

Statistical Analysis of Monochromatic Aberrations in Chinese Eyes with Glaucoma or Diabetes Retinopathy

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Abstract The diversity and uncertainty of ocular aberrations in abnormal eyes limit the usefulness of adaptive optics in clinical application. Aberrations are characterized in two populations of Chinese abnormal eyes, namely those with glaucoma and those with diabetes retinopathy. Furthermore, the impact of aberrations on retinal image quality and the requirements of wavefront correctors for aberration compensation are analyzed. The results show that higher-order aberrations of glaucoma eyes and diabetes retinopathy eyes are larger than what is typical in normal eyes, approximately 2.9 and 1.8 times respectively. To reach diffraction-limited imaging, correction of Zernike polynomials more than the 8th order is necessary for both glaucoma eyes and diabetes retinopathy eyes and the required corrector Strokes are over 39 μm and 14 μm , respectively. The results presented will help guide the development of wavefront correctors for clinical instrumentation.

Key words adaptive optics; ocular aberrations; wavefront correction; retinal imaging

OCIS codes 330.7310; 330.5370; 010.1080; 080.1010

患有青光眼或糖尿病的中国人眼像差特性统计分析

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摘要 由于人眼像差的多样性和不确定性, 自适应光学在活体人眼视网膜高分辨率成像临床应用中受到了限制。对患有青光眼或糖尿病的中国人眼像差数据进行统计分析, 并在此基础上分析了人眼像差对成像质量的影响及对波前校正器的性能需求。分析结果表明青光眼和糖尿病患者的人眼高阶像差分别是正常人眼高阶像差的 2.9 和 1.8 倍, 为了获得接近衍射极限分辨率的视网膜图像, 对这两类病眼的像差校正均应该高于 8 阶泽尼克多项式, 并且波前校正器的行程需要分别达到 39 μm 和 14 μm 以上。分析结果对基于自适应光学的临床眼科仪器开发有一定的指导意义。

关键词 自适应光学; 人眼像差; 波前校正; 视网膜成像

中图分类号 O439 文献标识码 A

doi: 10.3788/AOS201535.s133001

1 Introduction

Image quality at the retina is limited greatly by the ocular aberrations intrinsic to the cornea and crystalline lens. Ocular aberrations not only limit what the eye sees looking out, but also determine the smallest internal structures that can be observed when looking into the eye with a microscope. Conventional corrective methods such as spectacles, contact lenses, and refractive surgery provide a static

收稿日期: 2015-01-13; 收到修改稿日期: 2015-02-12

基金项目: 国家自然科学基金(61378064, 61205202)、国家重大仪器专项(2012YQ120080)

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correction of lower order sphere and cylinder. However, ocular image quality can be significantly improved by correcting lower-order and higher-order aberrations (HOAs) simultaneously, for example, using adaptive optics (AO) technology^[1]. AO has been successfully integrated into a variety of retina camera modalities, including conventional fundus cameras^[2-3], confocal scanning laser ophthalmoscopes (cSLO)^[4-5], and optical coherence tomography (OCT)^[6-7]. One of the most exciting applications of AO is for the diagnosis of retinal disease. The advantage offered by AO is that the microscopic structure of the diseased retina can be imaged *in vivo* and tracked in single eyes, monitoring the progression of the disease, or the efficacy of therapy over time.

