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Evaluation of Macular Pigment Optical Density in Healthy Eyes Based on Dual-Wavelength Autofluorescence Imaging in South Indian Population

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Purpose: To estimate macular pigment optical density (MPOD) values across different age groups in the South Indian population across various spatial profiles using dual-wavelength autofluorescence.

Methods: Sixty eyes of 31 healthy subjects underwent MPOD measurement with Spectralis HRA+OCT. The average MPOD and macular pigment optical volume (MPOV) at 1°, 2°, and 6° radii, the mean MPOD in the classical Early Treatment Diabetic Retinopathy Study (ETDRS) grid, and the spatial profiles of two different age groups across 12 plots covering the radial sectors were recorded.

Results: The mean age was 39.1 ± 12.7 years. The mean MPOD and MPOV values were 0.38 ± 0.11 and 787.95 ± 225.13 at 1° eccentricity, 0.23 ± 0.08 and 2000 ± 708.24 at 2° eccentricity, and 0.05 ± 0.02 and 4335 ± 2007.71 at 6° eccentricity, respectively. In the ETDRS grid, the mean MPOD was found to be highest in the central sector and lowest in the inferior peripheral ring. We also found that along the radial sectors the lower quadrants tended to have low MPOD as compared to the upper quadrants. Subjects 40 years of age or older had significantly higher averaged MPOD in certain areas (−15° to 15° and 75° to 105°) along the radial sectors than subjects less than 40 years of age.

Conclusions: This study establishes a reference value for future studies of diseased eyes in the South Indian population.

Translational Relevance: Our study is unique in that it reports MPOD among the South Indian population across different age groups, as well as the distribution of MPOD in all nine zones of the classical ETDRS grid and various spatial profiles covering the 30° radial sectors centered on the fovea.

Introduction

Macular pigment (MP), composed of hydroxycarotenoids (lutein, zeaxanthin, and meso-zeaxanthin), has been shown to enhance visual function in humans and is postulated to protect against age-related macular degeneration.[1,2] Previous studies have suggested that the spatial distribution of MP correlates with structural characteristics of the fovea, including the steepness, width, and depth of the foveal pit.[3] The optical density of macular pigment, known as macular pigment optical density (MPOD), peaks at the center of the foveola and characteristically decreases until it starts to plateau at approximately 6° to 8° eccentricity. Previous studies on normal eyes showed that MPOD measurement by dual-wavelength autofluorescence (AF) has an overall good intra-session and inter-session repeatability.[4,5] Previous studies have also shown good agreement between dual-wavelength autofluorescence technique and psychophysical techniques such as

heterochromatic flicker photometry and motion photometry.[5–8] Several studies have confirmed a bimodal spatial distribution of MP that is characterized by a central peak of highest MP density surrounded by a ring with high-density values at approximately 0.7° from the fovea.[9–11] However, most of these values are represented as rings of various diameters centered on the fovea. To correlate MPOD with macular structural characteristics, it may be necessary to estimate the values along 30° radial sectors centered at the fovea and with the classical Early Treatment Diabetic Retinopathy Study (ETDRS) grid, which is used in describing optical coherence tomography (OCT)-related parameters in diabetic retinopathy.[12] This approach is more robust in the case of radial asymmetry of MP and could help to determine spatial correlations among color fundus photographs, OCT thickness values, and MPOD in health and in disease. The aim of the present study was to estimate MPOD values across different age groups in an Indian population across various spatial profiles using dual-wavelength autofluorescence.

Methods

The data were collected from 60 eyes of 31 subjects of South Indian origin between June 2019 and October 2019. We included subjects with best-corrected visual acuity (BCVA) of 20/20 or better, intraocular pressure of ≥10 mm Hg and ≤21 mm Hg, and spherical equivalent of ±4.0 diopters (D) and who had no ocular or systemic diseases. The exclusion criteria were the presence of any ocular disease or opaque ocular media (clinically significant cataract or cataract leading to a decrease in visual acuity), intraocular surgery or previous trauma, use of carotenoids and/or vitamin or antioxidant supplementation, diabetes, hypertension or other metabolic diseases, family history of age-related macular degeneration, and current or past smoking. The study was approved by the institutional review board (Ethics Committee), Vision Research Foundation, and a written informed consent was obtained from the subjects per the tenets of the Declaration of Helsinki. Demographic data including age, sex, and education were collected. A comprehensive ocular examination was conducted; the pupils of all of the participants were dilated (using tropicamide 0.5 mg/mL) to ≥6 mm in diameter followed by assessment of MPOD with the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). All of the subjects were naive with regard to performing psychophysical tasks.

