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Original Article

Evaluation of Macular Pigment Optical Density in Eyes with Hyperopic Anisometropic Amblyopia Using Fundus Reflectometry

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Abstract

Objectives: This study aimed to evaluate the macular pigment optical density (MPOD) scores in eyes with hyperopic anisometropic amblyopia and compare those with their fellow and control eyes using one-wavelength fundus reflectometry.

Methods: This cross-sectional study enrolled 33 patients diagnosed with hyperopic anisometropic amblyopia aged 12–40 years. The control group consisted of 36 hyperopic and 42 emmetropic children, age-matched to the patients. Central macular thickness (CMT), MPOD, axial length (AL), best-corrected visual acuity, and refraction errors were measured between the study group and the control group.

Results: Eyes with the diagnosis of hyperopic anisometropic amblyopia had significantly higher mean and maximum (max) MPOD scores compared with their fellow eyes as well as hyperopic and emmetropic eyes ($p<0.001$ for all). The mean AL in eyes with hyperopic anisometropic amblyopia was statistically shorter than that in hyperopic and emmetropic controls ($p=0.027$, $p<0.001$, respectively). The mean CMT was found to be thicker in eyes with hyperopic anisometropic amblyopia when compared to their fellow eyes, as well as hyperopic and emmetropic controls, eventhough there was no significant difference was found among the four groups ($p=0.052$). The mean MPOD levels were significantly correlated with the difference in CMT ($r=-0.21$, $p=0.032$), and logMAR visual acuity scores ($r=-0.44$, $p<0.001$) in the hyperopic anisometropic amblyopia group.

Conclusion: The present study indicates that the MPOD is reduced in eyes with hyperopic anisometropic amblyopia. This reduction may be due to less visual stimulus-induced deterioration of foveal development and microarchitecture in anisometropic amblyopic eyes.

Keywords: Amblyopia, central macular thickness, fundus reflectometry, macular pigment optical density, visual acuity

Introduction

Amblyopia is a neurodevelopmental visual disorder that develops as a result of sensorial transmission impairment, which has a number of causes, including strabismus, refraction errors, and visual deprivation disorders that occur during the course of critical vision improvement (1-4). Anisometropic amblyopia constitutes approximately 1–5% of all causes of monocular vision impairment in children, secondary to anisomyopia of

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more than 2 diopters (D), anisohyperopia of more than 1.0 D, or anisoastigmatism of more than 1.5 D (2,3). Furthermore, amblyopia is defined as a decrease in the best-corrected visual acuity (BCVA) without identifiable ocular pathology. Unilateral amblyopia refers to a decrease in two Snellen lines in BCVA scores between both eyes (5). Robaei et al. (6) found that 58.6% of amblyopic eyes had significant hyperopia (≥+3D), and only 8.7% of those had myopia.

Macular pigments (MP) are highly concentrated at the center of the macula, which is composed of hydroxy-carotenoids such as lutein, zeaxanthin, and meso-zeaxanthin (7). Such MPs in Henle's fibers at the fovea centralis are particularly important for protecting the retinal photoreceptors and retinal pigment epithelium. The highest MP density has been found in the fovea. Due to their antioxidant properties and filtering function, especially for short-wavelength blue light, MPs are believed to play a positive role in visual performance (8-10). In addition to these effects, MPs are bound to the tubulin in the microtubules that form mechanical signal transmission pathways inside the axons of cone cells (11). MPs have also been shown to be associated with retinal cell differentiation and migration, nerve conduction, and oxidative stress (8,12).

MP optical density (MPOD) is used to evaluate the spectral absorption properties of lutein and zeaxanthin, taking into account the lens, melanin, and blood densities (13). The MPOD has been measured using a variety of techniques (14). A quantitative assessment of light intensity reflected from the fundus may be conducted by using fundus reflectometry, which is a reliable method for evaluating MPOD (15). The aim of this study was to use the one-wavelength reflectometry method to investigate whether changes in hyperopic anisometropic amblyopia can cause changes in MPs.

Methods

This cross-sectional study enrolled 111 consecutive cases admitted to our tertiary referral center. For the purpose of the study, anisometropia was defined as an interocular difference in refraction of more than 2.0 D, and an amblyopic eye was defined as its BCVA was two or more Snellen lines worse than the fellow. Hyperopia was defined as a spherical equivalent value of refractive error ≥+0.75 D, and emmetropia represented an SE between −0.75 and +0.75 D. The study population was divided into four subgroups as follows: Group 1 consisted of previously untreated 33 eyes with a novel diagnosis of hyperopic anisometropic amblyopia in 33 patients; however, the fellow eyes of those composed Group 2. Only the right eyes of 36 hyperopic patients and the right eyes of 42 emmetropic control subjects created the third and fourth study groups. Patients aged <12 years and those with the diagnosis of strabismus, eccentric fixation, nystagmus, glaucoma, or retinal disorders, as well as cases with a previous history of any ocular surgeries, were excluded. Moreover, eyes with poor image quality due to ocular media opacities or patients who have low cooperation were excluded. To reduce the effect of refractive errors on MPOD scores, myopic (≥−0.75 D) and severe hyperopic (>+5 D) eyes were also excluded from this study. This study adhered to the tenets of the Declaration of Helsinki. Votum of the institutional ethics committee was approved before the analysis (2015/08-10). An informed patient consent was taken from all patients. In addition, informed consent was obtained from the patient's parent for this study if the patient is a minor child.