It has been reported that both glaucoma and diabetes retinopathy are very common eye diseases. Glaucoma is the second leading cause of irreversible blindness and it is estimated that 67 millions people in the world have glaucoma and that 6.7 millions of them are blind in both eyes because of the disease^[8]. Diabetes is a major health problem that results from defective pancreatic β -cells in the islets of Langerhans, causing hyperglycemia^[9]. Persons with diabetes are at increased risk for debilitating complications such as renal failure, blindness, nerve damage and vascular disease. According to the World Health Organization (August 2011), 346 millions people worldwide suffer from diabetes. Early detection is crucial for these diseases to slow vision loss and delay or prevent blindness, but it is usually too late by the time using current clinical tests, such as visual field testing, reliably detect vision loss. High-resolution, *in vivo* images of the retina structure afforded with AO technology could make early detection become possible and even lend insights into mechanisms of these diseases. However, It is necessary to characterize the ocular aberrations in these abnormal eyes firstly because the effectiveness of AO fundamentally depends on its ability to measure, track, and correct it. Aberrations of the eye vary spatially across the eye's pupil, vary over time, and vary with field location at the retina. Today detailed measurements of the spatial distribution of wave aberrations have been made in large populations of normal, healthy adult eyes with large pupils^[10-12], including the pooling of data collected at 10 laboratories (2560 eyes)^[13]. More studies have expanded this to include the effect of age, accommodation, refractive state, refractive surgery and disease^[14-16]. Some research studied the aberration characteristics of abnormal eyes. In 2002, Maeda, *et al.*^[17] evaluated eyes with mild and moderate Keratoconus using a KR-9000 aberrometer (Topcon, Tokyo, Japan). In 2007, Pantanelli, *et al.*^[18] investigated dominant HOAs in eyes with Keratoconus and those that have undergone Penetrating Keratoplasty over a pupil of 6.0 mm or more. The aberration characteristics of glaucoma eyes and diabetes retinopathy eyes has not been studied before.

This study characterized aberrations in two populations of Chinese abnormal eyes, namely those with glaucoma and those with diabetes retinopathy. Furthermore, the impact of aberrations on retinal image quality and the requirements of wavefront correctors for aberration compensation had been analyzed. A commercial aberrometer OPD-Scan II (NIDEK, Tokyo, Japan) was used to measure the monochromatic aberrations of eyes for 22 glaucoma and 68 diabetes retinopathy subjects across a 6.0 mm pupil. Another 103 people with no pathologic features were also measured for comparison. The following data were compared among these three populations: root-mean-square (RMS) of HOAs, percent of HOAs variance on total aberrations variance, magnitude of individual Zernike modes and minimum Zernike orders need to be corrected to reach diffraction-limited imaging. Two tailed unpaired t-tests were used to access the statistical difference of the measurements between the abnormal eyes and normal eyes. The results are presented.

2 Methods

All aberration data were from clinical measurement and provided by West China Hospital, Chengdu, China. It was approved by the Ethics Committee of West China Hospital and informed consent was

obtained from all subjects after they received an explanation of this study. Subjects were grouped according to their ocular pathologic features, and the characteristic of aberrations were compared between groups.

2.1 Subjects and instruments

22 glaucoma subjects aged between 22 and 69 years (mean \pm SD age, 41 ± 17 years) and 68 diabetes retinopathy subjects aged between 25 and 68 years (49 ± 10 years) were recruited for this study. A population of 103 people aged between 27 and 71 years (43 ± 14 years) with no ocular pathologic features other than refractive error was also recruited for comparison. A commercial aberrometer OPD-Scan II (NIDEK, Tokyo, Japan) was used to measure the monochromatic ocular aberrations in this study.

2.2 Data collection

Before measurements, normal eyes and diabetes retinopathy eyes were cycloplegiaed and mydriatised by instilling one drop cyclopentolate 1% and one drop tropicamide 1%. Drugs were instilled in two cycles with an interval of 5 min. Aberrations measurement were performed in darkness 30 min after the instillation of the last drop ensuring no residual accommodation was present. Subjects whose pupil diameter is smaller than 6.0 mm were excluded from this study. The aberrometer automatically measures each eye three times and gives the average results. The ocular aberrations were calculated at a reference wavelength of 550 nm, and the pupil diameter was set at 6.0 mm for analysis. The Zernike aberrations up to the 8th order were calculated for each subject using the standards recommended by the Optical Society of America (OSA)^[19].

