAs changes are first to appear in fellow eyes of unilateral KC, which may makes them useful tool in monitoring progression and early detection of KC changes in fellow eyes.

**Keywords:** Corneal higher order aberrations, extreme asymmetry of keratoconus topography, forme fruste keratoconus

INTRODUCTION

Keratoconus (KC) is a progressive, noninflammatory, bilateral but asymmetric, corneal disorder characterized by an increase in the irregular curvature, thinning, and protrusion. KC usually presents at puberty and stabilizes around middle age.\(^1\) KC may have an extremely variable expression at the early stages, with subtle signs and borderline abnormal features that are difficult to identify with certainty.\(^1\)-\(^3\) Certain cases show significant asymmetric presentation (so called unilateral KC). The normal eye of unilateral KC eventually converted into bilateral KC.\(^4\) The fellow normal eye of unilateral KC called as forme fruste keratoconus (FFKC). The FFKC eyes does not reached the threshold of suspect KC but it may have some earlier KC changes.

The modern tomographer provides detail properties of anterior and posterior surface as well as elevation of the cornea. Several indices and artificial intelligence methods have been developed to help in early diagnose KC.\(^5\)-\(^7\) Various studies\(^8\)-\(^10\) shows importance of posterior surface and
pachymetry data in discriminating FFKC from normal eyes and others reported\textsuperscript{11,12} higher specificity and sensitivity of anterior corneal indices. Although various scheimpflug based and high definition tomographer are used by cornea specialist, corneal topography is still used in routine clinical practice to diagnose KC.

The purpose of our study is to compare topographic indices and anterior corneal higher order aberrations (HOAs) between FFKC (fellow) eyes with clinical KC and control eyes.

**MATERIALS AND METHODS**

The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. The patients with KC who visited a tertiary eye hospital were underwent a detailed ophthalmic examination. All the records of the patients were retrospectively reviewed. A total of 298 patients with KC visited between January 2014 and December 2018. Of these 298 patients, 21 had clinical and topographical KC in one eye and no topographical and clinical KC findings in the fellow eye were included in the study. Patients were divided into mild to moderate (<52.0 D) and severe to advanced (>52.0 D) group according to the severity of KC.

Clinical KC was diagnosed when the following features were observed: asymmetric bow tie pattern with or without skewed axes, inferior or central steepening, mean keratometry (K) >47 diopters (D) or an inferior–superior (I-S) value >1.4 diopters, according to the Rabinowitz and McDonnell criteria, and at least one KC sign (e.g., stromal thinning, conical protrusion of cornea at apex, Fleischer ring, Vogt striae, or anterior stromal scar on slit lamp examination). Patients in whom clinical KC was diagnosed in one eye (Group A) and those whose fellow eye had normal topography (Group B; mean keratometry <47, I-S value ≤1.2 diopters with no slit lamp sign) were included in the study.

The right eyes of 21 control cases (Group C) were selected from a database of candidates for refractive surgery with normal corneas, myopia, and myopic astigmatism (Sphere <6.00 diopters [D]; cylinder <1.5 D). Eyes were considered normal if they had no ocular pathology, had not been previously operated upon, and had no irregular corneal pattern. Patients with a history of corneal surgery or contact lens wear, significant corneal scarring, and significant ophthalmic diseases that may potentially affect the outcomes were excluded from the study.

Corneal topography and HOAs measurements were obtained from the database of the Placido-based topography system (ATLAS 9000 corneal topography system, software version 3.0.0.39. Carl Zeiss Meditec AG, Jena, Germany). PathFinder\textsuperscript{TM} II software in atlas analyzes 12 different corneal parameters and compares them to a comprehensive clinical database that contains reference values for normal, KC pattern and myopic or hyperopic laser vision correction. All the fellow eyes were showing normal probability on the software.

The central simulated flat (K1) and steep (K2) keratometry values, astigmatism power, I-S ratio, toric keratometric mean (TKM), shape factor (SF), corneal irregularity measurement (CIM), eccentricity, and HOAs (trefoil, coma, spherical aberration, total root mean square [RMS], and HOAs RMS of to sewventh order for a 6 mm diameter) were selected for statistical analysis. The fellow eyes were compared to the keratoconic and control eyes.

**Statistical analysis**

Statistical analysis was performed using the SPSS software (version 20.0. Armonk, NY: IBM corp.). The study data were evaluated using descriptive statistical methods (mean and standard deviation) as well as the independent-samples test for intergroup comparison of parameters with normal distribution and the Mann–Whitney U test for intergroup comparisons of parameters with abnormal distribution. The results were assessed within a 95% confidence interval and significance was accepted at $P < 0.05$.

