Ethnic Differences in Macular Pigment Density and Distribution

Ute E. K. Wolf-Schnurrbusch,1 Nicole Röösi,1 Eva Weyermann,1 Mirjam R. Heldner,1 Katja Höhne,2 and Sebastian Wolf1

PURPOSE. Many epidemiologic studies suggest a number of risk factors that may be associated with progression of age-related maculopathy (ARM). In this study, the authors investigate ethnic differences in macular pigment density (MPD) and macular pigment (MP) distribution.

METHODS. Inclusion criteria were healthy subjects, aged 35 to 49 years, visual acuity ≥20/20, race ethnicity white non-Hispanic (WNH) or African. All subjects underwent the following examinations: best-corrected ETDRS visual acuity (VA), measurements of MPD, and spatial distribution of MP with a modified confocal scanning laser ophthalmoscope according to a standard protocol. MPD maps were calculated from autofluorescence images recorded at 488 nm and 514 nm. Central macular pigment density (MPDc) was quantified from MPD maps within 0.5° around the center of the fovea.

RESULTS. In total, 118 healthy subjects (61 women, 57 men) aged 35 to 49 years (mean, 42.5 ± 3.6 years) were recruited for the study. Sixty-seven healthy subjects were WNH and 51 were African. Visual acuity ranged from 20/20 to 20/16 in the study eye. Significant differences were found among MPDc between the group of WNH (MPDc, 0.36 ± 0.13 density units [DU]; P < 0.0001) and African subjects (MPDc, 0.59 ± 0.14 DU). A parafoveal ring was significantly more frequent in African subjects than in WNH subjects (86% [African] vs. 68% [WNH]; P < 0.0001).

CONCLUSIONS. This study demonstrates that ethnicity plays a role in MPD values and in MP distribution. The association of different distribution patterns and their relevance as possible prognostic factors for diseases leading to oxidative retinal damage requires further studies. (Invest Ophtalmol Vis Sci. 2007; 48:3783–3787) DOI:10.1167/iovs.06-1218

The pathogenesis of age-related macular degeneration (ARMD) remains putative. It is assumed to be a multifactorial disease leading to oxidative retinal damage.1–5 It is classified as the end stage of age-related maculopathy (ARM), which is characterized by degenerative disorder of the central area of the retina.6 Recent studies report that the incidence of ARMD strongly depends on the age of the person and the stage of ARM.7,8 Many epidemiologic studies suggest a number of risk factors that may be associated with progression of ARM. These include personal characteristics such as race and ocular characteristics such as iris pigmentation and macular pigment density (MPD).9–11

Highly significant risk factors, such as genetic variants of complement factors H and B, which occur in more than 50% of all patients with ARMD were recently observed.12–13 Most observers agree that ARMD is more common in white persons than in persons of African race.14 Congdon et al.11 reported in 2004 that the leading cause of blindness among white persons older than 40 in the United States is ARMD (54.4%), whereas among African persons it is 4.4%, indicating the possibility that protective genetic variants may exist in African persons. Previously, we showed15 that central macular pigment density (MPDc) is similar in patients with ARM and healthy controls, but we found a large variation in macular pigment (MP) distribution.

By analyzing autofluorescence images, Delori et al.16 found a variation in the spatial distribution of MP from a single central peak that decreased monotonically with increasing eccentricity to a bimodal distribution with a central peak surrounded by a ring with high-density values of MP. Berendschot et al.17 confirmed and strengthened their results after adding the technique of reflectance spectroscopy.