MPOD Measurement

MPOD was measured with a dual-wavelength (excitation, 486 and 518 nm) autofluorescence method with Spectralis HRA + OCT after pupil dilation. Initial camera alignment, illumination, and focus were performed in infrared mode and were optimized after switching on simultaneous blue- and green autofluorescence imaging (BAF+GAF). Subjects' photopigments were bleached by the bright AF excitation lights for a time period of ∼30 seconds, while maintaining fixation. Under the same conditions, a 30-second BAF+GAF video was subsequently recorded. These videos were inspected for loss of fixation during the MPOD measurement, and if the subject's fixation was poor the measurements were repeated. Subsequently, a raster OCT scan centered on the foveola and covering 30° × 30° posterior pole was performed for clinical purposes. All images were collected by the same technician under the same light conditions with the same AF excitation intensity.

Estimation of MPOD and Its Spatial Distribution

Heidelberg Eye Explorer software (HEYEX, version 6.12.4.0) was used to align and average the images in the videos, and an MP density map was created. For analysis, the plateau (the reference point for assumed absence of MP) was set to 6° eccentricity automatically. The average MPOD at 1° and 2° radii and sum of macular pigment optical volume (MPOV) corresponding to the eccentricities of 1°, 2°, and 6° radii were recorded (Fig. 1).

The grid most commonly used to represent retinal thickness data was established by the ETDRS.[13] The cells of ETDRS grids divide the retina into nine large regions based on a central foveal ring 1 mm in diameter, an inner macula ring (pericentral) 3 mm in diameter, and an outer macula ring (peripheral) 6 mm in diameter. These three inner and outer rings are further divided into four quadrants: nasal, temporal, superior, and inferior. Our MPOD data were represented in these nine locations.

The final MPOD data were exported and analyzed using customized ImageJ software (National Institutes of Health, Bethesda, MD). The output from the ImageJ plugin includes a grayscale (floating) MPOD image, a colorized version of the MPOD image, 12 plots of MPOD as a function of eccentricity covering the radial sectors (15°, 45°, … , 345°), and the average MPOD values of the ETDRS grid (zone 1, central foveal; zones 2–5, pericentral; zones 6–9, peripheral). The MPOD values were measured in density units