**RESULTS**

Of 298 patients with clinical KC who visited the tertiary eye hospital, 21 patients were diagnosed with extreme asymmetry of KC (7.04%) at the time of presentation. Of the 21 patients, 15 were males and six were females. The mean age of patients was 21.98 ± 7.39 years (range: 12–37 years). Seventeen patients had mild to moderate KC in one eye [Figure 1] at the time of presentation with mean age 21.01 ± 6.02 years and only four patients [Figure 2] with mean age 26.07 ± 10.56 years had severe to advanced KC in one eye ($P = 0.206$).

Table 1 shows flat and steep keratometry, astigmatism, I-S ratio, TKM, CIM, and SF values in the three groups. All topographic indices were higher in Group A when compared to Group B ($P < 0.01$) and no significant difference was found between Group B and Group C ($P > 0.05$).

Table 2 shows trefoil, coma and spherical aberration, total RMS, and HOAs RMS values in the three groups. All HOAs were 3–4 times higher in Group A compared to Group B ($P < 0.05$).
Figure 1: Axial curvature maps of corneal topography pattern of mild to moderate keratoconus in one eye (<52D) with other eye showing normal topography.
The HOAs RMS, oblique trefoil Z (3, −3), and spherical aberration Z (4, 0) were found to be higher in Group B ($P < 0.05$) than in Group C.

DISCUSSION

The front surface of the cornea is the major refractive component in the eye, and it is strongly distorted in eyes with KC. Corneal topography is a valuable tool for diagnosing KC. Corneal wavefront technology provides a detailed model of the cornea’s optical properties. Analysis of HOAs of the anterior cornea was shown to be an effective tool for detecting and grading KC. Previous studies have reported that patients with unilateral KC, who have similar genetic makeup, will eventually develop KC in the fellow eye. Thus, the fellow eyes of patients with unilateral KC are affected early and by

**Table 1: Comparison of topographic indices of fellow eyes with keratoconus and control group ($n=21$)**

| Indices              | Keratoconus Group A | Fellow Group B | Control Group C | $P$            |
|----------------------|---------------------|----------------|-----------------|----------------|
| Flat K (D)           | 46.39±5.08          | 43.52±1.04     | 43.09±1.29      | 0.002**        |
| Steep K (D)          | 51.16±7.13          | 44.43±0.99     | 43.81±1.43      | 0.147          |
| AST (D)              | 4.78±3.34           | 0.91±0.59      | 0.75±0.44       | 0.001**        |
| I-S (D)              | 5.22±5.32           | 0.65±0.45      | 0.43±0.35       | 0.001**        |
| TKM (D)              | 48.59±13.05         | 44.78±1.03     | 44.11±1.29      | 0.001**        |
| CIM (μm)             | 3.41±1.58           | 0.78±0.19      | 0.71±0.13       | 0.001**        |
| Eccentricity         | 0.65±0.07           | 0.55±0.07      | 0.52±0.06       | 0.001**        |
| SF                   | 0.74±0.19           | 0.39±0.14      | 0.35±0.08       | 0.001**        |

**Table 2: Comparison of trefoil, coma, spherical aberrations, and root mean square of fellow eyes with keratoconus and control group ($n=21$)**

| Indices (μm) | Keratoconus Group A | Fellow Group B | Control Group C | $P$            |
|--------------|---------------------|----------------|-----------------|----------------|
| Z(3, −3) OT  | 0.540±0.814         | −0.025±0.138   | −0.125±0.084    | 0.003**        |
| Z (3, −1) VC | −1.281±1.936        | −0.141±0.190   | −0.038±0.119    | 0.013*         |
| Z (4, 0) SA   | −0.816±1.066        | 0.196±0.111    | 0.265±0.045     | 0.001**        |
| Z (5, −3) Trefoil II | −0.115±0.247 | −0.003±0.024 | 0.000±0.020 | 0.005**        |
| Z (5, −1) Coma II | 0.131±0.679    | −0.036±0.026 | 0.003±0.024 | 0.024*         |
| Z (6, 0) SA II | 0.129±0.437        | 0.006±0.026    | −0.003±0.019   | 0.037*         |
| Z (7, −3) Trefoil III | 0.027±0.147 | 0.003±0.018 | 0.000±0.017 | 0.045*         |
| Z (7, −1) Coma III | −0.044±0.250    | −0.007±0.024 | −0.003±0.014 | 0.016*         |
| HOAs RMS       | 3.053±1.841        | 0.519±0.197    | 0.405±0.074    | 0.001**        |
| Total RMS      | 5.870±3.005        | 1.224±0.762    | 0.929±0.369    | 0.001**        |

