Differences in macular pigment optical density across four ethnicities: a comparative study

Pinakin Gunvant Davey, Christopher Lievens and Stephanie Amonoo-Monney

Abstract
Objective: The aim of this study is to compare macular pigment optical density levels across four different ethnicities and study its influence on ganglion cell layer and retinal nerve fibre layer thickness across these ethnicities.

Methods: Consenting adults visiting the ophthalmology and optometry clinics for a routine eye examination without any ocular comorbidity were enrolled. Participants underwent optical coherence tomography for macular thickness, retinal nerve fibre layer thickness and ganglion cell layer thickness. The macular pigment optical density levels were determined in the dominant eye using the QuantifEye device by trained observers.

Results: In total, 336 eyes of 336 participants with a mean age of 39.2 ± 14.4 years were included of which 103 (30%) were Caucasians, 111 (33%) were African Americans, 29 (9%) were South Asian Indians and 94 (28%) were Hispanics. The mean macular pigment optical density value across the entire study population was 0.47 ± 0.15. South Asian Indians (0.58 ± 0.16) and Hispanics (0.52 ± 0.15) had significantly higher mean macular pigment optical density values compared with Caucasians (0.41 ± 0.16) and African Americans (0.38 ± 0.15). Linear regression analysis showed that there was a significant association between ethnicities and macular pigment optical density values when adjusted for age (β coefficient = 0.31, 95% confidence interval = 0.029–0.58, p < 0.001 for South Asian Indian and Hispanic ethnic groups compared with African Americans). There were no differences in the retinal nerve fibre layer and ganglion cell layer thickness across ethnic groups. Linear regression analysis also did not reveal any significant association between macular pigment optical density levels and retinal nerve fibre layer or ganglion cell layer thickness.

Conclusion: Caucasians and African Americans have lower macular pigment optical density compared with South Asian Indians and Hispanics. There is no clinically significant association between macular pigment optical density levels and retinal nerve fibre layer and ganglion cell layer thickness in healthy individuals across races.

Keywords: carotenoids, lutein, macula, macular pigment optical density, retinal nerve fibre layer, zeaxanthin

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Introduction
Macular pigment, seen as an area of yellowish pigmentation in the centre of the fovea, is composed of three carotenoids: lutein, zeaxanthin and meso-zeaxanthin. These pigments have been postulated to have antioxidant properties that prevent light-induced damage to macular photoreceptors.1–3 In addition, these pigments also absorb the shortwave blue light and help in reducing chromatic aberrations and glare sensitivity.2 Some studies have shown that there is gradual reduction in the amount of macular pigments with age4,5 and subjects with age-related macular degeneration (AMD) have significantly reduced levels of macular pigment

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compared with age-matched controls of those with the disease. There is also mounting evidence that the risk of AMD is reduced and the course of disease altered with improved dietary supplementation of lutein and zeaxanthin. The Age-Related Eye Disease Study 2 (AREDS2), the largest and most robust study on AMD, has shown clear benefits in reducing the risk of progression of AMD with supplemental macular pigments in the AREDS formulation.

Many epidemiological studies have shown racial differences in the incidence of AMD, especially the relatively lower risk of AMD among the African American population compared with Caucasians. Other studies have compared the levels of macular pigment optical density (MPOD) across different populations and have reported racial differences in MPOD levels, with Caucasians having significantly lower MPOD levels compared with African Americans and South Asians. Therefore, it is possible that racial differences in AMD incidence could be attributed to the racial differences in MPOD levels, though no large-scale epidemiological study has shown this consistently across the major races.

In addition to incidence of AMD, racial differences have been observed in the incidence and mechanisms of glaucoma across the globe with higher incidence of open angle glaucoma in African Americans and more angle closure in Asian ethnic groups. The incidence of glaucoma also increases with age, similar to AMD. As the macular pigments have antioxidant properties which may be protective for photoreceptors, this may also potentially influence and improve survival of retinal ganglion cells [ganglion cell layer (GCL)] under various oxidative stresses such as seen in glaucoma due to raised intraocular pressure. Studies have shown that individuals with primary open angle glaucoma may have lower MPOD, particularly the individuals who have foveal involvement with glaucomatous damage. Thus, it may be postulated that lower MPOD levels may also predispose to lower number of GCL leading to thinner GCL layer and retinal nerve fibre layer (RNFL).

While many previous studies have compared the MPOD levels across races, most have involved two races in the same setting and many have been limited by small sample sizes. We sought to compare MPOD levels across four different ethnicities in the same setting and also explored the hypothesis of racial differences in MPOD levels influencing GCL and RNFL thickness across these population groups.

