Axial length and cone density as assessed with adaptive optics in myopia

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Aim: To assess the variations in cone mosaic in myopia and its correlation with axial length (AL). **Subjects and Methods:** Twenty-five healthy myopic volunteers underwent assessment of photoreceptors using adaptive optics retinal camera at 2° and 3° from the foveal center in four quadrants superior, inferior, temporal and nasal. Data was analyzed using SPSS version 17 (IBM). Multivariable regression analysis was conducted to study the relation between cone density and AL, quadrant around the fovea and eccentricity from the fovea. **Results:** The mean cone density was significantly lower as the eccentricity increased from 2° from the fovea to 3° (18,560 ± 5455–16,404 ± 4494/mm^2 respectively). There was also a statistically significant difference between four quadrants around the fovea. The correlation of cone density and spacing with AL showed that there was a significant inverse relation of AL with the cone density. **Conclusion:** In myopic patients with good visual acuity cone density around the fovea depends on the quadrant, distance from the fovea as well as the AL. The strength of the relation of AL with cone density depends on the quadrant and distance.

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Myopia is a common visual imperfection mostly due to an increase in the axial length (AL) of the eye. It can lead to severe visual loss when myopic degeneration develops. It may also cause both lower as well as higher order aberrations.[1] In a less severe stage, its vision loss can be corrected with glasses or contact lenses. Even with glasses the quality of vision with best-corrected visual acuity of 20/20 between myopes and emmetropes is not the same, and this may be due to multiple anatomical and physiological factors.[2-6] These could include the spatial distribution and orientation of the photoreceptors stretched along the posterior pole of the retina due to a larger AL in a myopic eye. It is to be expected that the cone density decreases with increasing myopia.[7-9] However, to what extend this occurs in relation to changes in the AL or extend of the refractive error is largely unknown. With the advent of adaptive optics (AO) technology in vision science, it is now feasible to determine the photoreceptor cone distribution.[7-9] In this study, we measured the variations in the cone mosaic in a population of young myopic adults in relation to the AL and extent of the refractive error. This may help to understand the missing link between increasing severity of myopia and changes in the visual acuity or quality of vision in patients with myopia and enhance the opportunity to monitor essential anatomic changes in myopia.

Subjects and Methods

Subjects

Twenty-five consecutive patients who visited the comprehensive out-patient and the refractive out-patient departments with myopia within the age group of 20–40 years were included in the prospective study. An informed consent was obtained from all subjects, and the nature of the study was explained to them. The study adhered to the tenets of the declaration of Helsinki and was approved by the Ethics Committee and review board of the hospital. The patients in the study group were those who presented with myopia with the spherical equivalent between −1D and −12D and best corrected visual acuity of 20/20. Pathological myopia, and those with any ocular or systemic pathology were not included in the study and all patients enrolled had a clinically normal fundus. We grouped the myopes as low, moderate and high based on their spherical equivalent (mild being 1D–3D, moderate = 3D–6D and high >6D) for analysis.

All the subjects underwent a comprehensive ophthalmic examination including an assessment with the Tonoref RKT-7000 autorefractometer, Nidek, noncontact biometry (IOL master; Carl Zeiss Meditec, Germany) for AL and spectral-domain optical coherence tomography (Spectralis, Heidelberg) for central foveal thickness. A compact AO retinal camera prototype, the rtx 1 (Imagine Eyes, Orsay, France), was used to image the photoreceptor layer.

Adaptive optics imaging

As mentioned in our previous study on emmetropes,[10] the AO imaging sessions were conducted after dilating the pupils with 1 drop each of 0.5% tropicamide and 10% phenylephrine hydrochloride to achieve mid-dilated pupils. Aberrations induced by pupil dilation are negated by the AO system. Stable fixation was maintained by having the patient look at the system's inbuilt target and then as moved by the investigator to predetermined coordinates. The patient was instructed to fixate at 0°, 1°, 2° and 3° eccentricity along all the four quadrants, superior, inferior, nasal and temporal retina. A video (i.e., a series of 40 frames; 4° field size) was captured at each of the above retinal locations. After the acquisition, a program provided by the manufacturer correlated and averaged the captured image frames to produce a final image. Cone

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density (cones/mm^2) was measured at 1°, 2° and 3° eccentricity along all the four quadrants, superior, inferior, nasal and temporal retina. There has been no standardized protocol on which areas to image and size of the sampling window to choose the region of interest. The sampling window we choose was 100 μ and we placed it at specific coordinates calculated by a prefixed formula intentionally avoiding blood vessels. Eccentricity was computed as the distance between the center of each window and the foveal center reference point (identified as the point with fixation coordinates: x = 0°, y = 0°). The images were captured at temporal (−3°,0°) superior (0°,3°) nasal (3°,0°) and inferior (0°,−3°).[10] The cone counting software AO detect created on MATLAB by imagine eyes was used to process the images and calculate the data. The repeatability has been mentioned in our previous study.