2.3 Data analysis

To compensate for the enantiomorphism that is present^[10] when comparing the aberrations in left eyes and right eyes, the sign of Zernike modes that are not symmetric about the vertical axis was reversed in all data sets acquired from left eyes (i. e. , $Z(2, -2)$, $Z(3, 1)$, $Z(3, 3)$, etc.). Ocular aberrations were fitted with eight order Zernike expansion. We calculated the variance contribution that Zernike modes up to the 5th order has on the total aberration variance (P_{5th}) using the following formula:

$$P_{5th} = \frac{\sum_{n=2}^5 (Z_n^m)^2}{\sum_{n=2}^8 (Z_n^m)^2}, \quad (1)$$

where Z_n^m is the Zernike mode, n is the radial index and m is the azimuthally frequency. In order to find out which Zernike mode is dominant in the HOAs, we calculated the contribution an individual Zernike mode with radial index n and azimuthally frequency m has on the HOAs (P_{HOA}) by

$$P_{HOA} = \frac{(Z_n^m)^2}{\sum_{n=3}^8 (Z_n^m)^2}. \quad (2)$$

To aid interpretation, the second-order Zernike coefficients (c_2^0 , c_2^{+2} , c_2^{-2}) were converted to an ophthalmic prescription for a correcting lens in power vector notation in units of diopters by

$$M = \frac{-c_2^0 4\sqrt{3}}{r^2}, J_0 = \frac{-c_2^{+2} 2\sqrt{6}}{r^2},$$

$$J_{45} = \frac{-c_2^{-2} 2\sqrt{6}}{r^2}, J = \sqrt{J_0^2 + J_{45}^2}, \quad (3)$$

where r is pupil radius, M is the spherical equivalent error, J_0 is the component of astigmatism that has a vertical or horizontal axis, J_{45} is the component of astigmatism with oblique axis, and J is the total amount of astigmatism. Furthermore, the following values were calculated and compared among the three populations: RMS of HOAs, percent of higher-order variance on total variance, magnitude of individual Zernike modes from the third order to the fifth order.

Normality of all data samples was checked by means of the Anderson-Darling test. When normally distributed, we used the Student's *t*-test for unpaired data to compare normal and abnormal eyes. When the distribution was not normally, we used the nonparametric Mann-Whitney test. A *P* value less than 0.05 was considered significant.

3 Results

3.1 Glaucoma population

The Glaucoma population used included 33 eyes form 22 subjects. For this population, the variance contribution that Zernike modes up to the 5th order has on total aberration variance P_{5th} is $98.61 \pm 1.99\%$ [mean \pm standard deviation(SD)] and has no statistical difference from normal eyes (mean \pm SD, $98.96 \pm 1.08\%$). Average Zernike wavefront coefficients from the 2nd to the 5th order are presented in Fig. 1. The range of spherical equivalent errors (*M*) was -10.81 D to -0.32 D, with mean value of -4.75 D and standard deviation value of 3.45 D. The magnitude of astigmatism (*J*) ranged from 0.03 D to 0.86 D, with mean value of 0.49 D and standard deviation value of 0.26 D. HOAs were significantly larger than those typically found in normal population; the glaucoma eyes had an average higher-order RMS of $(1.13 \pm 0.75) \mu\text{m}$ (mean \pm SD) over a 6.0 mm pupil, which was 2.9 times more than the $(0.39 \pm 0.17) \mu\text{m}$ (mean \pm SD) found in the normal eyes ($P \approx 0$). The most dominant HOAs in the glaucoma eyes was spherical aberration and it accounted for $10.67 \pm 13.42\%$ of the higher-order variance which was 4.2 times more than that found in normal eyes ($P < 0.05$). Finally, $19.04 \pm 10.48\%$ of the total variance in glaucoma eyes was due to HOAs, whereas only $10.32 \pm 4.90\%$ (mean \pm SD) was found in normal eyes.

