

Inter-Ocular Asymmetry in Anterior Corneal Aberrations Using Placido Disk-Based Topography

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Objective: Inter-ocular asymmetry in anterior corneal high-order aberrations has previously not been investigated. This study aims to investigate the normal range of inter-ocular asymmetry in corneal high-order aberrations (HOAs) using a Placido disk-based corneal topographer to explore the relationship between the HOA parameters of the anterior corneal for each eye individually and the refractive error.

Patients and Methods: A total of 257 subjects (98 males and 159 females) were participated, with an age range of 6 to 81 years (average of 40.2 ± 17.53). Participants were divided into three groups: myopia (spherical equivalent (SEQ) of refraction ≥ -0.50 D), hypermetropia (SEQ $\geq +0.50$ D), and emmetropia. For all patients, high-order aberrations were measured using a corneal topographer (CA.200TM; Topcon). Inter-ocular asymmetry was represented by RMS (root mean square) for three, five, and seven mm as pupil entry; aberrations for five mm pupil (vertical and oblique trefoil, vertical and horizontal comma, and primary spherical aberration) were recorded using the instrument's built-in software.

Results: Hypermetropes exhibit the highest inter-ocular asymmetry of all RMS values, mostly in spherical aberrations, and higher-order trefoil values. Oblique trefoil aberrations had the highest interocular asymmetry in the myopic groups. The interocular asymmetry in horizontal coma values was the highest in emmetropes and the lowest in hypermetropes.

Conclusion: To our knowledge, this is the first observational study of inter-ocular differences in high-order aberrations of the anterior corneal surface of the human eye. This study's results could be used to establish normal values of inter-ocular asymmetry of HOAs of the anterior cornea. The use of such normal values should be investigated further to serve as a guideline for clinicians when establishing the best management route for the patient's refractive error.

Keywords: anterior corneal aberrations, high-order aberrations, inter-ocular asymmetry, Zernike analysis

Introduction

Previous studies have reported that high-order aberrations may play a role in the development or progression of refractive errors by altering the quality of the retinal image.¹ Furthermore, HOAs are of clinical relevance as some dysphotopsias such as night halos and glare have been associated with high amounts of high-order aberrations.^{2,3} With the advancement in diagnostic techniques and precise corrections of corneal aberrations with lasers, the HOAs have been at the center stage of research for improving the efficiency of the ocular system.⁴⁻¹⁰

There is currently no gold standard modality for the evaluation of corneal aberrations.¹¹ Nevertheless, the widespread use of corneal topographers is permitting

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researchers and clinicians to explore the corneal changes associated with refractive errors.^{11,12}

The relationship between the anterior corneal aberrations and the changes in the vision of patients is still unclear. To the knowledge of the authors, no studies have evaluated inter-ocular asymmetry in anterior corneal high-order aberrations (measured using corneal topography) and their correlations with refractive error. Therefore, understanding the nature and degree of association between morphological changes of the cornea and presence or absence of HOAs in patients without refractive error (emmetropic) and with refractive error (ametropic) is of vital importance since it could serve as a guideline for clinicians when considering the best strategy for the management of the present refractive error.

Previous studies have explored the symmetrical distribution of the anterior corneal surface HOAs in healthy patients between right and left eye without establishing any difference limits to be used as a guideline for the clinician to detect any abnormality in the anterior corneal surface.¹³ This study aimed to 1) Measure the inter-ocular asymmetry in anterior corneal high-order aberrations using corneal topography in emmetropia, myopia, and hypermetropia; 2) Establish a possible relationship between HOAs of the anterior cornea with refractive error. Thus, establishing the different tolerance limits for each refractive type and the amount of the inter-ocular asymmetry for each subject.

Patients and Methods

Subjects

In this observational study, a total of 257 patients were included. These patients included 94 emmetropic, 93 myopic, and 70 hypermetropic patients. The inclusion criteria for the control group (ie, emmetropes) were patients with spherical equivalent between +0.50 D and -0.50 D. Myopia was defined as a spherical equivalent of refraction ≥ -0.50 D. Hyperopia was defined as a spherical equivalent of $\geq +0.50$ D.