Data analysis

The statistical analysis was performed using the IBM SPSS version 20 (SPSS Inc. Chicago, IL) and MedCalc version 11. The Shapiro–Wilk test was performed to determine whether the continuous data were parametric or nonparametric in distribution. We first described the values of cone density and spacing with AO per quadrant and per eccentricity, 2° and 3° from the fovea. Secondly, we tested by means of dependent *t*-test whether there was a difference in these parameters between the four quadrants per degree of eccentricity. Thirdly, we tested whether there was a difference between the degrees of eccentricity per quadrant. We finally studied the relation between either AL or degree of myopia expressed as spherical equivalents and AO parameters per quadrant and per degree of eccentricity. A linear regression analysis was conducted and a multivariable model was developed with the interaction of AL with the quadrant and degree of eccentricity. In both models the cone density was the dependent variable. The same analyses were conducted with refractive error instead of AL as the dependent variable.

Results

Fifty eyes of 25 myopic subjects (10 female, 15 male) between the ages of 20 and 40 years, refractive error of −1D to −12D and an AL of 22.68–28.20 mm were included in the study. The mean cone count and spacing the four quadrants (temporal, superior, nasal, inferior to the fovea) and at different eccentricities (2° and 3° from the fovea) are represented in Table 1. The mean cone density was found to be significantly lower in the myopic group when compared to the age matched emmetropic group as reported in our previous study.[10]

There was a significant decrease in the mean cone density from 18560/mm^2 ± 5455 to 16404/mm^2 ± 4494 respectively and a significant increase in spacing from 8.40 μm ± 1.4 to 8.81 μm ± 1.7 with increase in eccentricity from 2° to 3° from the fovea respectively in the myopic group as seen in Table 2, a mirror trend similar to that of the emmetropes (decrease in cone density and increase in cone spacing as the distance from fovea increases).

The linear regression test performed to relate the cone density and spacing with AL showed that there was significant relation of AL with the cone density in all separate quadrants, at 2° as well as at 3° eccentric from the fovea [Figs. 1 and 2] and is lower when AL is higher. The results for cone spacing showed an increase in the spacing between adjacent cones as eccentricity from the fovea increased. Moreover, there is interaction between AL on one hand and quadrant and degrees on the other implying that the strength of the relation between AL and cone density depends on the degree and quadrant as seen in Table 3. The relation strength was not different for the square of the radius (= half AL), a measure directly related to the surface area. Fig. 3 shows the variation in the cone density between the mild, moderate and high myopia groups. There was no statistically significant difference between these groups. When refractive error was used as the independent variable instead of AL the strength of the relation in all analyses was lower as seen in Table 4. The Pearson's coefficient, used to find the correlation between refractive errors versus AL s, was significant ($r^2 = 0.352$, $P = 0.012$ [$P < 0.05$]).

Discussion

There have been multiple studies that have looked at the axial elongation of the eye in myopia, rather than the equatorial elongation.[11] This is because it is easier to study changes in the photoreceptor mosaic at the posterior pole than at the equator.[3,12] It is well established that the cones do not get distributed evenly as the expansion occurs nonuniformly. The retinal vasculature is said to restrict the cone migration along the entire surface.[13,14] Curcio *et al*. in his histological analysis found the density at 1 mm in the parafoveal retina to be 16,000 cells/mm^2, corresponding to a cone spacing of 7.4 mm.[15] In our previous study on emmetropes we found a statistically significant difference in the cone density was observed from 2° to 3°. At 2° eccentricity the mean was 25,350/mm^2 (5,300/mm^2, 8,400–34,800/mm^2), at 3° eccentricity the mean was 20,750/mm^2 (6,000 mm^2, 9,000–33,670/mm^2) $P < 0.05$. The spacing correspondingly was lower at 2° of eccentricity as compared to 3°. At 2° the mean was 6.9 mm (0.70 mm, 5.95–11.6 mm) and at 3° the mean was 7.80 mm (1.00 mm, 6.5–13.5 mm) $P < 0.05$.[10] In our current study, we found cone density was significantly less in myopes and also showed a similar difference in the count as the eccentricity increased from 2° from the fovea to 3° (18,560 ± 5,455–16,404 ± 4,494/mm^2 respectively).