In this study, we investigated the ethnic differences of different patterns of MP distribution and their relation to MPDc in healthy subjects of various ethnic phenotypes. Most current studies about MP are mainly derived from white non-Hispanic (WNH) subjects, and only a few are derived from Asian subjects.18,19

MATERIALS AND METHODS

We included healthy subjects between 35 and 49 years of age with a race ethnicity of WNH or African. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject after explanation of the nature and possible risks of our study. Institutional Review Board approval was granted. In total we recruited 118 healthy subjects (61 women, 57 men) from 35 to 49 years of age (mean, 43 ± 4 years) for the study. Sixty-seven healthy subjects were WNH (35 women, 32 men) and 51 were African (26 women, 25 men). Visual acuity ranged from 20/20 to 20/16 in the study eye. Neither distribution of additional ARMD risk factors (e.g., gender, family history, status of smoking) nor mean age distribution differed between the groups (mean ageWNH: 45.0 ± 3.8 years vs. mean ageAfrican: 41.8 ± 3.3 years).

One eye of each subject was randomly selected and included in the study. All subjects underwent comprehensive ocular examination. The pupil of the study eye was dilated with eye drops containing 0.5% tropicamide and 2.5% phenylephrine. Macular pigment measurements were obtained with the modified confocal scanning laser ophthalmoscope (mPHRA; Heidelberg Engineering, Heidelberg, Germany)20 using autofluorescence images obtained at two wavelengths based on the pioneering work of Delori et al.31 Subjects were positioned in front of the tabletop and instructed to look straight ahead and to remain steady. We then obtained 20° autofluorescence images at excitation wave-
lengths of 488 nm and 514 nm of the posterior pole, with a high-pass filter transmitting at a wavelength greater than 530 nm.

As reported previously, we quantified macular pigment densities by calculating a MPD map and comparing foveal and parafoveal autofluorescence at 488 nm and 514 nm (Fig. 1). Density maps were processed to calculate MPDc within a 1°-diameter circle centered on the fovea. MPDc is expressed in optical density units (DU). All quantitative analyses were performed by the software provided by the manufacturer of the scanning laser ophthalmoscope.

In addition to the value of MPDc, we looked at the spatial distribution of MP. We assumed that the spatial distribution of MP is circularly symmetric around the fovea. Therefore, we calculated radial density profiles by calculating the mean MPD for each radius around the fovea. The mean MPD for each eccentricity was calculated by dividing the sum of all optical densities at a given radius by the number of pixels making up a circle at a given radius. These values were plotted against the distance to the fovea and were graphically displayed (Fig. 2). Density profiles were analyzed for the presence of a parafoveal

FIGURE 1. Modified confocal scanning laser ophthalmoscope (a). Autofluorescence images at 488 nm (b) and 514 nm (c). Wavelengths, absorbance spectrum of MP (d). Formula for calculation of MPD map (e). Three-dimensional image of spatial distribution of MP (f).

FIGURE 2. Screen shot of MP maps and distribution profiles. (a) Typical MP distribution with a central peak (MPD_{0.5}/MPDc = 0.50). (b) MP distribution with a parafoveal ring (MPD_{0.5}/MPDc = 0.74).
ring and for the location of the maximum of this parafoveal ring. A parafoveal ring was assumed to be present if the density profile could not be approximated by a monotonic decay function and a shoulder could be identified within 3° from the peak density. Because width at half maximum is a key descriptor of distribution, we analyzed our profiles looking for the width of the spatial macular pigment distribution. All profiles were examined by two independent observers. In the event of a discrepancy between the two observers, the differences were discussed and a third observer was asked for the final decision. Additionally, we calculated the mean MPD (MPD_{mpd}) within the interval between 0.5° and 1° radius around the fovea. We calculated the ratio MPD_{mpd}/MPDc to characterize the significance of the parafoveal ring.

Mean value and SD are given for all samples with normal distributions (Kolmogorov-Smirnov test) and for abnormal distributions, medians, and percentiles (2.5% and 97%). The Mann-Whitney U test was used to assess the significance of the differences between the groups. Findings with an error probability of < 0.05 were considered statistically significant; χ² analysis was used to determine the differences in frequency of the presence of a parafoveal ring among the different groups.