Methods
This was a cross-sectional observational study involving healthy patients visiting the Western University of Health Sciences (Pomona, California) and Southern College of Optometry (Memphis, Tennessee). The study was approved by the institutional ethics committee at both institutions separately and was performed according to the tenets of the Declaration of Helsinki. The approval numbers were Western University of Health Sciences # 13/IRB/008, and the Southern College of Optometry IRB # IRB0000673. A signed informed consent was obtained from all patients before enrolment and the study execution complied with the Health Insurance Portability and Accountability Act (HIPAA).

All patients visiting the ophthalmology and optometry clinics for a routine eye examination were invited to enrol for the study at the two centres. Recruitment was enhanced further by advertising using flyers and individuals could participate in the study by choice. Inclusion criteria included age (over 18 years), best-corrected vision of 20/20 using the logMAR vision chart, and normal ophthalmic evaluation anytime during the past year. Patients from four ethnicities – Caucasians, African Americans, South Asian Indians and Hispanics – attending the clinics were enrolled in the study. The ethnic group was determined by patients’ self-reporting.

All consenting subjects underwent a comprehensive dilated eye examination at the time of recruitment, including recording of demographics such as age and gender, best-corrected visual acuity (BCVA), intraocular pressure using the ocular response analyser or Goldmannplanation tonometer, slit lamp examination for anterior segment findings and fundus evaluation to detect any pathology in the optic nerve, macula or peripheral retina. Following examination, all patients underwent digital fundus photography using a camera system with 5 megapixel resolution (Visucam Pro, Carl Zeiss Meditec, Jena, Germany) and optical coherence tomography (OCT; Cirrus, Carl Zeiss Meditec) using the raster scan for macular thickness and the glaucoma module to record the RNFL thickness and GCL layer thickness using automated image
analysis provided by the OCT machine. The RNFL thickness was reported in four quadrants centred on the optic disc, and the GCL thickness was reported in six regions centred on the fovea.

The dominant eye was determined using the Miles technique as described before. The MPOD levels were determined in the dominant eye using the QuantifEye (ZeaVision, St. Louis, MO, USA) device by trained observers. All participants were shown a brief tutorial explaining the procedure of testing as well as a picture of what target will be visible during testing. The precise technique used for obtaining the MPOD values is described elsewhere. Briefly, the in vivo measurement of MPOD levels by QuantifEye was based on the heterochromatic flicker photometer (HFP). The ability of the macular pigment to absorb blue light of short wavelength and not green-yellow light of longer wavelength was utilized to determine the optical density of the macular pigment at the central 0.5° around the centre of the fovea by the machine and was displayed as the final MPOD level after accounting for the built-in correction factor for the age-related yellowing of the lens.

Statistical analysis

All continuous variables were expressed as mean with standard deviation of median with interquartile range (IQR) and categorical variables were expressed as proportions (n, %). Group differences in continuous variables between two groups were analysed using the Student’s t-test or the Wilcoxon Rank-Sum Test, and between four ethnic groups using the one-way analysis of variance (ANOVA). The homogeneity of variance assumption as tested by Levene’s test of homogeneity of variances was reasonably satisfied and not violated. A two-way ANOVA was also conducted to examine the effect of age and ethnicity on mean MPOD value in the dominant eye. Differences in categorical variables between groups were determined using the chi-square or Fischer’s exact test. A linear regression analysis was used to explore the association between the mean MPOD and different ethnicities after adjusting for age. Similarly, univariate linear regression analysis was also carried out to find an association between mean MPOD values and RNFL and GCL layer thickness. Outcomes of linear regression were expressed as coefficient with 95% confidence interval (CI). The correlation between MPOD levels and RNFL and GCL thickness was analysed using the Pearson’s correlation coefficient and plotted using locally weighted scatterplot smoothing. For a very modest correlation coefficient of \( r = 0.2 \) and alpha of 0.05 and beta of 0.1, a sample size of at least 259 was determined to provide statistically significant association.