Patients with a history of trauma or ocular pathology, ocular or refractive surgery, diabetes mellitus, without central fixation, and those with corneal topographers' predictors that are compatible with keratoconus were excluded from the study, as well as those with anisometropia ≥ 0.5 D. Patients were also excluded if they did not sign the consent form and if they did not understand the test requirements.

All patients were informed of the purpose of the study (parents were informed if the patients are minors) and

received a written document containing information related to the tests. They signed a consent form regarding the details of the exam and the right to analyze all the data collected and for use in future investigations while guaranteeing all participants the confidential treatment of all personal data. A parent or legal guardian provided written informed consent for any participants who were minors. The study was conducted in accordance with the principles of the Helsinki Declaration. This study received the approval of the Ethics Review Board of the Hospital Universitari de Girona Doctor Josep Trueta, Spain.

Instruments Used

To fulfill the objectives of the study, the instruments found in an optometry clinic were used to perform a routine visual examination. These instruments included the retinoscope, manual phoropter (Nidek), digital slit lamp (SL-D4; Topcon), automatic keratorefractometer (ARK.1; Nidek), Early Treatment Diabetic Retinopathy Study (ETDRS) logarithmic visual acuity chart with annotations for testing at 4 meters (13 feet) from the "1" card - Precision Vision™, and a near visual acuity chart (Gold standard ETDRS near visual acuity chart).

In addition to these instruments, the following instrument was used for the evaluation of the cornea:

CA.200 Corneal Topographer; Topcon.

Procedure

At the first visit, an optometric/ophthalmological history of all patients was recorded, including demographic information of name, sex, age, general medical history, family ocular history any previous or current use of medications.

Next, the patients had a complete visual evaluation and an exam to determine if they were candidates for the study according to the inclusion/exclusion criteria.

Retinoscopy was performed to determine the amount and type of refractive error. Then, the best-corrected visual acuity for distance vision was measured with an ETDRS (Precision Vision™) test - a backlit box presented at a distance of four meters. Visual acuity data were recorded in logMAR notation.

Corneal Topography

A bite bar was used to maintain the head, and an auxiliary monitor was employed to align the center of the pupil, while the patient was focusing on a central green fixation point, which provides accurate alignment of the subject's line of sight to the measurement axis. Corneal asphericity for

4.5mm pupil, keratoconus prediction index, and high-order aberration values represented by RMS for three, five, and seven mm as pupil entry, and aberrations for five mm pupil (vertical and oblique trefoil, vertical and horizontal coma values, and spherical aberration) were recorded using the instrument's built-in software (CA.200, Topcon). The integrated software of the corneal topography has a computational method, which was used for reducing pupil size to simulate the experimental situation of different pupil entries in mm. All measurements of the corneal topography device were taken by the same examiner.

Data Analysis

All data obtained were analyzed using the Statistical Package for Social Sciences (IBM SPSS, V.24; IBM, Inc) Windows software. Data were evaluated for normality with the Kolmogorov–Smirnov test, which revealed that all variables under examination followed a normal distribution. The detailed statistics for controlled, myopic, and hyperopic groups were obtained in mean and standard deviation (SD) from which the absolute intraocular differences of high-order aberrations were obtained, and a 95% confidence interval (CI) was calculated. Inferential statistics were conducted with the Student's *t*-test for matched pairs when comparing data from the right (RE) and left eyes (LE) or with the Student's *t*-test for unmatched pairs if data belonged to different study groups (such as control, myopic, and hypermetropic groups). Post hoc a test Bonferroni correction was conducted. Inter-ocular differences are shown as (2.5%-97.5%). Pearson's correlation coefficients were calculated to find the correlations (if any) between anterior corneal high-order aberrations and the mean

of the refractive error. A P value of 0.05 was considered as the threshold for statistical significance.