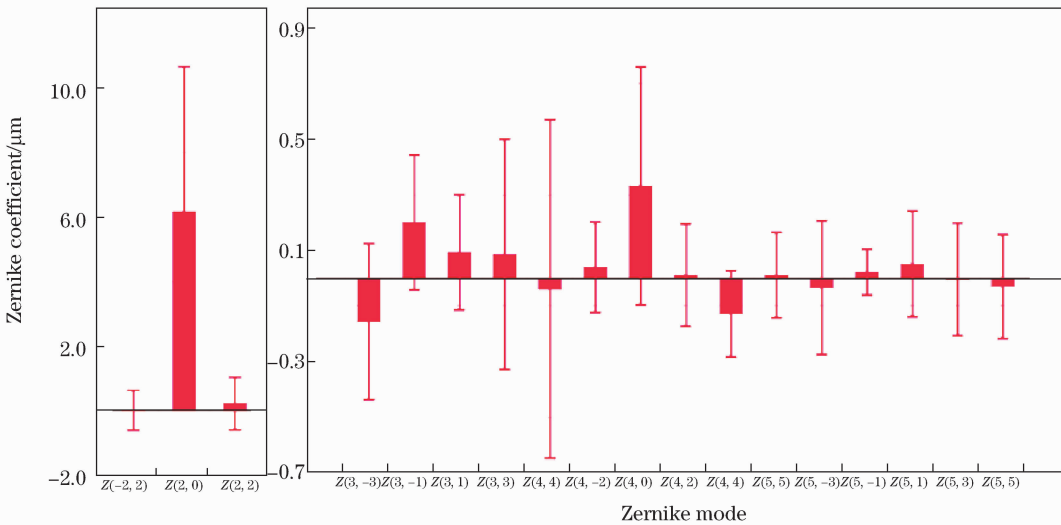


Fig. 1 Mean values of Zernike coefficients from the 2nd to the 5th order in the glaucoma population across a 6.0 mm pupil (error bars represent plus and minus one standard deviation from the mean value)

3.2 Diabetes retinopathy populations

The diabetes retinopathy population used included 107 eyes form 68 subjects. For this population, the variance contribution that Zernike modes up to the 5th order has on total aberration variance P_{5th} is $99.17 \pm 1.89\%$ (mean \pm SD) and also has no statistical difference from normal eyes (mean \pm SD, $98.96 \pm 1.08\%$). The data were processed using the method described above for the glaucoma eyes and average Zernike wavefront coefficients from the 2nd to the 5th order are presented in Fig. 2. The range of spherical equivalent errors (*M*) was -8.80 D to -3.32 D, with mean value of -1.45 D and standard deviation value of 1.80 D. The magnitude of astigmatism (*J*) ranged from 0.05 D to 1.22 D, with mean value of 0.39 D and standard deviation value of 0.24 D. The diabetes retinopathy eyes had 1.8 times more higher-order RMS ($0.71 \pm 0.46 \mu\text{m}$, mean \pm SD) than normal eyes ($0.39 \pm 0.17 \mu\text{m}$, mean \pm SD) over a 6.0 mm pupil ($P \approx 0$). The most dominant HOAs was y-trefoil (Z_3^{-3}) and it accounted for $12.12 \pm 9.11\%$ of the higher-order variance which was 2.8 times more than that found in normal eyes ($P < 0.05$). Finally, these eyes had a

higher-order variance-to-total variance ratio of $33.83 \pm 18.01\%$ (mean \pm SD).