RESULTS

Significant differences were found among MPDc between the groups of WNH and African subjects (0.36 ± 0.13 DU vs. 0.59 ± 0.14 DU; P < 0.01; Fig. 3). The parafoveal ring was significantly more frequent in African subjects than in WNH subjects (44 of 51, 86% [African] vs. 46 of 67, 68% [WNH]; P < 0.01). The maximum of this parafoveal ring was found at 0.66° ± 0.13° (range, 0.48°–1.2°) from the fovea. The maximum of the ring was located at a mean of 0.67° ± 0.13° in the African subjects and at a mean of 0.64° ± 0.10° in WNH subjects. Width at half maximum, as a key descriptor of distribution, was significantly larger in African subjects than in WNH subjects (0.91° ± 0.23° vs. 0.75° ± 0.15°; P < 0.05).

Significant differences were found among the ratio MPD_{mpd}/MPDc between the groups of WNH and African subjects (0.77 ± 0.12 vs. 0.85 ± 0.09; P < 0.01; Fig. 4). The mean ratio MPD_{mpd}/MPDc was 0.86 ± 0.07 for subjects with a visible parafoveal ring compared with 0.71 ± 0.42 for subjects with a peak (P < 0.001). We could not detect any statistically significant effect of additional factors, such as family history of ARMD, smoking status, or iris color.

DISCUSSION

Various epidemiologic studies have focused on the analysis of risk factors for the development of ARM and ARMD.53–26 Besides other factors, MPD is under investigation as a predictive factor in the development of ARMD.4,15,27–29 Growing evidence indicates that oxidative damage contributes to the development of ARM4,30,31 and that MP protects against ARM and ARMD.4,27,54 though the latter remains unproven and is a matter of considerable controversy.55

It is proposed that MP protects the macular region by filtering blue light,54,55 presuming that cumulative ocular exposure to blue light is associated with the prevalence of ARM. Studies with laboratory animals have examined the effect of cumulative photochemical damage, and it has been shown that the threshold for retinal damage induced by different wavelengths of light falls exponentially with decreasing wavelength.56 Moreover, it has been shown that the pattern of light-induced retinal damage is similar to the pattern of degenerative changes observed in human eyes with ARMD. However, measuring lifetime light exposure in humans is difficult; therefore, epidemiologic evidence remains incomplete.57,58 In addition to its blue-light-filtering properties, the MP is capable of scavenging free radicals.52 In the photoreceptor outer segments, the antioxidant effect of lutein and zeaxanthin may be an important mechanism.4,59 Antioxidant properties enable the carotenoids to quench singlet oxygen.

We have examined a group of 118 healthy subjects with various ethnic phenotypes to obtain functional maps of MP based on autofluorescence images.22 We quantified mean macular pigment density (MPDc) in a 1°-diameter circle centered on the fovea.

We found significant differences among MPDc values between the groups of WNH and African subjects. MPDc in WNH subjects (0.36 ± 0.13 DU) was significantly lower than in African subjects (MPDc 0.59 ± 0.14 DU).

What factors could contribute to our observation of significant differences in MPD between the WNH and the African subjects? First, in view of recent observations that genetic variants contribute a highly significant risk for ARM in white persons, it may be that also in African persons genetic variants will be found that confer protection. Thus, genetics may underlie the observed “ethnicity.” Second, exogenous factors, such as diet, smoking, and possibly inflammatory components resulting from systemic or ocular diseases, may influence pigment density. Additionally, illumination levels may affect pigment density, possibly regulated by iris color.