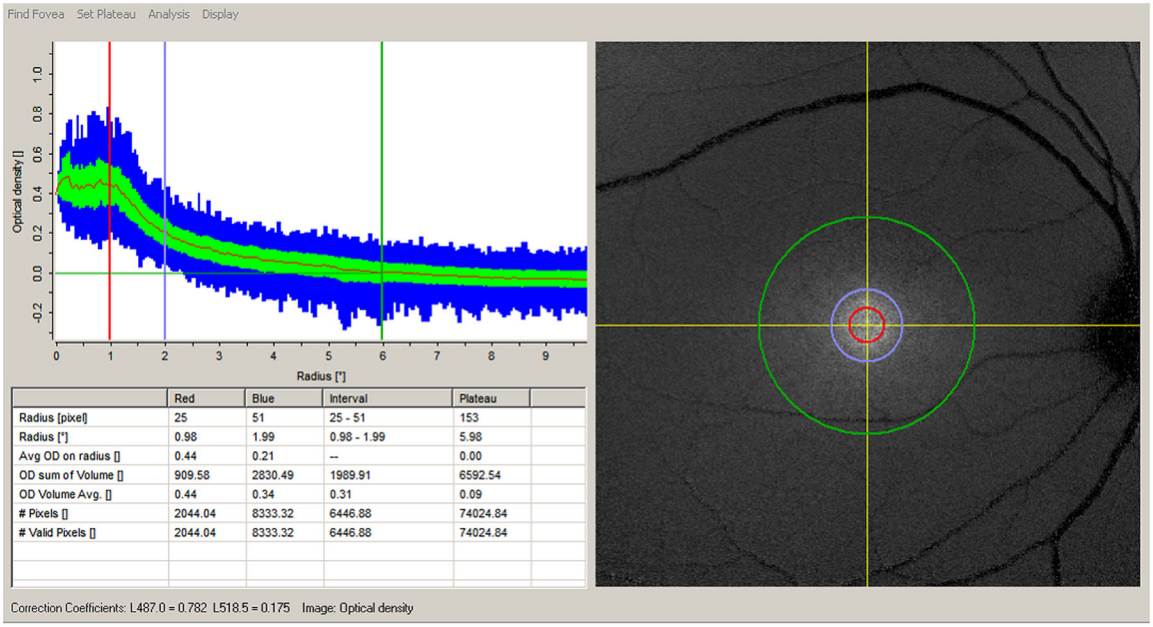

Figure 1. Example of MPOD analysis by Heidelberg Eye Explorer software based on dual-wavelength autofluorescence.

Table 1. Demographic Data

Demographic	Value
Subjects enrolled, *n*	31 (60 eyes)
Male/female, *n*	12/19
Age (y), mean ± SD (range)	39.10 ± 12.74 (21–65)
20–40 y, *n* (%)	13 (41.9)
41–65 y, *n* (%)	18 (58.1)
South Indian ethnicity, %	100
BCVA (Snellen equivalent), mean (range)	20/20 (20/20–20/20)
Refractive error (range)	–3.00 to +2.00 DS
Phakic/pseudophakic lens status, *n*	57/3

(d.u.), and the MPOD volume corresponds to the sum of the optical density values at all points, expressed as d.u.degrees^2.

Statistical Analysis

SPSS Statistics 21 (IBM Corp., Armonk, NY) was used for analysis. Data are presented as mean ± SD throughout. The data were tested for normality using the Shapiro–Wilk test. The Wilcoxon test for paired data was used to check for the presence of a significant difference between the MPOD variables (mean MPOD and MPOV) measured in the right and left eyes. Linear regression analysis was used to determine whether there was any correlation between the mean MPOD at 1° eccentricity and age. Independent-samples *t*-tests were used to check for the existence of a significant difference between the mean MPOD (along the radial sectors) and different age groups in normally distributed data, and Mann–Whitney test was used for non-normally distributed data. $P < 0.05$ was considered statistically significant.

Results

A total of 60 eyes of 31 subjects who met the inclusion and exclusion criteria were recruited for the study. There were 12 males and 19 females. The mean age was 39.10 ± 12.74 years (range, 21–65). The demographic characteristics of the participants are summarized in Table 1. The mean MPOD was 0.38 ± 0.11 d.u.

Table 2. Macular Pigment Optical Density Values at 1°, 2°, and 6° Eccentricity

Variable	Radius Eccentricity		
	1°	2°	6°
Mean MPOD (d.u.)			
All	0.38 ± 0.11	0.23 ± 0.08	0.05 ± 0.02
Male	0.37 ± 0.13	0.23 ± 0.10	0.05 ± 0.03
Female	0.39 ± 0.09	0.24 ± 0.07	0.05 ± 0.02
Age, <40 y	0.35 ± 0.09	0.20 ± 0.07	0.04 ± 0.02
Age, ≥40 y	0.40 ± 0.11	0.26 ± 0.08	0.06 ± 0.02
Minimum MPOD (d.u.)			
All	0.11	0.04	0.00
Male	0.11	0.04	0.00
Female	0.19	0.08	0.00
Age, <40 y	0.19	0.08	0.01
Age, ≥40 y	0.11	0.04	0.00
Maximum MPOD (d.u.)			
All	0.67	0.41	0.11
Male	0.67	0.41	0.11
Female	0.55	0.38	0.11
Age, <40 y	0.55	0.34	0.09
Age, ≥40 y	0.67	0.41	0.11
Mean MPOV (d.u.degree^2)			
All	787.95 ± 225.13	2000 ± 708.24	4335 ± 2007.71
Male	760.87 ± 276.62	1929.27 ± 835.02	4346.77 ± 2381.02
Female	806 ± 185.32	2048.11 ± 617.77	4328.66 ± 1751.83
Age, <40 y	734.91 ± 204.23	1728.54 ± 599.58	3551.27 ± 1532.67
Age, ≥40 y	828.51 ± 234.81	2208.59 ± 722.26	4935.93 ± 2137.94

(range, 0.11–0.67) at 1° foveal eccentricity and was 0.23 ± 0.08 d.u. (range, 0.04–0.41) at 2° foveal eccentricity. Figure 2 shows the frequency distribution of the MPOD values at 1°, 2°, and 6° foveal eccentricities. The mean MPOV was 787.95 ± 225.13 d.u.degrees^2 (range, 234.89–1359.52) at 1° foveal eccentricity, 2000 ± 708.24 d.u.degrees^2 (range, 367.05–3415.44) at 2° foveal eccentricity, and 4335 ± 2007.71 d.u.degrees^2 (range, 118.54–7923.40) at 6° foveal eccentricity. Table 2 shows the mean MPOD values at 1°, 2° and 6° eccentricity.