When we used the variable as refractive error the relation with cone density was less strong as compared to AL as a variable.

Table 1: The mean and SD of the cone density and spacing at the 4 quadrants (temporal, superior, nasal, inferior) and at 2° and 3° retinal eccentricities

	Temporal		Superior		Nasal		Inferior	
	2°	3°	2°	3°	2°	3°	2°	3°
Cone count (/mm^2)	18,410±5790	18,650±4370	19,600±5080	15,495±3854	17,030±5892	16,845±4953	19,193±4780	14,625±3759
Spacing (μm)	8.44±1.53	8.30±1.25	8.14±1.47	9.14±1.63	8.83±1.61	8.51±2.28	8.17±1.14	9.30±1.27

SD: Standard deviation

Table 2: Mean and SD of cone density and cone spacing between 2° and 3°retinal eccentricity among myopic subjects

	2°	3°	Significance (*P*)
Cone count (/mm²)	18,560±5455	16,404±4494	<0.001
Spacing (µm)	8.40±1.4	8.81±1.7	0.010

SD: Standard deviation

Table 3: The effects of fixed factors on the cone count by LMM

Parameter	Parameter estimate	Significant	95% CI	
			Lower limit	Upper limit
Intercept	32,307	0.010	7845	56,770
Degree=2	16,986	0.022	2423	31,549
Degree=3⁺	0			
Site=I	28,465	0.007	7870	49,061
Site=N	25,416	0.016	4821	46,011
Site=S	12,930	0.218	−7665	33,525
Site=T+	0			
Axial length	−600	0.231	−1588	387
Degree=2×AL	−599	0.046	−1187	−11
Degree=3×AL⁺	0			
Site=I×AL	−1216	0.004	−2047	−384
Site=N×AL	−1091	0.010	−1923	−260
Site=S×AL	−562	0.184	−1394	269
Site=T×AL⁺	0			

⁺Factors set to zero, since they are redundant. Dependent variable: Cone count, AL: Axial length, CI: Confidence interval, LMM: Linear mixed models

Table 4: The correlation between AL and refractive error

Degree	Quadrant	AL		Refractive error	
		R^2	*P*	R^2	*P*
2	Temporal	−0.195	0.174	−0.131	0.365
2	Superior	−0.492	<0.001	−0.245	0.086
2	Nasal	−0.404	0.004	−0.197	0.171
2	Inferior	−0.619	<0.001	−0.284	0.046
3	Temporal	−0.223	0.12	−0.211	0.142
3	Superior	−0.239	0.094	−0.58	0.689
3	Nasal	−0.46	0.001	−0.174	0.226
3	Inferior	−0.53	<0.001	−0.203	0.157

AL: Axial length

Lombardo *et al*. studied 11 eyes and found cone density in moderately myopic eyes (up to −7.50 D) was significantly lower than in emmetropic eyes within (or at) 2.0 mm from the fovea, similar to our results. They reported the spatial vision and the Nyquist limit of resolution of the retinal cone mosaic to reduce with increasing AL from 22.60 to 26.60 mm.[9]

Kitaguchi *et al*. reported the cone spacing in the moderate-to high-myopic group to be larger than that in the emmetropic and low-myopic group. They found the cone spacing in a −15 D

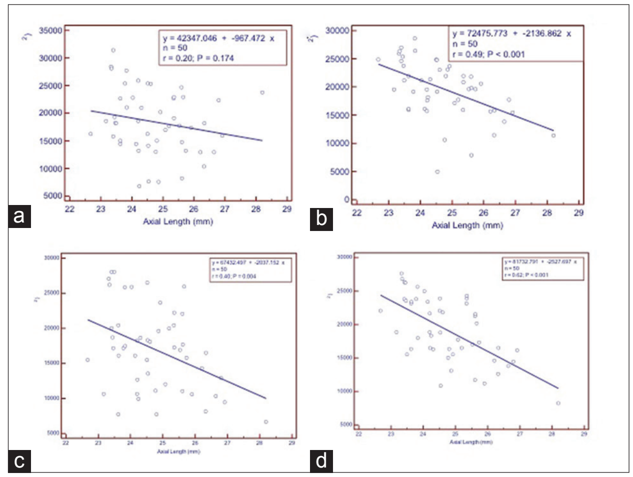

Figure 1: (a-d) scatter plots showing the variation in cone density with axial length in the 4 quadrants (temporal, superior, nasal, inferior) at 2° eccentricity