Those factors could be the reason ARMD, a disease likely to be enhanced by oxidative damage, is more common in white persons than in persons of African phenotype.14 No studies have been published of the differences in MPDc values or MP spatial distribution between ethnic groups. Most studies of MP were conducted primarily in WNH subjects and included only
a few Asian subjects.\textsuperscript{18,19} Yet, ethnicity may play a role in MPDc values. The MPDc value is known to vary with diet and iris color. Given these factors, it is reasonable to speculate that MPDc might vary with ethnicity as far as lifestyle is concerned. However, it is difficult to compare MPDc across studies because of the different methodological set-ups and procedures used. By comparing the foveal luminosity function of Egyptian subjects with those of Western subjects, Isahak speculated that Egyptians might have higher MPDc.\textsuperscript{40} Hammond et al.\textsuperscript{41} and Hammond and Caruso-Avery\textsuperscript{42} report a higher MPDc in subjects with dark rises. Our findings of differences among MPDc values between the studied ethnic groups may be a result of environmental factors, genetic influences, or dietary habits. Hammond\textsuperscript{42} speculated that a shared tendency might have developed to accumulate melanin of the iris and carotenoids in the retina because of similar environmental factors (e.g., light and oxygen).

Could increased retinal illuminance resulting from light iris color contribute to a depletion of MP? In other words, can high exposure alter the molecular structure so that the antioxidants lutein and zeaxanthin are consumed and metabolized into nonprotective chemical forms? The blue light-filtering effect of lutein and zeaxanthin, found in Henle fibers of the fovea, is a passive function. It is thought to reduce blue light exposure and, with that, the formation of reactive radicals.\textsuperscript{43} However, lutein and zeaxanthin are present in rod outer segments\textsuperscript{44} (and potentially cones) and are thought to act directly as antioxidants. Several mechanisms of action are possible, some of which could deplete the original molecules. A detailed discussion of such mechanisms is given in Krinsky.\textsuperscript{43} Furthermore, the physiological turnover of rod and cone outer segments with shedding of disks from the tips and renewal at the base necessitate the replenishment of outer segment components, including lutein and zeaxanthin. In vitro studies by Kim et al.\textsuperscript{45} indicate that lutein and zeaxanthin provide good protection against oxidative stress induced by the retinoid derivatives A2PE and A2E. Both molecules act as blue light filters and as antioxidants and are not depleted while exerting their filtering and antioxidant effects. However, chronic exposure to very high oxygen levels, as found in photoreceptors comitant with presumed increased bright light exposure resulting from light iris color, cannot be compared directly in a short-term in vitro study.

In our opinion, the different distribution types of MP with significant ethnic differences could indicate the genetic effect of ARM-related prevalence.

The maximum parafoveal ring found was 0.66° ± 0.13° from the fovea. Delori et al.\textsuperscript{16} found, in more than half their subjects, an annulus of higher density superimposed on a central monotonic-like distribution. This annulus was located 0.7° from the fovea. There were no differences in the localization of the ring maximum between African subjects and WNH subjects. However, we found significant differences of the width at a half maximum between the groups, showing a broader distribution in African subjects. These differences may be caused by the anatomic width of the fovea, which may be associated with race.

We calculated the ratio MPD_{0.5}/MPDc to assess the significance of the parafoveal ring. Theoretically, higher values of MPD_{0.5}/MPDc indicate a more prominent parafoveal ring, whereas lower values show a peak-like distribution. We found significant differences for the ratio MPD_{0.5}/MPDc between the ethnic groups, confirming the presence of race-associated differences in the MP distribution.

Our results were analyzed in light of gender and age dependence and of ethnic distribution. We found no evident gender-related, age-related, or risk factor (e.g., smoking, family history of ARM)-associated difference in MPDc. This is in agreement with findings of other groups.\textsuperscript{8,21–26}

Mean MPDc measured within a 0.5°-diameter circle centered on the fovea may not represent the protective properties of MP. As in previous studies,\textsuperscript{21–24,27–29} we observed a large variability of mean MPDc and the distribution of MP around the fovea. We found a high degree of intersubject variability in the lateral extent and shape of distribution of MPDc. Distribution profiles varied from broad distribution with low peaks to sharp, cusped peaks with different widths. Given that the total amount of MP cannot always be predicted from the mean MPDc, as calculated in our study, bias can occur if the lateral extent and shape of distribution are unaccounted for.\textsuperscript{49}

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