The linear regression of age and mean MPOD at 1° foveal eccentricity is shown in Figure 3. There was low but positive correlation between mean MPOD and age ($R^2 = 0.084$; $P = 0.02$). The odds ratio from the two-eye analysis, with inter-eye correlation adjusted using generalized linear mixed models, was 0.003 (95% confidence interval [CI], 0.001–0.005; $P = 0.024$); the odds ratio determined using a generalized estimating equation with a working independence correlation matrix and with a compound symmetry correlation matrix was 0.003 (95% CI, 0.002–0.003; $P < 0.0001$). There was no statistically significant difference in the comparison between mean MPOD and gender. There were no statistically significant differences in MPOD values among myopic, emmetropic, and hyperopic subjects. There was also no statistically significant difference between the MPOD values of left eyes and right eyes.

The distribution of mean MPOD along the ETDRS grid is shown in Figure 4A,with maximum MPOD in the central foveal ring. The mean MPOD was lower in the pericentral ring and lowest in the peripheral ring. In the pericentral ring, the distribution was more or less uniform, and slightly lower mean MPOD was found in the inferior pericentral sector; however, in the peripheral ring, the inferior sector had the lowest MPOD. Twelve plots of mean MPOD covering the 30° radial sectors are shown in Figure 4B; higher values were found in the superior sectors compared to the inferior sectors, and the lowest was found in the 225° to 255° sector. Figure 5 shows the mean MPOD values of two different age groups across 12 spatial profiles. The age

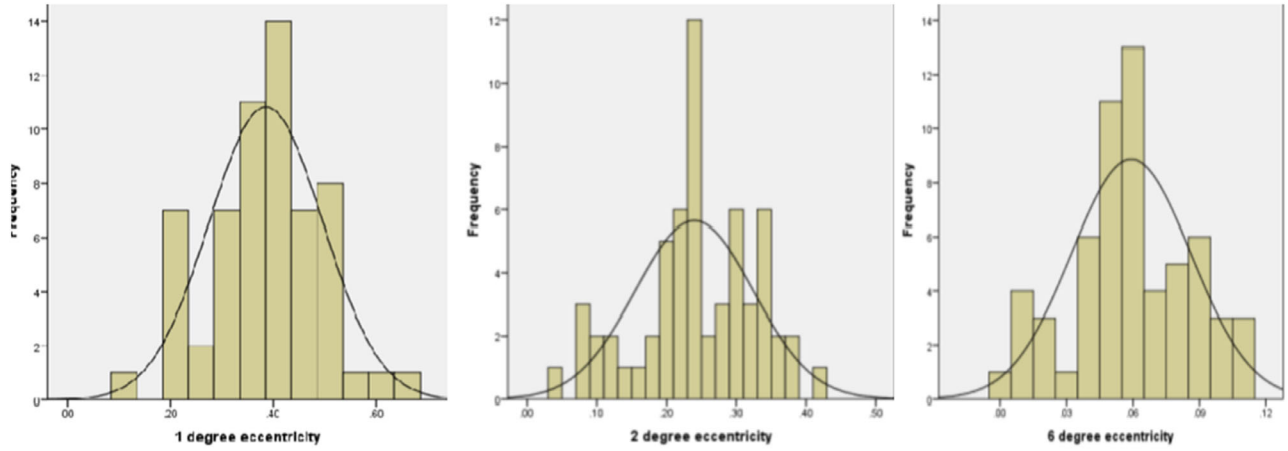

Figure 2. Frequency distribution of MPOD at the three foveal eccentricities.

