Intereye Asymmetry in Eyes With Keratoconus and High Ammetropia: Scheimpflug Imaging Analysis

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Purpose: To evaluate intereye asymmetry using several parameters obtained from Scheimpflug imaging to discriminate between normal eyes, high-ammetropic eyes with very early keratoconus (VEKC), and keratoconus eyes in all stages.

Methods: This prospective comparative study includes 685 patients (1370 eyes), of which 294 patients had bilateral keratoconus, 50 patients had high ammetropia, and 341 patients were normal. These patients were studied from July 2012 to July 2014. Thirty parameters, which were obtained from Scheimpflug imaging (Oculus GmBH) and derived from pachymetry, curvature, anterior and posterior elevation, asphericity, and others, were analyzed. Asymmetry was determined by subtracting the right eye value from the left eye value for each variable and by considering the absolute value of the result. Receiver operating characteristic curves and logistic regression analysis were used.

Results: In the hyperopic astigmatism group, the mean intereye asymmetries in maximum keratometry, maximum posterior elevation, and maximum anterior elevation were 0.35 diopters (D), 4.67 μm, and 2.5 μm, respectively. In the myopic astigmatism group the asymmetries were 0.33 D, 5.38 μm, and 2.13 μm, respectively. In the astigmatism group the asymmetries were 0.18 D, 3.33 μm, and 1.66 μm, respectively. In the VEKC group the asymmetries were 0.96 D, 10.76 μm, and 4.95 μm, respectively. A mixed model that includes the asymmetry and the nonasymmetry values shows an AUROC value of 0.9957, discriminating between normal and VEKC eyes.

Conclusions: Specific asymmetry values derived from the Scheimpflug analysis effectively discriminate between patients with VEKC and normal patients. Patients with VEKC showed higher asymmetry values than those presented in high-ammetropic groups.

Key Words: keratoconus, intereye, asymmetry, scheimpflug imaging

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Keratoconus (KC) is bilateral corneal ectasia, which affects both eyes in an asymmetrical way.[1] The definition of unilateral KC is under debate, given that subtle changes compatible with KC in tomographic analysis have been observed in "nonKC" eyes[2]; which supports the fact that KC affects both eyes.

Bilateral diseases usually require bilateral evaluation. For example, the percentage of asymmetry between eyes with regard to retinal nerve fiber layers is used in glaucoma diagnosis and progression.[3] Asymmetry, meaning "bilateral," evaluation in KC and normal eyes has been previously described in terms of clinical signs, manifest refraction, corneal curvature, topographic indices, and pachymetry.[4,5] We initially described the asymmetry in patients with KC assessed by Scheimpflug imaging,[6] which has been corroborated by others.[7]

Discriminating between normal and KC eyes using topography and tomography analyses is possible with extremely low rates of false-positive and false-negative results.[8] However, discriminating between low ammetropia and clear KC is obviously different than discriminating between high-ammetropic and very early keratoconus (VEKC) eyes, because these types of eyes sometimes show similar values to VEKC[9] and for the refractive surgeons this can represent as a challenging scenario.

The aim of this study was to evaluate the asymmetry values in normal eyes, high-ammetropic eyes, and different patients with KC.

METHODS

This prospective, case-controlled study includes 685 patients (1370 eyes), of which 294 patients had bilateral KC, 50 patients had high ammetropia and 341 were normal patients. Patients were studied between July 2012 and July 2014. The following parameters were obtained from the Scheimpflug Imaging Analyzer (Pentacam; Oculus GmBH, Wetzlar, Germany): steeper, flatter, and maximum keratometry (K2, K1, and Kmax, respectively); anterior and posterior corneal astigmatism (AstF and AstP, respectively); asphericity at the front and back of the cornea (AsphQfront and AsphQback, respectively); pachymetry at the apex of the cornea, at the thinnest point (TP) of the cornea, and at the pupil center (PachyApex, PachyTP, and PachyPupil, respectively); the anterior chamber volume and depth; anterior elevation with an 8-mm best fit sphere (BFS) at the apex of the cornea, at the TP, and at the maximum value in the central 4 mm (EleFapex, EleFTP, and EleFmax, respectively); posterior elevation with an 8-mm BFS at the apex of the cornea, the TP, and the maximum value in the central 4 mm (EleBapex, EleBTP, and EleBmax, respectively); the Belin/Ambrosio-Enhanced Ectasia Display (BAD) final D; change in anterior

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elevation from BFS to enhanced reference surface (Df); change in posterior elevation (Db); pachymetry progression (Dp); pachymetry value at the TP (Dt); vertical displacement of the TP from the apex (Dy); minimum, maximum, and average pachymetry progression indices (PImin, PImax, and PIavg, respectively); index of surface variance (ISV); index of height decentration; and index of vertical asymmetry.