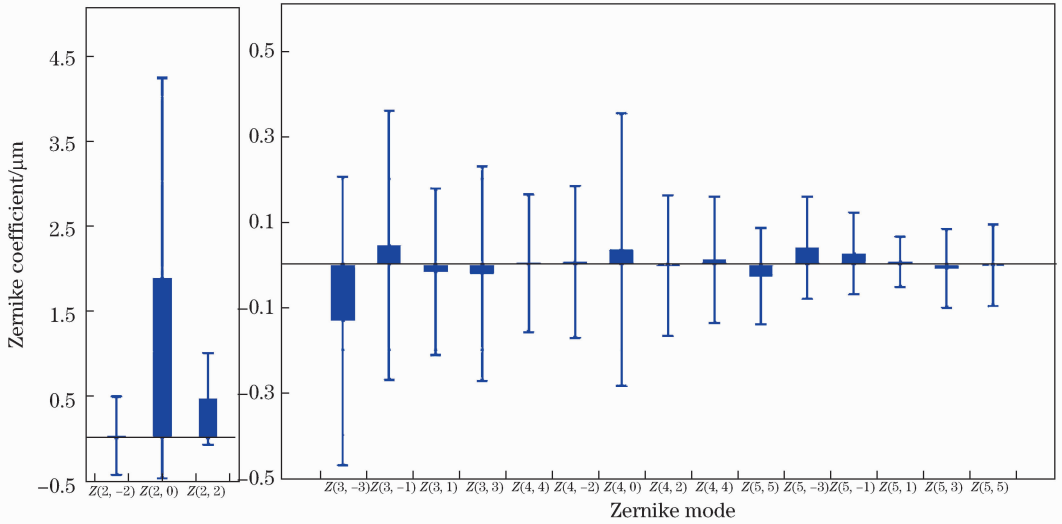


Fig. 2 Mean values of Zernike coefficients from the 2nd to the 5th order in the diabetes retinopathy population across a 6.0 mm pupil (error bars represent plus and minus one standard deviation from the mean value)

3.3 Comparison with normal eyes

This prospective study included 193 subjects: 22 subjects (33 eyes) with glaucoma (mean \pm SD age, 41 ± 17 years), 68 subjects (107 eyes) with diabetes retinopathy (49 ± 10 years), and 103 subjects (186 eyes) with no ocular pathologic features (43 ± 14 years). Fig. 3 plots the magnitude of the Zernike coefficients from the 3rd to the 5th order for these three populations over a 6.0 mm pupil. The plots reinforce what has been mentioned previously: abnormal eyes have larger amounts of HOAs when compared with normal eyes. The magnitude of Zernike coefficients from the 3rd to the 5th order in glaucoma eyes was between 1.5 and 9.8 times the magnitude found in normal eyes, while in diabetes retinopathy eyes the magnitude was between 1.4 and 2.7 times. Table 1 lists the RMS of total aberration, HOAs RMS and the ratio of the HOAs RMS over the total RMS for these populations. The ratio indicated that HOAs are more serve in abnormal eyes than in normal eyes. In glaucoma and diabetes retinopathy eyes, HOAs contributed $19.04 \pm 10.48\%$ and $33.83 \pm 18.01\%$ (mean \pm SD), respectively, to the amount of total aberration. In the normal eyes, the contribution was $10.32 \pm 4.90\%$ (mean \pm SD).

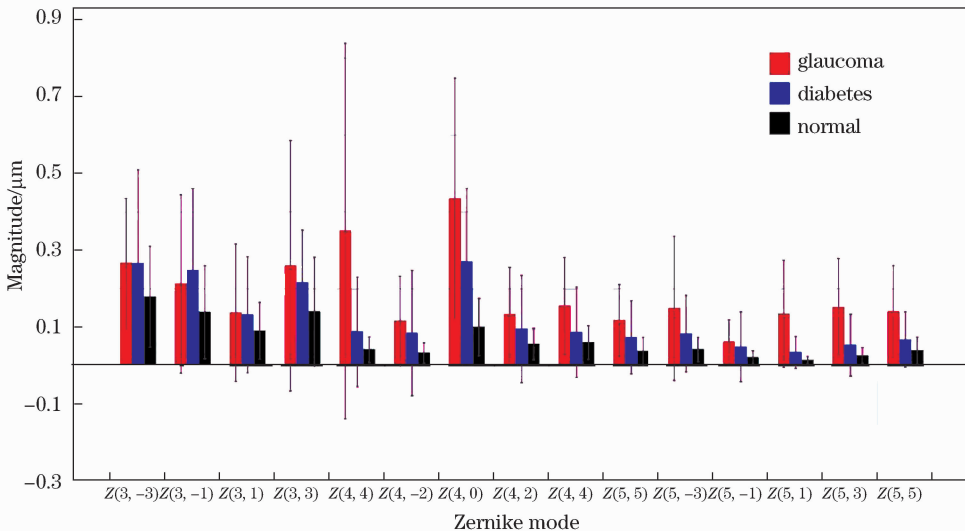


Fig. 3 Comparison of abnormal eyes and normal eyes. Abnormal eyes have greater amounts of HOAs when compared with normal eyes (error bars represent plus and minus one standard deviation from the mean value)