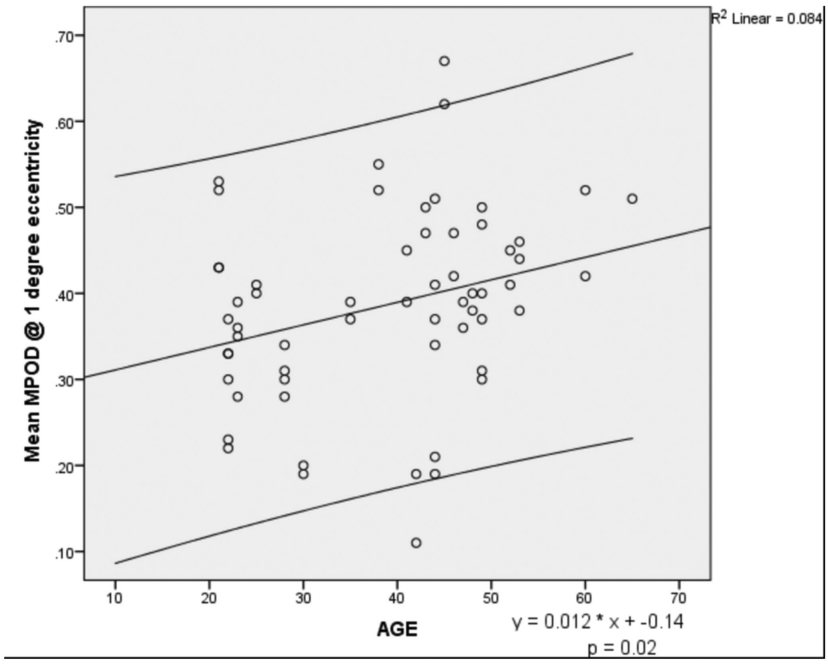

Figure 3. Linear regression of age and mean MPOD at 1° foveal eccentricity.

groups include under 40 years of age (43.3%) and ≥40 years of age (56.7%). There was a significant difference in specific areas of the spatial profile, including the –15° to 15° (nasal) and 75° to 105° (superior) radial sectors.

Discussion

In this study, we found that in a wide range of ages (21–65 years) among the South Indian population, the mean MPOD and volume as measured by dual-wavelength autofluorescence imaging was 0.38 ± 0.11 d.u. and 787.95 ± 225.13 d.u.degree^2 at 1° foveal eccentricity. There was low but positive correlation between mean MPOD and age. There was no statistically significant gender difference in the MPOD variables (mean and volume). For the MPOD frequency distributions at the three foveal eccentricities, we found an exponential decrease in MPOD with increasing eccentricity from the fovea. In the ETDRS grid, the distribution of mean MPOD was found to be highest in the central foveal ring and lowest in the inferior peripheral ring. We also found that, along the radial sectors, the inferior quadrants tended to have lower mean MPOD compared to the superior quadrants. We found that

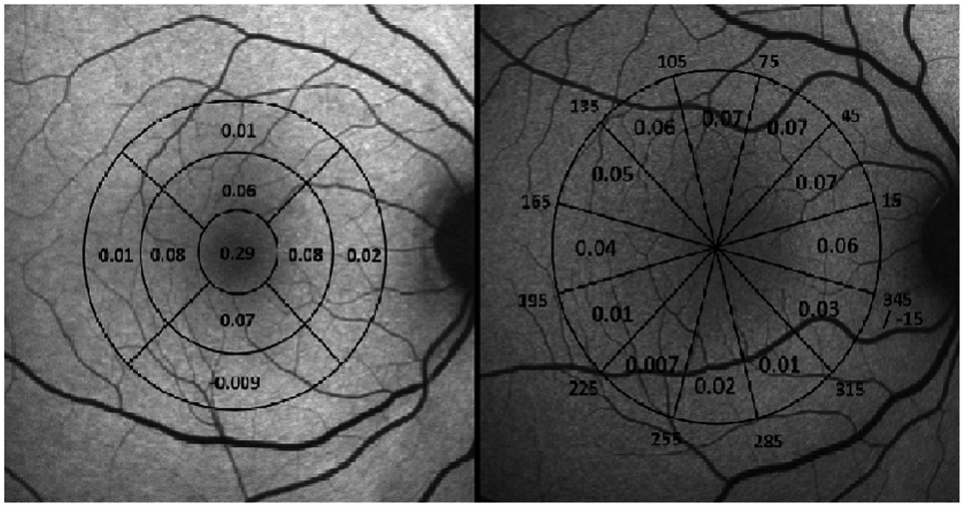

Figure 4. (**A**) Mean MPOD of the ETDRS grid (zones 1–9). (**B**) Radial sector analysis results for mean MPOD.