Results

Demographic Distribution

A total of 257 subjects (98 males and 159 females) participated in the study, which was conducted from October 2018 to March 2019. The control group had 27 males, 67 females (n=94) with an age of 37.73 ± 16.27 (range from six to 81 years). Refractive error in the control group was OD $+0.005 \pm 0.28$ (range $+0.50$ to -0.50) and OS -0.001 ± 0.28 (range $+0.50$ to -0.50); $P = 0.77$.

The myopic group comprised of 43 males, 50 females (n=93). The mean age was 31.99 ± 14.33 (range from nine to 69 years), and the refractive error OD -1.79 ± 1.29 D (Range -0.50 to -6.75), OS -1.76 ± 1.26 D (Range -0.50 to -7.88) with $P = 0.56$ was present.

The hypermetropic group had 28 males, 42 females (n=70) with an average age of 54.14 ± 14.24 (range from 11 to 77 years) and a refractive error of OD $+1.43 \pm 0.86$ D (Range $+0.75$ to $+4.38$), OS $+1.49 \pm 0.91$ D (Range $+0.75$ to $+5.13$); $P = 0.09$. Descriptive statistics of refractive and corneal astigmatism for control, myopia, and hypermetropia groups are shown in Table 1.

Higher-Order Aberrations

Data were analyzed for the correlation of high-order aberrations (RMS for pupil entry of three, five, and seven mm), and aberrations for five mm pupil (Vertical Trefoil, Horizontal Trefoil, Vertical Coma, Horizontal Coma, Primary Spherical). The inter-ocular variation of Horizontal Coma

Table 1 Descriptive Statistics of Refractive and Corneal Astigmatism for Control, Myopia, and Hypermetropia Groups

	Control Group		Myopia Group		Hypermetropia Group	
	Refractive Astigmatism (RE)	Refractive Astigmatism (LE)	Refractive Astigmatism (RE)	Refractive Astigmatism (LE)	Refractive Astigmatism (RE)	Refractive Astigmatism (LE)
Mean	-0.26	-0.24	-0.72	-0.74	-0.56	-0.58
SD	0.37	0.38	0.69	0.78	0.66	0.64
Maximum	0.75	0.75	0.00	0.00	0.00	0.00
Minimum	-1.50	-1.50	-2.75	-4.00	-3.75	-3.75
	Corneal Astigmatism (RE)	Corneal Astigmatism (LE)	Corneal Astigmatism (RE)	Corneal Astigmatism (LE)	Corneal Astigmatism (RE)	Corneal Astigmatism (LE)
	Corneal Astigmatism (RE)	Corneal Astigmatism (LE)	Corneal Astigmatism (RE)	Corneal Astigmatism (LE)	Corneal Astigmatism (RE)	Corneal Astigmatism (LE)
Mean	-0.71	-0.73	-0.87	-0.94	-0.65	-0.64
SD	0.40	0.49	0.58	0.73	0.52	0.67
Maximum	0.00	0.57	0.00	0.92	0.60	0.80
Minimum	-1.90	-2.37	-2.75	-3.38	-3.07	-3.95

Note: Results are presented as mean $\pm$ SD, maximum and minimum for RE and LE, in diopter unit.

Table 2 Mean High-Order Aberrations for Control, Myopia, and Hypermetropia Groups