Table 1 Total RMS, HOAs RMS and the ratio of the HOAs RMS over the total aberration RMS in glaucoma, diabetes and normal eyes (data presented as mean \pm SD)

	Glaucoma	Diabetes	Normal
RMS/ μm	6.60 \pm 4.13	2.62 \pm 1.89	4.43 \pm 2.03
HOAs/ μm	1.13 \pm 0.75	0.71 \pm 0.46	0.39 \pm 0.17
Ratio/%	19.04 \pm 10.48	33.83 \pm 18.01	10.32 \pm 4.90

4 Discussion

The distribution and magnitude of the monochromatic aberrations in these three populations shown above does not inform us directly about their impact on image quality and therefore about the improvement from correcting them. Fig. 4 depicts the impact of the different orders by showing the modulation transfer function (MTF), averaged in each population, when additional aberration orders are progressively corrected in monochromatic light. Obviously, image quality is affected by the HOAs, which is even severer in abnormal eyes as Fig. 4(c) shows. Fig. 4(d) shows that after correcting aberrations up through fifth order, the improvement of image quality in abnormal eyes is smaller than that in normal eyes, even though the P5ths are very approximate for all populations. This indicates that for abnormal eyes, the correction of aberrations higher than fifth order cannot be ignored.

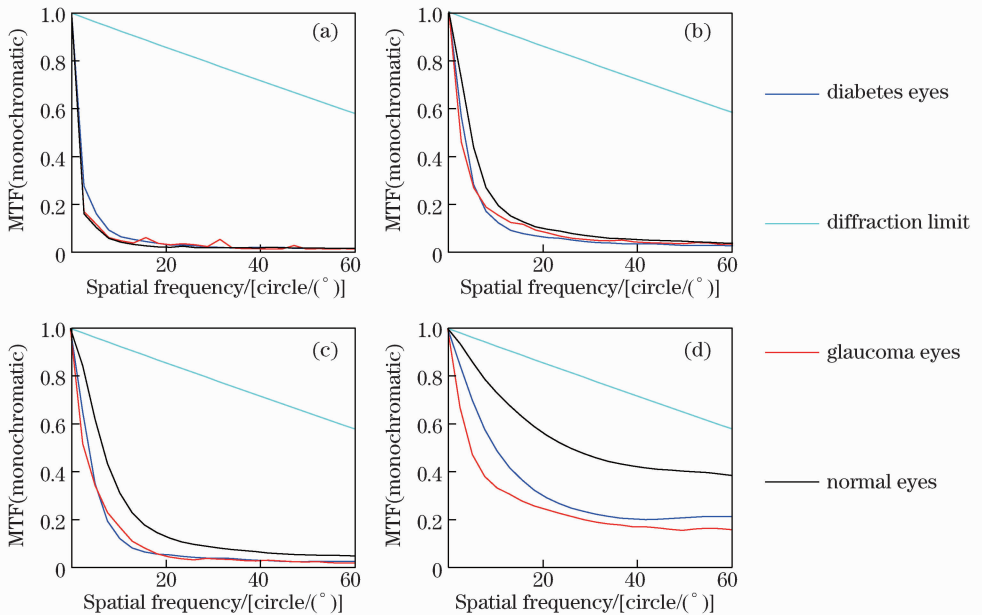


Fig. 4 MTFs averaged in glaucoma eyes, diabetes eyes and normal eyes for a 6.0 mm pupil with $\lambda=0.587 \mu\text{m}$ and the blue solid curves presented as diffraction limit. (a) All aberrations presented with no correction; (b) defocus corrected; (c) defocus and Astigmatic corrected; (d) all aberrations up through 5th order corrected

The spatial characteristics of the ocular aberrations most important for AO are spatial frequency and magnitude [peak-to-valley (PV) wavefront error] and these properties finally determine the requirements for wavefront correctors. Fig. 5 depicts the wavefront variance decomposed by Zernike order for the three populations over a 6.0 mm pupil. For this pupil size, correction of Zernike polynomials up through at least 7th order is necessary to reach diffraction-limited imaging ($\lambda/14$ RMS error) in approximately 95 percent of the population, that is, two times the standard variance (logarithm of wavefront variance) $\lg C$ for the normal population. In the glaucoma eyes and the diabetes retinopathy eyes, however, correction of more than 8th order is needed to reach this goal as shown in Fig. 5.