Patient Division

Normal Group

The database of normal patients was provided by an outside practice and represented a large previously published database.[10] All patients have normal ocular examination results, a best-corrected visual acuity of 20/20 or better, and no family history of ectatic disease. Simple and compound astigmatism were included [range = −0.5 to 10 diopters (D)]; patients were included whether they proceeded to refractive surgery or not. All patients have at least 3 years of clinically uneventful follow-up.

High-Ammetropic Group

Normal patients who underwent bilateral femto-laser in situ keratomileusis surgery with uneventful follow-up for 1 year with astigmatism greater than 1.5 D in one or both eyes at subjective refraction. For bilateral evaluation (asymmetry), patients were subclassified into 3 groups: (1) simple astigmatism, if both eyes have astigmatism or if one eye has simple astigmatism and the other eye was emmetrope; (2) hyperopic astigmatism, if one or both eyes have hyperopic astigmatism; and (3) myopic astigmatism, if one or both eyes have myopic astigmatism.

KC Group

Patients who have eyes with an increased area of corneal power surrounded by concentric areas of decreasing power, inferior–superior power asymmetry, and skewing of the steepest radial axes above and below the horizontal meridian at topography in both eyes.[11,12]

VEKC Group

Patients with bilateral KC with a Kmax equal or smaller than 48 D in "both" eyes.

The study followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all subjects. Statistical analysis was performed using Stata 13. Receiver operating characteristic curves was used. A value under the receiver operating characteristic (AUROC) curve of 1 implies that the test discriminates between the 2 groups perfectly.

RESULTS

The mean, SD and AUROC of 12 parameters that discriminate between normal eyes and KC eyes are described in Table 1 using "unilateral" analysis, meaning "standard/normal" evaluation.

Table 2 describes the same parameters using "bilateral" analysis, meaning "asymmetry" evaluation. Using logistic regression analysis, a model that includes the asymmetry, the Kmax, AsphQfront, EleFTP, EleBTP, EleFmax, EleBmax, ISV, Df, and D have an AUROC value of 0.90, discriminating between the VEKC group and the normal group. Furthermore, adding a nonasymmetric variable (final D) to this model shows an AUROC value of 0.9957, discriminating between VEKC eyes and normal eyes.

DISCUSSION

Currently, the evaluation of KC is based on unilateral analysis. Using tomographic and topographic assessment has been proven to effectively discriminate between normal eyes and KC eyes.[8,13]

TABLE 1. Unilateral Analysis of the Selected Variables in Each Group

Variable	VEKC Mean (SD) n = 82	KC All Stages Mean (SD) n = 588	Normal Mean (SD) n = 682	Astigmatism Mean (SD) n = 20	Hyperopic Astigmatism Mean (SD) n = 44	Myopic Astigmatism Mean (SD) n = 36	AUROC Normal vs. VEKC	AUROC Normal vs. KC All Stages
Kmax, D	45.79 (1.34)	53.27 (7.53)	45.33 (1.47)	45.375 (1.53)	45.65 (1.52)*	45.40 (1.79)	0.61	0.9
EleBmax, μm	26.45 (14.41)	24.65 (26.36)	13.75 (0.19)	22.00 (4.64)*	26.83 (6.63)*	18.5 (7.36)*	0.87	0.97
EleBTP, μm	5.98 (3.81)	18.22 (13.55)	1.68 (4.11)	5.25 (1.42)*	6.875 (2.25)*	7.43 (4.14)*	0.95	0.98
EleFmax, μm	11.23 (7.82)	24.38 (14.23)	4.80 (2.33)	12.16 (2.76)	17.08 (3.32)*	9.75 (4.61)	0.87	0.97
EleFTP, μm	16.13 (8.24)	18.19 (13.56)	1.68 (0.06)	9.50 (5.62)	6.87 (2.25)	3.93 (2.22)	0.88	0.97
Final D	2.82 (1.01)	6.74 (5.21)	0.69 (0.58)	1.588 (0.50)*	1.676 (0.54)*	1.30 (0.57)*	0.98	0.99
Df	2.29 (1.64)	7.74 (7.09)	−0.05 (1.00)	0.27 (0.5)*	1.342 (1.03)*	0.47 (1.06)*	0.88	0.97
Db	1.89 (1.42)	5.80 (6.32)	−0.10 (0.10)	0.01 (0.91)*	0.49 (0.59)*	0.13 (0.60)*	0.89	0.96
ISV	31.56 (11.61)	67.27 (35.78)	15.81 (5.51)	30.833 (5.10)*	41.17 (9.89)*	27.09 (9.10)*	0.91	0.98
AstF, D	1.88 (1.42)	4.18 (2.50)	0.98 (0.76)	3.63 (0.76)	4.55 (0.89)*	2.65 (1.18)*	0.71	0.91
PImax	1.77 (0.45)	2.75 (2.84)	1.17 (0.18)	1.41 (0.20)	1.30 (0.15)*	1.32 (0.14)	0.91	0.98
AsphQFront	−0.42 (0.22)	−0.83 (0.58)	−0.19 (0.12)	−0.32 (0.065)*	−0.40 (0.166)	−0.30 (0.12)*	0.86	0.92

*Statistically significant difference when comparing with the VEKC group.