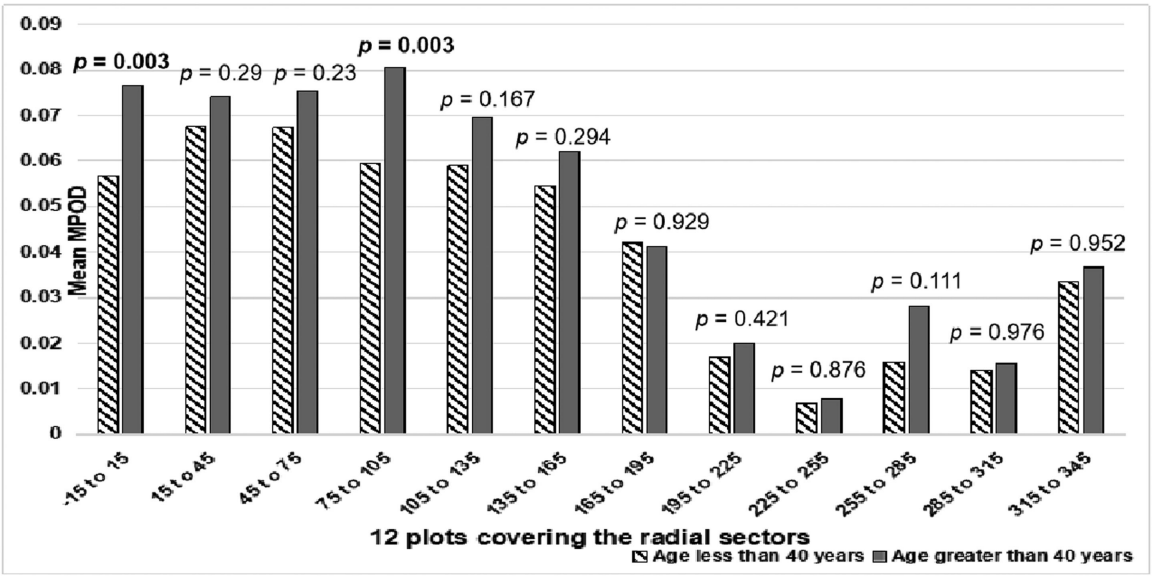

Figure 5. Mean MPOD for two different age groups across 12 spatial profiles.

MPOD had a positive correlation with age and showed the highest mean values in the –15° to 15° and 75° to 105° radial sectors.

The mean MPOD of the entire healthy study population was 0.38 ± 0.11 at 1° eccentricity as determined using dual-wavelength autofluorescence imaging with the Spectralis device. The normal mean value of MPOD in an adult South Indian sample was reported to be 0.37 ± 0.19 at 1° in a previous study using heterochromatic flicker photometry, similar to what we found.[14] Likewise, previous studies have shown good agreement between dual-wavelength autofluorescence technique and psychophysical techniques.[5–8] You et al.[4] demonstrated high reproducibility of MPOD measurements with Spectralis. It is believed that different populations have different distributions of MPOD, including those in Australia (0.41 ± 0.20 d.u.),[15] South Asia (0.43 ± 0.14 d.u.),[4] China (0.303 ± 0.097 d.u.),[17] Central Europe (0.126 ± 0.004 d.u.),[18] and Brazil (0.14 ± 0.05 d.u.).[19] These findings indicate that differences can be due to differences in ethnicity, geographical location, lifestyle, and dietary habits.