For an AO system, regardless of corrector type and number of actuators, effective compensation requires the dynamic range of the corrector to be at least equal to the PV error of the aberrations. For reflective

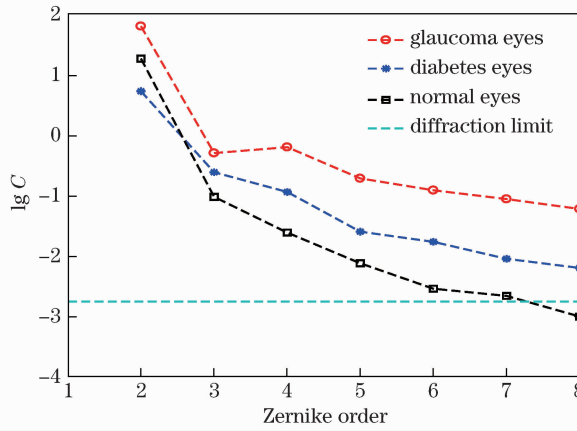


Fig. 5 Wavefront variance $\lg C$ is plotted as a function of Zernike order of glaucoma, diabetes and normal eyes (curves represent mean + two times the standard variance of the logarithm of wavefront variance, horizontal dashed line corresponds to $\lambda/14$ RMS for $\lambda=0.587 \mu\text{m}$)

correctors, this means the maximum physical excursion of their reflective surface must be at least one-half of the PV error. We calculated the corresponding PV wavefront error of each Zernike mode up to fifth order and the results are showed in Fig. 6. Table 2 lists the PV wavefront error that encompasses 95 percent of the three populations with three different second-order aberration states; All three second-order modes took their measured values, the defocus coefficient was set to zero, and all three second-order Zernike coefficients were set to zero. We noticed that although normal eyes have larger PV wavefront error than diabetes retinopathy eyes when all aberrations presented, after correction of lower-order aberrations, both glaucoma and diabetes retinopathy eyes have larger PV wavefront error than normal eyes. Since most current adaptive optics systems compensate the defocus and astigmatism with trial lens, the required corrector stroke (reflective correctors) for the glaucoma, diabetes retinopathy and normal populations are 8.5, 3.2, 1.5 μm respectively.