High-Order Aberrations, μm	Control Group					Myopia Group					Hypermetropia Group				
	RE		LE		P	RE		LE		P	RE		LE		P
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
RMS 3 mm	0.14	0.05	0.15	0.07	0.10	0.16	0.08	0.17	0.10	0.05	0.16	0.09	0.16	0.07	0.80
RMS 5 mm	0.49	0.20	0.53	0.26	0.06	0.55	0.28	0.67	0.85	0.13	0.56	0.33	0.53	0.30	0.62
RMS 7 mm	1.57	1.14	1.60	0.88	0.81	1.63	1.03	1.84	2.20	0.32	1.68	1.95	1.64	1.40	0.86
Vertical Trefoil	0.11	0.10	0.11	0.10	0.96	0.10	0.09	0.13	0.31	0.37	0.14	0.15	0.14	0.13	0.96
Oblique Trefoil	0.07	0.07	0.07	0.09	0.78	0.06	0.08	0.09	0.23	0.23	0.08	0.09	0.07	0.06	0.62
Vertical Coma	0.12	0.12	0.12	0.12	0.65	0.12	0.14	0.14	0.44	0.62	0.13	0.16	0.11	0.12	0.33
Horizontal Coma	0.12	0.07	0.14	0.08	<0.001	0.09	0.06	0.11	0.10	0.02	0.12	0.07	0.15	0.08	<0.001
Primary Spherical	0.17	0.07	0.18	0.07	0.72	0.17	0.07	0.20	0.30	0.31	0.18	0.11	0.19	0.09	0.69

Notes: Results are presented as mean $\pm$ SD for RE and LE, and the outcome of the Student t test for matched pairs for each group is also shown. P values in bold denote statistically significant interocular differences.

Abbreviation: RMS, root mean square for pupil entry of 3 mm, 5 mm, and 7 mm.

was found to be more prevalent in all three of the study groups compared to other high-order aberrations, as shown in [Tables 2](#) and [3](#). The mean absolute inter-ocular differences of Horizontal Coma in control were -0.02 ± 0.1 SD (95% CI), in the myopic group was -0.03 ± 0.1 SD (95% CI), and the hyperopic group was -0.02 ± 0.07 SD (95% CI). The post hoc test Bonferroni correction revealed that the horizontal coma was statistically different for the three groups. The absolute inter-ocular differences of other high-order aberrations with Mean $\pm$ SD (95% CI) are listed in [Table 4](#).

For most eyes in our study, the significance of anterior corneal aberrations increased with pupil diameter.

[Table 5](#) displays the 95% limits of difference in terms of the 2.5% and 97.5% percentiles.

High-Order Aberrations and Refractive Errors

Statistically significant, albeit weak correlation, was found only in the myopic group, between the mean spherical equivalent of refraction and RMS for pupil entry of 7 mm in the left eye ($r = 0.23$; $p = 0.02$), as well as between mean spherical equivalent and horizontal coma for pupil entry of 5 mm in the right eye ($r = 0.40$; $p < 0.001$). There was no statistically significant correlation between either anterior corneal aberrations or the spherical equivalent of refraction with age.

Discussion

Low-order aberrations such as myopia, hyperopia, and astigmatism can be easily and efficiently corrected with

the use of spectacles, contact lenses, laser procedures, and intraocular lens (IOL) implantation.¹⁴ On the other hand, patients with high-order aberrations require detailed ocular examination and complex procedures for the correction of their visual acuity. Nevertheless, the return of 100% corrected vision remains a matter of concern, with many complications arising after corrective procedures. This highlights the importance of understanding the anterior

Table 3 P values of High-Order Aberrations for All Groups Using Post Hoc Bonferroni Test for Right and Left Eyes

High-Order Aberrations, μm	P
RMS 3 mm (RE)	0.13
RMS 3 mm (LE)	0.90
RMS 5 mm (RE)	0.30
RMS 5 mm (LE)	0.27
RMS 7 mm (RE)	1
RMS 7 mm (LE)	0.85
Vertical Trefoil (RE)	0.11
Vertical Trefoil (LE)	0.83
Oblique Trefoil (RE)	0.30
Oblique Trefoil (LE)	1
Vertical Coma (RE)	1
Vertical Coma (LE)	1
Horizontal Coma (RE)	0.01
Horizontal Coma (LE)	0.01
Primary Spherical (RE)	0.03
Primary Spherical (LE)	0.03

Notes: Results are presented as Post Hoc Bonferroni Test for RE and LE for each group shown. P values in bold denote statistically significant interocular differences at alpha level of 0.05.

Abbreviation: RMS, root mean square for pupil entry of 3 mm, 5 mm, and 7 mm.