Results

We included 336 eyes of 336 patients of which 103 (30%) were Caucasians, 111 (33%) were African Americans, 29 (9%) were South Asian Indians and 94 (28%) were Hispanics. The mean age of participants was 39.2 ± 14.4 years (range = 18–81 years) and 122 (36%) were men. South Asian Indians were significantly younger than participants from other races (Table 1). The overall MPOD value across the entire study population was 0.47 ± 0.15. There were statistically significant differences in the MPOD value across the ethnic groups (Table 1) with African Americans having the least and South Asian Indians having the highest values. Figure 1 shows distribution of MPOD values between the ethnic groups. In group-wise comparisons, there was no difference in the MPOD values between Caucasians and African Americans (\( p = 0.31 \)) and between South Asian Indians and Hispanics (\( p = 0.26 \)). However, the difference between South Asian Indians and Caucasians and African Americans was statistically significant (\( p < 0.001 \) for both). Similarly, the difference in MPOD values between Hispanics and Caucasians (\( p < 0.001 \)) and African Americans (\( p < 0.001 \)) was also significant. There were no gender differences in the MPOD values across the groups (\( p = 0.97 \)). There were no differences in the RNFL and GCL thickness across ethnic groups either (Table 1).

The MPOD values did not significantly vary with increasing age (Table 2). Linear regression analysis showed that there was significant association between ethnicities and MPOD values when adjusted for age (\( \beta \) coefficient = 0.31, 95% CI = 0.029–0.58, \( p < 0.001 \) for South Asian Indian and Hispanic ethnic groups compared with African Americans; Table 2). The average RNFL and GCL thickness showed a significant negative correlation with age (\( r = -0.263 \) and -0.291 respectively, \( p < 0.001 \) for both). However, there was no correlation between MPOD levels and RNFL (Figure 2) or GCL thickness (Figure 3). Linear regression analysis also did not reveal any significant association between MPOD levels and RNFL or GCL thickness (Table 2).
### Table 1. Comparison of demographics and MPOD between ethnicities.

| Variable                      | Caucasian     | African American | Asian    | Hispanic  |
|-------------------------------|--------------|-----------------|---------|-----------|
| Age (mean, SD)**              | 38.8, 14.5   | 42.0, 15.5      | 29.1, 9.2 | 39.6, 13.1 |
| Gender (% Men)                | 45.6%        | 35.1%           | 28.6%   | 34%       |
| MPOD value in DE (mean, SD)** | 0.41, 0.16   | 0.38, 0.15      | 0.58, 0.16 | 0.52, 0.15 |
| Average RNFL thickness (mean, SD) | 92.9, 13.1 | 95.1, 11.6      | 93.4, 9.6 | 96.6, 8.8 |
| RNFL-1 (S)                    | 112.5, 18.7  | 121.2, 19.2     | 120.5, 23.2 | 118.6, 19.3 |
| RNFL-2 (N)                    | 71.6, 15.7   | 73.9, 11.3      | 68.6, 9.1 | 72.2, 12.9 |
| RNFL-3 (I)                    | 119.7, 22.3  | 124.2, 20.0     | 120.9, 14.2 | 128.3, 16.5 |
| RNFL-4 (T)                    | 67.7, 15.3   | 61.1, 10.5      | 67.5, 13.5 |           |
| Average GCL thickness (mean, SD) | 82.3, 5.7   | 81.4, 8.4       | 82.1, 5.9 | 84.0, 5.7 |
| GCL-1 (S)                     | 82.4, 5.7    | 82.8, 8.5       | 82.5, 6.0 | 84.6, 6.6 |
| GCL-2 (S-N)                   | 83.9, 6.0    | 84.0, 7.5       | 83.6, 7.2 | 86.2, 6.5 |
| GCL-3 (I-N)                   | 82.9, 6.2    | 81.7, 9.0       | 82.8, 6.9 | 84.2, 6.6 |
| GCL-4 (I)                     | 80.1, 6.0    | 79.4, 10.2      | 80.6, 5.6 | 82.1, 6.1 |
| GCL-5 (I-T)                   | 82.8, 6.3    | 80.7, 9.7       | 81.2, 5.6 | 83.8, 6.0 |
| GCL-6 (S-T)                   | 80.1, 10.1   | 80.0, 8.9       | 81.1, 6.2 | 83.1, 5.8 |

DE, dominant eye; GCL, ganglion cell layer; I, inferior; I-N, inferonasal; I-T, inferotemporal; MPOD, macular pigment optical density; N, nasal; RNFL, retinal nerve fibre layer; S, superior; SD, standard deviation; S-N, superonasal; S-T, superotemporal; T, temporal.