AsphQfront, asphericity at the front of the cornea; AstF, anterior corneal astigmatism; Db, change in posterior elevation; Df, change in anterior elevation from BFS to enhanced reference surface; EleBmax, maximum posterior elevation value; EleBTP, posterior elevation the thinnest point; EleFmax, maximum anterior elevation value; EleFTP, anterior elevation the thinnest point; ISV, index of surface variance; PImax, pachymetry progression index maximum.

TABLE 2. Asymmetry (Bilateral) Analysis of the Selected Variables in Each Group

Variable	VEKC Mean (SD) n = 41	KC All Stages Mean (SD) n = 294	Normal Mean (SD) n = 341	Astigmatism Mean (SD) n = 10	Hyperopic Astigmatism Mean (SD) n = 22	Myopic Astigmatism Mean (SD) n = 18	AUROC Normal vs. VEKC	AUROC Normal vs. KC All Stages
Kmax, D	0.96 (0.8)	4.68 (6.279)	0.45 (0.41)	0.18 (0.17)*	0.35 (0.37)*	0.33 (0.37)*	0.71	0.90
EleBmax, μm	10.76 (16.41)	18.27 (20.16)	3.19 (2.649	3.33 (2.80)*	4.67 (2.46)*	5.38 (4.53)*	0.72	0.83
EleBTP, μm	5.10 (4.41)	17.88 (20.52)	2.11 (1.95)	2.83 (1.17)*	2.16 (1.90)*	2.6 (1.14)*	0.75	0.86
EleFmax, μm	4.95 (1.85)	10.27 (11.03)	1.41 (1.40)	1.66 (1.51)*	2.5 (2.15)*	2.13 (1.09)*	0.87	0.70
EleFTP, μm	2.39 (2.33)	8.69 (9.85)	1.05 (0.96)	1.16 (0.98)*	0.92 (0.67)*	2.12 (1.67)*	0.70	0.97
Final D	0.56 (0.55)	2.92 (4.36)	0.28 (0.24)	0.16 (0.13)*	0.18 (0.09)*	0.27 (0.17)*	0.68	0.87
Df	1.19 (0.84)	4.33 (5.17)	0.35 (0.47)	0.285 (0.32)*	0.75 (0.83)*	0.92 (0.83)*	0.84	0.92
Db	0.98 (0.86)	3.38 (5.29)	0.44 (0.37)	0.50 (0.32)*	0.41 (0.26)*	0.39 (0.32)*	0.69	0.84
ISV	7.32 (6.75)	22.08 (23.76)	3.12 (3.04)	3 (2.68)*	5 (6.47)*	4.31 (3.88)*	0.71	0.86
AstF, D	0.90 (1.11)	1.74 (1.74)	0.36 (0.35)	0.38 (0.29)*	0.51 (0.28)*	0.44 (0.29)*	0.68	0.82
PImax	0.26 (0.28)	0.83 (1.477)	0.16 (0.13)	0.15 (0.09)*	0.03 (0.03)*	0.10 (0.07)*	0.58	0.75
AsphQFront	0.12 (0.16)	0.36 (0.41)	0.05 (0.05)	0.08 (0.033)*	0.10 (0.13)*	0.10 (0.11)*	0.71	0.92

*Statistically significant difference when comparing with the VEKC group.

AsphQfront, asphericity at the front of the cornea; AstF, anterior corneal astigmatism; Db, change in posterior elevation; Df, change in anterior elevation from BFS to enhanced reference surface; EleBmax, maximum posterior elevation value; EleBTP, posterior elevation the thinnest point; EleFmax, maximum anterior elevation value; EleFTP, anterior elevation the thinnest point; ISV, index of surface variance; PImax, pachymetry progression index maximum.

However, we still have cases in which topographic analysis shows no measurable signs of KC, but patients are still at risk for ectasia after laser in situ keratomileusis.[14] In contrast, we have high-ammetropic eyes that can show higher values in some parameters than those presented in the early stages of KC and in low-ammetropic eyes, making it more difficult to discriminate from VEKC. Table 1 shows the unilateral/standard analysis and similarities between the mean values in the 3 high-ammetropic groups and the VEKC group; in fact, high-ammetropic eyes show higher values than those presented in the VEKC group in some parameters. The hyperopic astigmatism group showed higher mean values than those presented in the VEKC group in terms of EleBmax, EleFmax, EleBTP, ISV, AstF, and AsphQfront, and for this reason the BAD display uses a separate hyperopic database.[9] The astigmatism group showed higher values in EleFmax, AsphQfront, and AstF, whereas the myopic astigmatism group presented higher values in EleBTP, AstF, and AsphQfront. Table 1 also shows how the AUROC value decreases when comparing VEKC eyes from normal eyes than when comparing KC in all stages from normal eyes using the unilateral analysis.