*Student’s t-test, **Mann-Whitney U-test. *P* < 0.01. K – Keratometry, AST – Astigmatism, I-S – Inferior superior ratio, TKM – Toric keratometric mean, CIM – Corneal irregularity measurement, SF – Shape factor, D – Dioptrds, SD – Standard deviation, HOAs – Higher order aberrations.
the mildest form of the disease. These fellow eyes are ideal model to study earlier changes in KC.

CIM highlights irregular astigmatism that may result in visual distortions. Aksoy et al.\cite{24} found a twice higher surface irregularity index in fellow normal eyes with unilateral KC. Wei et al.\cite{25} reported that irregularities of 3 and 5 mm on the receptor operator characteristic can discriminate between fellow normal eyes and control eyes. In contrast to these studies, we could not find any significant difference in CIM between control (0.71 ± 0.13 µm) and fellow eyes (0.78 ± 0.19 µm). However, KC eyes showed a higher irregularity (3.41 ± 1.59 µm) compared to fellow eyes.

The I-S value quantifies the I-S dioptic asymmetry of the cornea. Values <1.4 are considered normal, while values above 1.9, if associated with other clinical symptoms, are classified as KC. Gordon-Shaag et al.\cite{26} found that the traditional corneal topographic values, such as the I-S asymmetry, remain important predictors for identifying possible KC. Rabinowitz and Rasheed\cite{40} initially proposed using a cut-off value of 1.2 D to diagnose subclinical KC. In our study, fellow eyes and control eyes had mean I-S values <0.75 D, while the mean I-S values for KC eyes were three to five times higher (5.22 ± 5.32 D) compared to fellow eyes.

Eccentricity describes the rate of corneal flattening from the center to the periphery. The value for eccentricity in normal adults ranges from 0.4 to 0.6.\cite{27, 28, 29} Dao et al.\cite{30} proposed corneal eccentricity as a tool for diagnosing KC, and they found that values >0.8 were suggestive of KC. In the present study, the fellow eyes and control group had eccentricity values of 0.55 and 0.52, respectively, while the KC group had a higher eccentricity value of 0.65.

In our study, the topographic indices of fellow eyes and control eyes were comparable. Previous studies\cite{19, 26} have reported that combining corneal topography with corneal wavefront aberrations when diagnosing KC may result in higher detection rates. Therefore, for the early detection of KC, we also compared HOAs between the groups.

Corneal aberrations describe the optical quality of the eye. Various studies\cite{18, 19, 26, 31} have demonstrated that keratoconic corneas exhibit increased wavefront aberrations compared to normal corneas. In these studies, since different equipment and techniques were used to measure the HOAs, it is difficult to directly compare the zernike values. Similar to previous studies, all HOAs were found to be significantly higher in our KC group.

KC progresses rapidly between the ages of 15 and 20 years.\cite{33} In our study, the ages of patients with unilateral KC ranged from 12 to 37 years at the time of presentation. In the present study, only four subjects had severe to advanced unilateral KC. The mean age of advances KC were higher (26.07 ± 10.56 years) than with mild to moderate KC (21.01 ± 6.02). This suggest that patients with mild to moderate unilateral KC may eventually progress to bilateral KC.

CONCLUSIONS

That unilateral KC is rare and the prevalence of extreme asymmetry in our population is 7.04% of cases. HOAs may be a useful tool for the early detection of KC in fellow eyes and for monitoring its progression. Evaluation of posterior surface indices and the elevation data of fellow eyes with extreme asymmetry in our population is 7.04% of cases. HOAs may be a useful tool for the early detection of KC in fellow eyes and for monitoring its progression. Evaluation of posterior surface indices and the elevation data of fellow eyes with extreme asymmetry in our population is 7.04% of cases. HOAs may be a useful tool for the early detection of KC in fellow eyes and for monitoring its progression. Evaluation of posterior surface indices and the elevation data of fellow eyes with extreme asymmetry in our population is 7.04% of cases. HOAs may be a useful tool for the early detection of KC in fellow eyes and for monitoring its progression. 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**Conflicts of interest**

There are no conflicts of interest.

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