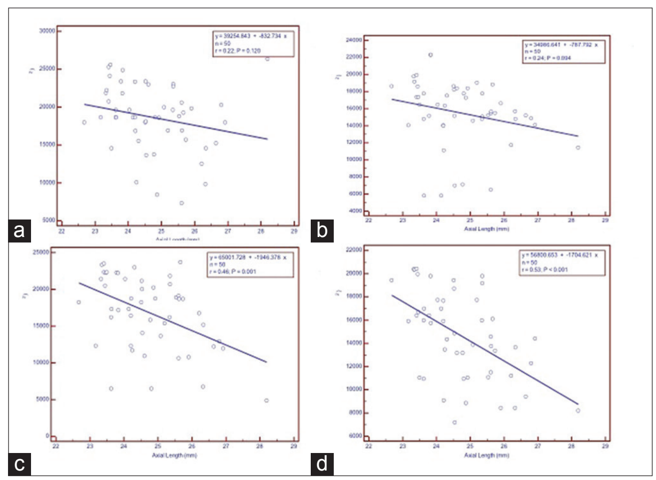

Figure 2: (a-d) scatter plots showing the variation in cone density with axial length in the 4 quadrants (temporal, superior, nasal, inferior) at 3° eccentricity

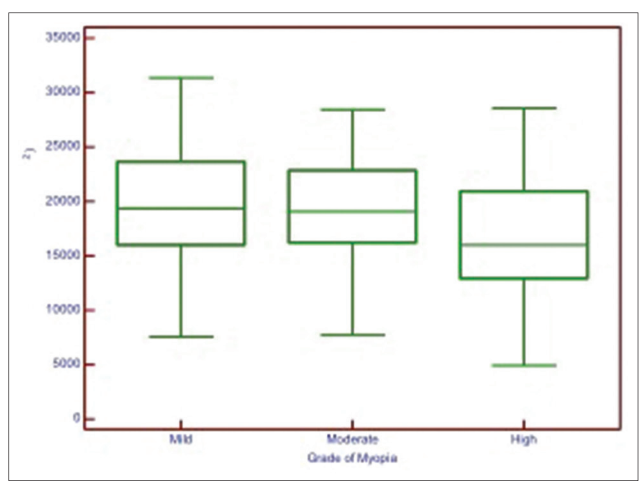

Figure 3: Box plot showing the difference in the cone density between the sub groups (mild, moderate, high) in the myopic subjects

myopic eye was 5.92 μm, which is 1.48 times the cone spacing in emmetropic eyes (4.00 μm), unlike a mathematical model where it would be 1.26-fold. We grouped the myopes as low, moderate and high based on their spherical equivalent (mild being 1D–3D, moderate = 3D–6D and high >6D) and evaluated the cone density at different eccentricities from the fovea to understand local anisotropia in correlation to increase in AL. The cone count and spacing between the mild and moderate group was not found to be significantly different but statistically significant variation was found between the mild and the moderate group with the high myopes [Fig. 3]. This adds to the theory that the expansion is nonuniform.[7]

The limitations of our study was the cone mosaic at the fovea could not be assessed due to their dense arrangement[9] and absence of a correction factor due to the retinal magnification factor.[7]

Conclusion

The variables affecting vision in myopes is multifactorial. The higher order aberrations, size of the pupil, stretching of the photoreceptors, reduced retinal sampling and the contribution of postreceptor neural factors play a role. With AO we are now able to understand the placement of the photoreceptors with respect to the AL in myopes. In myopic patients with good visual acuity cone density around the fovea depends on the quadrant, distance from the fovea as well as the AL. The strength of the relation of AL with cone density depends on the quadrant and distance. Further research on the relation between cone density, visual acuity, psychophysical tests and micro-perimetry may help us understand the structural and functional vision of these patients. This may aid us better in counseling our patients, e.g., prior to any refractive or retinal surgical procedure.

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