**Bold-**p<0.05 across groups.

**Figure 1.** Box and whisker plots for MPOD for the four ethnicities. DE, dominant eye; MPOD, macular pigment optical density.
Discussion

There are various methods to measure MPOD; although clinically the most popular method of measuring MPOD is using heterochromatic flicker photometry, there are objective techniques like reflectometry, autofluorescence and Raman spectroscopy that are in either research stages of development or available for use outside the United States. In the present study, we used a subjective, clinically validated technology QuantifEye that measured the overall MPOD in central macula. We found statistically significant differences in MPOD levels with the lowest values in African Americans and highest values in South Asian Indians, even after adjusting with age. Caucasians had values similar to African Americans whereas Hispanics had values very similar to South Asian Indians. Our data did not show decrease in MPOD values with increasing age, though RNFL and GCL thickness decreased significantly with advancing age. Although higher MPOD values were associated with greater RNFL and greater GCL thickness, the trend was not statistically significant.

Racial differences between MPOD levels have been reported before. Wolf-Schnurrbusch and colleagues studied the MPOD levels in 118 healthy subjects including 67 Caucasians and 51 African Americans using a confocal scanning laser ophthalmoscope-based technique and found significantly lower levels of MPOD in Caucasians (0.36 ± 0.13 versus 0.59 ± 0.14). We found no differences between Caucasians and African Americans in our study. Given that these studies are cross-sectional in design, it is difficult to be certain what caused the difference in outcome. The methodological differences due to difference in sample size selection in nutrition and dietary differences based on locations can also exist. In addition, the technology that was used to measure MPOD was based on different principles with Wolf-Schnurrbusch using confocal imaging which is an objective test, whereas the present study utilized heterochromatic flicker photometry a subjective test.

Obana and colleagues showed that the heterochromatic flicker photometry can be used to obtain reliable values of MPOD. The MPOD was measured in a group of Japanese individuals, and although not the primary aim of the study, MPOD measured using heterochromatic flicker photometry was 0.63 which is higher than reported in studies that have examined Caucasians.

Table 2. Regression analysis for factors predictive of MPOD.

| Variable                | Univariate linear regression analysis |
|-------------------------|--------------------------------------|
|                        | b coefficient | 95% CI          | p value |
| Age                    | -0.001        | -0.002 to .001  | 0.33    |
| Gender                 | 0.005         | -0.033 to .043  | 0.80    |
| MPOD valuesa           | 0.31          | 0.029 to 0.58   | <0.001b |
| Average RNFL           | -0.001        | -0.003 to .001  | 0.19    |
| RNFL-1 (S)             | -0.001        | -0.002 to .000  | 0.14    |
| DE RNFL-2 (N)          | -0.001        | -0.003 to .000  | 0.08    |
| DE RNFL-3 (I)          | -0.001        | -0.002 to .000  | 0.16    |
| DE RNFL-4 (T)          | 0.001         | .000 to .002    | 0.11    |
| Average GCL thickness  | 0.002         | -0.003 to .003  | 0.99    |
| GCL-1 (S)              | -0.001        | -0.003 to .002  | 0.46    |
| GCL-2 (S-N)            | 0             | -0.003 to .002  | 0.74    |
| GCL-3 (I-N)            | 0             | -0.003 to .002  | 0.82    |
| GCL-4 (I)              | 0             | -0.003 to .002  | 0.74    |
| GCL-5 (I-T)            | 0.001         | -0.002 to .003  | 0.57    |
| GCL-6 (S-T)            | 0.001         | -0.001 to .003  | 0.34    |

CI, confidence interval; DE, dominant eye; GCL, ganglion cell layer; I, inferior; I-N, inferonasal; I-T, inferotemporal; MPOD, macular pigment optical density; N, nasal; RNFL, retinal nerve fibre layer; S, superior; SD, standard deviation; S-N, superonasal; S-T, superotemporal; T, temporal.

aAsian Indian and Hispanic compared with African American.
bAge-adjusted p value.

Huntjens and colleagues studied differences in MPOD levels and its spatial distribution in 54 healthy, young South Asian and 19 Caucasian subjects of similar age using the same heterochromatic flicker photometry employed in our study and found that central MPOD was significantly greater in South Asian Indian (0.56 ± 0.17) compared with Caucasian subjects (0.45 ± 0.18). We found similar results in our patient population, though the number of South Asian Indians was smaller in our study. Yu and colleagues reported on MPOD levels from an ethnic Chinese population (n = 281) using the heterochromatic flicker photometry and found the mean MPOD to be 0.56 ± 0.19 at the centre of the fovea, a value similar to our results from the South Asian Indian cohort. Recently, Jorge and colleagues reported results from 103 healthy Brazilians, predominantly consisting of Hispanics, using a different imaging
modality (Visucam 500 Digital Fundus Camera from Carl Zeiss Meditec, in combination with the MPOD module) and reported a much low mean MPOD level of 0.14 ± 0.05. In another study from South India, Raman and colleagues\textsuperscript{27} studied the MPOD values in 60 healthy volunteers using a macular densitometer and reported similar values (0.64 ± 0.23 at 0.25° eccentricity, 0.50 ± 0.21 at 0.5°) as seen in our cohort of South Asian Indians.