The "bilateral/asymmetry analysis," in which the asymmetry was calculated between eyes, showed opposite results. Table 2 shows the asymmetry value in the comparison groups; all 3 high-ammetropic groups showed lower asymmetric values than those presented in the VEKC group. There were statistically significant differences between high-ammetropic groups and the VEKC group in all asymmetry parameters. It is clear from our results that KC is an asymmetrical disease, and the this asymmetry is present even in the very early stages.

It is a well-known fact that clear, evident patients with KC show asymmetry with regard to central power, spherical equivalent, cylinder, posterior elevation, and pachymetry.[1,4,5] But asymmetry in VEKC using Scheimpflug imaging has not been described, our results come from a selection of bilateral KC patients with a bilateral Kmax below 48 D, and a model constructed using the asymmetry values shows an AUROC value of 0.90 discriminating between VEKC eyes and normal eyes. The best parameter discriminating between normal eyes and VEKC eyes in unilateral analysis is the final D value from the BAD, with an AUROC value of 0.975, in agreement with previous work.[8] In a mixed model that included the non-asymmetry parameter (final D) and asymmetry values (described in the model) reaches an AUROC value of 0.9957, meaning that asymmetry analysis can improve the actual discriminative power of the unilateral analysis.

In conclusion, this study demonstrates that parameters derived from Scheimpflug imaging can effectively discriminate between normal eyes and VEKC eyes, and that VEKC shows higher asymmetric values than those presented in high-ammetropic eyes. We believe that bilateral/asymmetry evaluation should be used in addition to the unilateral analysis for KC diagnosis.

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REFERENCES

1. Burns DM, Johnston FM, Frazer DG, et al. Keratoconus: an analysis of corneal asymmetry. *Br J Ophthalmol.* 2004;88:1252–1255.
2. Bae GH, Kim JR, Kim CH, et al. Corneal topographic and tomographic analysis of fellow eyes in unilateral keratoconus patients using Pentacam. *Am J Ophthalmol.* 2014;157:103–109.
3. Field MG, Alasil T, Baniasadi N, et al. Facilitating glaucoma diagnosis with intereye retinal nerve fiber layer asymmetry using spectral-domain optical coherence tomography. *J Glaucoma.* 2014 [epub ahead of print].
4. Zadnik K, Steger-May K, Fink BA, et al. Between-eye asymmetry in keratoconus. *Cornea*. 2002;21:671–679.
5. Khachikian SS, Belin MW, Ciolino JB. Intrasubject corneal thickness asymmetry. *J Refract Surg.* 2008;24:606–609.
6. Henriquez MA, Izquierdo L Jr, Mannis MJ. Intereye asymmetry detected by Scheimpflug imaging in subjects with normal corneas and keratoconus. *Cornea*. 2013;32:779–782.

7. Saad A, Guilbert E, Gatinel D. Corneal enantiomorphism in normal and keratoconic eyes. *J Refract Surg.* 2014;30:542–547.
8. Villavicencio OF, Gilani F, Henriquez MA, et al. Independent population validation of the Belin/Ambrosio enhanced ectasia display implications for keratoconus studies and screening. *Int J Kerat Ect Cor Dis.* 2014;3: 1–8.
9. Kim JT, Cortese M, Belin MW, et al. Tomopgraphic normal values for corneal elevation and pachymetry in a hyperopic population. *J Clin Exp Ophthalmol.* 2011;2:130.
10. Gilani F, Cortese M, Ambrósio RR Jr, et al. Comprehensive anterior segment normal values generated by rotating scheimpflug tomography. *J Cataract Refract Surg.* 2013;36:1327–1335.
11. Maeda N, Klyce SD, Smolek MK. Neural network classification of corneal tomography. Prelyminary demostration. *Invest Ophthalmol Vis Sci.* 1995;159:733–738.
12. Goebels S, Eppig T, Wagenpfeil S, et al. Staging of keratoconus indices regarding tomography, topography, and biomechanical measurements. *Am J Ophthalmol.* 2015;159:733–738.
13. Belin MW, Villavicencio OF, Ambrósio RR Jr. Tomographic parameters for the detection of keratoconus: suggestions for screening and treatment parameters. *Eye Contact Lens.* 2014;40:326–330.
14. Ambrosio R Jr, Dawson DG, Belin MW. Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal preoperative topography. *Am J Ophthalmol.* 2014;158:1358–1359.