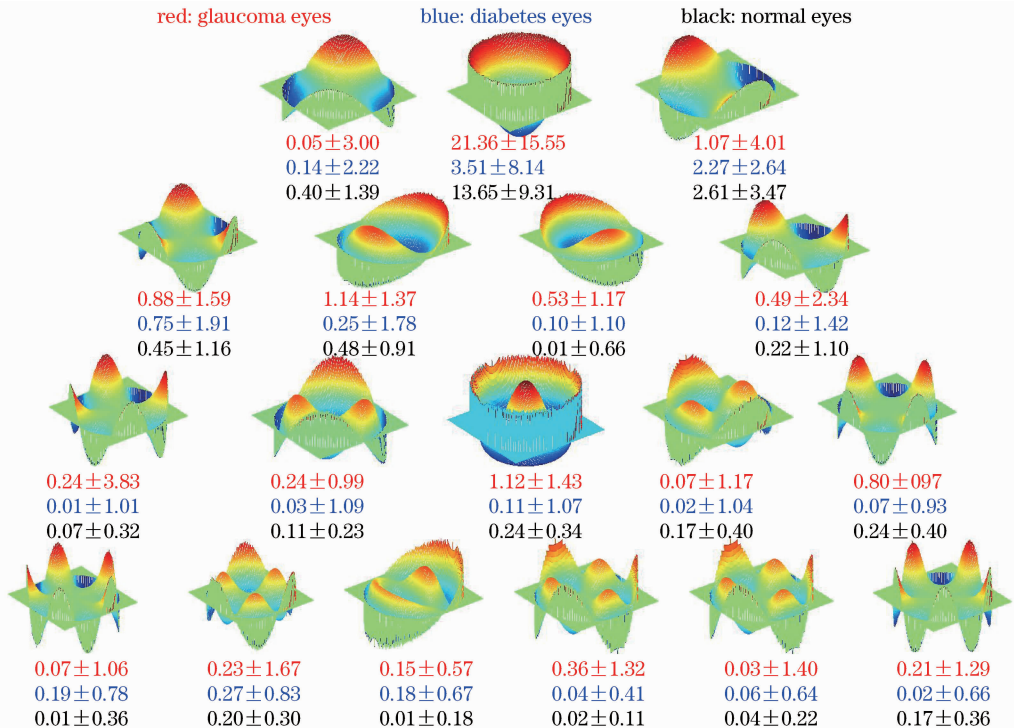


Fig. 6 PV wavefront error (μm) of each Zernike mode up to fifth order for glaucoma, diabetes and normal eyes (data presented as mean \pm SD)

Table 2 PV wavefront error (μm) of glaucoma, diabetes and normal eyes with three second-order aberrations states (data presented as mean + two times SD)

	Glaucoma	Diabetes	Normal
All aberrations/ μm	38.7	13.9	19.2
Defocus removed/ μm	20.1	8.4	5.9
Lower order removed/ μm	17.1	6.3	2.9

The results mentioned above show that HOAs of glaucoma eyes and diabetes retinopathy eyes are larger than what is typical in normal eyes. In order to achieve high-resolution retinal imaging for these abnormal eyes, the following aspects should be considered when developing adaptive optics ophthalmology instruments. Firstly, the wavefront sensor should have enough dynamic range and this can be achieved by increasing the wavefront sensor's lenslet diameter and decreasing the lenslet focal length. Secondly, wavefront corrector for compensating higher-order aberrations must have enough spatial frequency. Generally, this can be done by increasing the number of actuators and narrowing their influence function. Lastly, in order to achieve high-resolution retinal imaging for these abnormal eyes, both lower-order and higher-order aberrations should be correct effectively. However, current correctors cannot provide high spatial frequency and high dynamic range at the same time. Therefore, for these abnormal eyes, AO systems with two wavefront correctors, one of high spatial frequency and the other of large stroke are of great potential for aberration compensation.

There are limitations to this study. The sample is small and the population measurements essentially static wave aberrations and therefore do not capture the temporal behavior of the ocular aberrations. Given the wavefront aberrations are only fitted to the 8th Zernike order, the results only show that in the abnormal eyes correction up to the 8th Zernike order is not enough to reach diffraction-limited imaging. The exact number is not obtained yet.

5 Conclusion

The wavefront aberrations in Chinese eyes with glaucoma or diabetes retinopathy are characterized and the impact of HOAs on retinal image quality are analyzed. The results showed that HOAs of glaucoma eyes and diabetes retinopathy eyes are larger than what is typical in normal eyes, approximately 2.9 and 1.8 times respectively, and correction of Zernike polynomials more than 8th order is necessary for both glaucoma eyes and diabetes retinopathy eyes to reach diffraction-limited imaging over a 6.0 mm pupil. Furthermore, the stroke requirements of wavefront correctors for aberration compensation had also been discussed and the results showed that, for glaucoma eyes and diabetes retinopathy eyes, the required strokes are 39 μm and 14 μm , respectively. The results presented will help guide the development of wavefront correctors for clinical instrumentation.

Acknowledgment: We would like to thank the colleagues in West China Hospital for providing the raw data and we also grateful to Xu Liu and Bo Liang for their suggestions, which improved the manuscript.

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栏目编辑: 史 敏