This study did not find a significant difference in the MPOD values (mean and volume) between men and women. Previous reports also found no correlations between MPOD values and gender,[15,17,18,20] although higher MPOD values have been reported in men[16,21] or women.[22] We found a low but positive correla-

tion between mean MPOD at 1° eccentricity and age ($R^2 = 0.084$; $P = 0.02$). Jorge et al.[19] also showed a similar correlation between mean MPOD and age ($R^2 = 0.37996$; $P < 0.001$) in Brazilian subjects evaluated using a VISUCAM 500 digital fundus camera (Carl Zeiss Meditec, Jena, Germany). In our study, the mean MPOD was found to be higher in the age group comprised of those ≥40 years old. Lam et al.[23] also found that the highest average MPODs were recorded in the 40- to 59-year-old age group. Berendschot et al.[24] found an increased tendency of age and MPOD in people older than 55 years. In a previous study, the normative data for an adult South Indian population indicated that the macular pigment level increased up to the 30- to 39-year-old age group and then declined at all eccentricities.[14] This negative correlation of age and MPOD has been seen in other studies.[21,23–25] Ciulla et al.[26] did not find a correlation between age and MPOD in an age group between 18 and 50 years, whereas Ji et al.[17] reported a reduction in MPOD with increasing age.

We found no significant difference in MPOD values obtained from right eyes and left eyes. Davey et al.[27] reported that MPOD values obtained from one eye can predict the value of the fellow eye with an accuracy of 89%. In healthy subjects, results of one eye could be an indicator of an individual's MPOD measurements. We found no statistically significant differences in MPOD values and refractive error. This is consistent with results of Jorge et al.[19] and Zheng et al.[28]

To the best of our knowledge, our study is unique in that it examined MPOD in the classical ETDRS grid and the various spatial profiles across radial sectors centered on the fovea. The localization of MP within the retina has been reported to be in the fibers of Henle at the fovea, whereas in the parafovea MP is located in the inner and outer plexiform layers.[29] The morphology and thickness of these layers change across the retinal topography; thus, the distribution across the retina is expected to vary across different zones. Previous studies have shown that the spatial profile of MPOD is related to an individual's foveal architecture. Foveal thickness and foveal width were positively correlated with MPOD.[30] When correlating OCT-related quantitative parameters at the macula, it would be useful to have MPOD values across the ETDRS grid.

In the ETDRS grid, the distribution of mean MPOD was reduced from the central foveal to peripheral rings. Previous studies have shown that MPOD decreases with increasing eccentricities.[4,14] The inferior grid sectors had lower MPOD than superior sectors. The exact reason for this differential MPOD density is not known. Because of the additional protection of a mobile upper eyelid, the need to protect against light-induced oxidative damage in the form of macular pigment density may be less in the inferior hemiretina. Snodderly et al.[29] described the spatial distribution of macular pigments in their histology experiments and concluded that photoreceptors contribute most to the macular pigment screening density until about 200- to 250-μm eccentricity. After that, the interneurons make an equal or greater contribution to the filtering effect.[2,10] Differences in the thickness of plexiform layer may account for differences in MPOD in the superior and inferior retina. The normative data of Mwanza et al.[32] showed that the ganglion cell–inner plexiform layer was thinner inferiorly compared to superiorly. These factors may account for lower MPOD values in the inferior peripheral grid. Likewise, we also found low mean MPOD in the inferior radial sectors. Analysis of MPOD across these sectors also offers the opportunity to explore structural correlations with macular lesions in retinal diseases.

The age group 40 years of age or older showed significantly higher mean MPOD in the –15° to 15° (nasal) and 75° to 105° (superior) sectors ($P = 0.003$). Although the mean MPOD profiles are well fit by an exponential function at various points of eccentricities, different age groups had different spatial profiles along these sectors which differed from the values at single points of eccentricity. Comparisons between the age groups of ≥40 years and <40 years suggest that temporal changes with increasing age probably do not also cause a uniform increase in MPOD across all areas of the retina. The significant increase that occurs at the nasal and superior quadrants could be due to higher retinal thickness in the nasal quadrant and perhaps to greater oxidative stress in the superior versus inferior retina.

This study had a few limitations. We did not track the dietary information or measure the serum lutein and zeaxanthin levels of the participants in relation to the MPOD levels. Being a descriptive study, we did not examine the factors that might influence MPOD levels except age and sex. We looked at the effect of self-screening by visual pigment (VP) and bleaching of VP through Spectralis MPOD measurements. This method relies on univariance (i.e., macular pigment being the only difference between the measuring and reference sites), which could be a general failing of this technique.

In summary, we determined MPOD values (mean and volume) at 1°, 2°, and 6° radii of eccentricity, as well as mean MPOD values in the classical ETDRS grid and at the various spatial profiles across radial foveal sectors using dual-wavelength autofluorescence. This study established a reference value for

future studies on diseased eyes in the South Indian population.

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