Table 4 Absolute Interocular Differences in High-Order Aberrations in Mean $\pm$ SD (95% CI) for Control, Myopia, and Hypermetropia Groups

Absolute Interocular Difference in High Order Aberrations (μm)	Control Group				Myopia Group				Hypermetropia Group				P
	Mean	SD	95% CI		Mean	SD	95% CI		Mean	SD	95% CI		
RMS 3 mm	−0.01	0.06	−0.02	0.00	−0.01	0.07	−0.03	0.00	0.00	0.10	−0.02	0.02	0.38
RMS 5 mm	−0.04	0.22	−0.09	0.00	−0.12	0.73	−0.27	0.04	0.03	0.38	−0.06	0.12	0.19
RMS 7 mm	−0.03	1.06	−0.24	0.19	−0.22	2.12	−0.65	0.22	0.03	1.70	−0.38	0.43	0.61
Vertical Trefoil	0.00	0.10	−0.02	0.02	−0.27	0.28	−0.08	0.03	0.00	0.16	−0.04	0.04	0.60
Oblique Trefoil	0.00	0.10	−0.24	0.18	−0.03	0.24	−0.08	0.02	0.01	0.10	−0.02	0.03	0.34
Vertical Coma	−0.01	0.15	−0.04	0.02	−0.02	0.40	−0.10	0.06	0.02	0.18	−0.02	0.06	0.66
Horizontal Coma	−0.02	0.10	−0.04	−0.01	−0.03	0.11	−0.05	0.00	−0.02	0.07	−0.04	−0.01	0.98
Primary Spherical	0.00	0.06	−0.01	0.01	−0.03	0.31	−0.10	0.03	−0.01	0.11	−0.03	0.02	0.52

Notes: The results of the nonmatched pairs Student *t* test are shown.

Abbreviations: CI, confidence interval; RMS, root mean square for pupil entry of 3 mm, 5 mm, and 7 mm.

Table 5 Percentile Distribution of Interocular Differences (Right Eye Minus Left Eye) in High-Order Aberrations (μ m) for Control, Myopia, and Hypermetropia Groups

High-Order Aberrations (μm)	Control Group		Myopia Group		Hypermetropia Group	
	Percentiles					
	2.5th	97.5th	2.5th	97.5th	2.5th	97.5th
RMS 3 mm	−0.17	0.14	−0.24	0.13	−0.19	0.27
RMS 5 mm	−0.78	0.42	−1.36	0.55	−0.98	1.08
RMS 7 mm	−2.65	2.84	−4.22	3.72	−3.81	6.19
Vertical Trefoil	−0.25	0.20	−0.36	0.24	−0.31	0.42
Oblique Trefoil	−0.25	0.18	−0.52	0.10	−0.19	0.37
Vertical Coma	−0.53	0.37	−0.36	0.39	−0.35	0.49
Horizontal Coma	−0.21	0.19	−0.16	0.20	−0.17	0.13
Primary Spherical	−0.14	0.12	−0.22	0.15	−0.22	0.40

Note: The results of the 2.5th and 97.5th percentiles of interocular difference tolerance limits for the control, myopia, and hypermetropia groups.

Abbreviation: RMS, root mean square for pupil entry of 3 mm, 5 mm, and 7 mm.

corneal high-order aberrations to establish normative data on their asymmetry, and on how this asymmetry may change with different refractive errors. Thus, enabling the clinician to better understand how the anterior corneal surface changes a wave-front of light entering the eye.

The main objective of the present study was to determine the limits of normal anterior corneal asymmetry in a sample of Caucasian patients using a corneal topographer. Evaluation of asymmetry of HOAs at the anterior corneal surface level is of relevance for predicting the visual outcomes after refractive surgeries, which may lead to a significant alteration of the optical quality before changes are documented with standard visual acuity measurement. This would be important as previous studies demonstrated a strong correlation between the presence

of high-order aberrations and corneal astigmatism.¹⁵ The CA200 provides asymmetry value within the same corneal surface (ie, for each eye) to detect if there is keratoconus. In our study, all subjects have a normal asymmetry value, presented by the green numerical color in our maps. Thus, all HOAs shown were for normal corneal asymmetries.