The reason for racial differences in MPOD levels is unclear. Factors influencing MPOD levels include age, dietary intake of carotenoids, race, skin pigmentation, history of smoking, and differences in iris pigmentation.\textsuperscript{8,28–31} The strongest association appears to be related to the dietary intake of lutein and zeaxanthin and serum levels of these carotenoids. To the best of our knowledge, no study that found a strong association between dietary carotenoids and MPOD reports on racial differences in MPOD after adjusting for serum levels of carotenoids. Therefore, it is unclear whether racial differences in MPOD can be attributed to dietary differences. The highest

\begin{figure}[h]
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\caption{(a) Two-way scatterplot with a LOWESS curve for average RNFL with MPOD and (b) scatterplot for average RNFL with MPOD with four different LOWESS curves for the four ethnicities. AVG, average; DE, dominant eye; MPOD, macular pigment optical density; RNFL, retinal nerve fibre layer.}
\end{figure}
dietary levels of lutein and zeaxanthin are found in foodstuff such as green leafy vegetables, including basil, parsley and spinach, corn and wheat flour. The dietary patterns of Hispanics and Asian Indians include these ingredients as part of their daily meals twice a day where as these may be infrequently consumed by Caucasians and African Americans, especially corn (tortillas, chips, etc.) and wheat flour (roti – a type of flat South Asian bread) which are the richest sources of carotenoids. We believe that racial differences as seen from our study may be attributable to differences in dietary intake of these carotenoids. However, this postulation requires further research because we did not measure serum levels of lutein and zeaxanthin in our study. Also, the lack of food diary or dietary assessment is a short coming and we cannot be sure about the kind of dietary habits the participants followed. Another possible explanation would stem from having darker iris pigment and smaller pupil size in bright environment which may have prevented the harmful radiation from reaching the retina and hence preventing

Figure 3. (a) Two-way scatterplot with a LOWESS curve for average GCA with MPOD and scatterplot for average GCA with MPOD with four different LOWESS curves for the four ethnicities. AVG, average; DE, dominant eye; MPOD, macular pigment optical density; RNFL, retinal nerve fibre layer; GCA, Ganglion Cell Analysis.
depletion of MPOD. This hypothesis will require further investigation.

A reduction in the levels of MPOD has been shown to result in higher risk of AMD in many studies before.4,5,34,35 Similarly, racial differences have also been observed with lower risk of AMD in African Americans compared with Caucasians.11,12,17 However, longitudinal studies with long-term follow-up do not exist to implicate gradual loss of macular carotenoids and increased risk of AMD in different racial groups. It may be prudent to follow-up our cohort of patients over time to see development of signs of AMD such as drusen and retinal pigment alterations.

Racial differences in the risk of glaucoma have been established with South Asian Indians being at higher risk of angle closure and African Americans predisposed to open angle glaucoma.16,17 Previously, Igras and colleagues36 have shown that MPOD is lower in patients with glaucoma. In an exploratory analysis, we found no correlation or association between MPOD levels and RNFL and GCL thickness in our study population, though none of our patients had glaucoma. Also, this was a secondary outcome in our analysis and our study was not powered enough to find associations between MPOD levels and RNFL/GCL thickness. It is possible that in the absence of risk factors of glaucoma like elevated eye pressure, higher levels of MPOD do not offer much of a protection to observe a statistically significant or thicker RNFL and GCL. Whereas in the presence of elevated pressure and other risk factors of glaucoma, the RNFL and the GCL may benefit from an increased MPOD. So, we believe that the hypothesis that macular carotenoids exert a protective effect and improve survival of retinal ganglion cells requires further study in humans.

In conclusion, there are racial differences in the levels of macular pigment with Caucasians and African Americans toward the lower end of the spectrum and South Asian Indians and Hispanics at the higher end of the spectrum. These differences may be attributed to the dietary patterns in these populations, though this is speculative and requires further study. There is no association between MPOD levels and RNFL/GCL thickness in healthy individuals across races.

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Conflict of interest statement
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Pinakin Gunvant Davey is a consultant to ZeaVision on research studies not related to the material discussed in this paper. ZeaVision LLC provided grant for the study to Western University of Health Sciences.

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