The corneal topographer (CA200; Topcon) employed, has 24 rings that measure over 10,000 data points resulting in an axial resolution of 3 microns. To provide improved workflow, the capture system of the CA-200 is automatic and selects the best-focused image to be captured. Without this automatic feature, the corneal rings from the observational screen would look ruptured or defocused. To control the influence of dynamic tear film changes after eye-opening, the patients were asked to blink after the corneal

rings had been defocused so that we would get a uniformed tear film covering; thus, ensuring results obtained are related to the corneal surface.

Given the significant role of the cornea in the refractive ocular system, establishing a normative data about the asymmetry of anterior corneal aberrations would lead to a change of the patient's refractive error management strategy by better understanding the inter-ocular difference tolerance limits. For that, the concept of inter-ocular asymmetry is crucial in both the planning of clinical evaluations and the interpretation of their results. The previous studies have explored the symmetrical distribution of high-order aberrations parameters in small samples without establishing normal difference limits to be employed as a guideline for any abnormality of the anterior cornea such as corneal dystrophy.³ The current study found an association between the variations in the inter-ocular values of HOAs in emmetropic and ametropic groups. The asymmetric presence of horizontal coma was the most common of all HOAs in these groups.

Marcos and Burns¹⁶ explored the symmetry between eyes of wave-front aberration and cone directionality in a sample of 12 subjects (Spherical refraction ranged from 0 to -6.0) using a spatially resolved refractometer and a reflectometric imaging technique, respectively. The pupils were dilated with tropicamide 5%. They assumed that, in general, the pattern of aberrations is non-symmetric. This is in agreement with our study; where the inter-ocular differences demonstrate that the aberration value of each parameter under evaluation was higher in the left eye than the right eye for all groups, except the horizontal coma in hypermetropia, which was highest in the right eye.

The normal tolerance difference limits were presented in Table 5. The asymmetry of each explored RMS value, as well as the primary spherical of the Zernike aberration coefficients, was highest in the hypermetropia group and lowest in the control group. Similarly, all higher-order trefoil values were highest in the hypermetropia group and lowest in the control group, except for the oblique trefoil aberration where it was highest in the myopic group. On the contrary, horizontal coma values were highest in the control group and lowest in the hypermetropia group.

The above results highlight the difference between the higher-order aberrations of one eye in comparison to the fellow eye and to estimate how much variation the ocular health practitioners should expect to enable them to evaluate the higher-order aberrations of the anterior corneal surface beyond emmetropia and ametropia.

The study was aimed at assessing the inter-ocular asymmetry in anterior corneal aberrations using instruments that are readily and commonly available in most optometric practices or stand-alone ophthalmology clinics which has led to some limitations in the study. First, as also noted by previous authors,¹⁷ the inability to have precisely equal pupil size in the explored eyes affects reliable comparison and requires caution. Second, the Placido-based topographers are limited to providing analysis of data obtained from the anterior cornea; thus, the lack of information about the posterior corneal surface indicates that further research would be beneficial to study the concept of inter-ocular asymmetry in posterior corneal aberrations using an aberrometer, which is not commonly available in an optometric setting or many stand-alone ophthalmology clinics.

As far as the authors' knowledge, this is the first study to investigate the inter-ocular differences in high-order aberrations of the anterior corneal surface using a Placido disk-based topography in emmetropia, myopia, and hypermetropia in the absence of ocular complications. Our findings revealed a range of inter-ocular differences in ametropia within a controlled clinical setting. This study demonstrates how practitioners can use the tools already available at their disposal to maximize the best results for a patient. The established normal values of inter-ocular differences in high-order aberrations at the anterior cornea could be investigated further as a potential guideline for clinicians during decision making when refractive error correction is considered.

Disclosure

The authors report no conflicts of interest in this work.

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