All patients underwent a regular, detailed ophthalmologic examination, including the assessment of BCVA with the Snellen chart, slit-lamp biomicroscopy, intraocular pressure evaluation with air-puff tonometry, dilated fundoscopy, and orthoptic examinations such as extraocular motility and strabismus tests. Snellen visual acuities were converted to logMAR visual acuities for further statistical analysis. Refraction errors were tested under noncycloplegic conditions through a Nidek autorefractometer (Nidek ARK-510A autorefractor/keratometer, Gamagori, Japan), and SE values were measured as the spherical power plus half of the minus cylinder power for each study eye. Axial length (AL) measurements were performed by an optical biometry system (IOL-Master 500, Carl Zeiss Meditec AG, Germany). A spectral-domain optical coherence tomography (HRA Spectralis, Heidelberg Engineering, Heidelberg 2, Germany) was used to evaluate central macular thickness (CMT), whereas a single-wavelength reflectometry (Visucam® 500, Carl Zeiss Meditec AG, Germany) was used to measure MPOD scores in all study eyes.

MPOD Measurements

The optional MP density module for Visucam® 500 was used to determine the reflectance of a single 460 nm wavelength based on a single blue-reflection fundus image to determine MPOD and its spatial distribution. A shading correction is used that approximates the reflectance of the fundus in the absence of MP. It is based on a three-dimensional parabolic function automatically fitted to fundus reflectance at peripheral locations. The participant was positioned in front of the fundus camera and instructed to look at a target inside. The fundus was illuminated by a monochromatic blue light. Four MPOD parameters were automatically calculated: maximum OD (max MPOD measured at the peak), mean OD (mean MPOD within the measurement area), area (area where MP could be detected), and volume (sum of all ODs, as recommended by the manufacturer). The mean MPOD and max MPOD measurements of each eye were noted and statistically analyzed.

Statistical Analysis

Data analysis was performed using SPSS version 24.0 (IBM, Armonk, NY, USA). Values were recorded as n (%) and mean±standard deviation (SD). After normality was evaluated with the Kolmogorov-Smirnov test, chi-square with Bonferroni correction and one-way ANOVA tests were applied to assess the statistical differences in studied parameters among the four study groups. Subgroup binary analyses were performed using an independent t-test. The correlations of mean MPOD and max MPOD levels with age, SE of refractive errors, AL, CMT, and BCVA were analyzed using Pearson's correlation test. Probabilities p<0.012 were considered statistically significant among the four study groups.

Results

Demographic Data

The study population of 111 patients consisted of 75 females (67.6%) and 36 males (32.4%), with a mean age of 29.9±12.3 years (range, 12–40 years). There was no significant difference in patient age and gender distribution among the four study groups (p=0.156 and p=0.264, respectively). Table 1 demonstrates the comparisons of background factors between study groups according to diagnosis. The mean SE of refractive error was +3.55 D (range, +1.75–5.00 D) in Group 1, whereas it was +0.92 D (range, +0.50–3.50 D), +1.75 D (range, +0.75 to 4.75 D), and +0.01 D (range, −0.50–+0.50 D) in Groups 2, 3, and 4, respectively (p<0.001). The anisometropic amblyopia eyes were significantly more hyperopic in comparison to their fellow eyes, hyperopic controls, and emmetropic controls (p<0.001 for all). However, no statistically significant difference was found in the mean SE of refractive errors between the fellow eyes and the hyperopic controls (p=0.08). The mean AL in the hyperopic amblyopic eyes was statistically shorter than in the fellow eyes, hyperopic eyes, and emmetropic eyes (p≤0.01 for all). However, there was no significant difference between the fellow eye and control groups (p=0.265 and p=0.186, respectively).

Comparison of CMT among Study Groups

Table 2 shows the mean (±SD) values of the CMT scores obtained using SD-OCT. The mean CMT tended to be thicker in the hyperopic amblyopic eyes than in their fellow eyes, the hyperopic and emmetropic controls; however, no statistically significant difference was found among the four groups (p=0.052).

Comparison of MPOD among Study Groups

A one-way ANOVA test revealed a significant difference in mean and maximum MPOD scores among the four study groups (p<0.001 and p<0.001, respectively). The hyperopic anisometropic amblyopic eyes had significantly lower levels of mean MPOD and max MPOD compared with their fellow

Table 1. Demographics and ophthalmologic findings

	Hyperopic anisometropic amblyopia (group 1) n=33	Fellow eye (group 2) n=33	Hyperopic controls (group 3) n=36	Emmetropic controls (group 4) n=42	p
Age (years)	25.17±7.99	25.17±7.99	27.62±5.76	26.52±3.69	0.156
Gender (F/M)	21/12	21/12	24/12	30/12	0.264
BCVA (logMAR)	0.43±0.33	≤ 0	≤ 0	≤ 0	<0.001*
SE (D)	+3.55±2.43	+0.92±1.72	+1.75±1.20	+0.01±0.21	<0.001†
AL (mm)	21.84±0.76	22.61±1.85	22.38±0.55	23.17±0.95	0.001‡

F/M: Female/Male, BCVA: Best corrected visual acuity, SE: Spherical Equivalent, AL: Axial Length. P<0.01 is statistically significant. *P<0.01, Group 1 versus Groups 2, 3, and 4. †P<0.01, Group 1 versus Groups 2, 3, and 4. ‡P<0.01, Group 1 versus Groups 2, 3, and 4.

Table 2. MPOD and CMT scores

	Hyperopic anisometropic amblyopia (group 1) n=33	Fellow eye (group 2) n=33	Hyperopic controls (group 3) n=36	Emmetropic controls (group 4) n=42	p
Mean MPOD	0.098±0.025	0.122±0.192	0.124±0.038	0.127±0.035	<0.001*
Max MPOD	0.287±0.092	0.350±0.043	0.348±0.078	0.351±0.065	0.002†
CMT (μm)	227.7±21.5	226.3±21.3	222.7±16.5	224.3±18.3	0.052

P<0.01 is statistically significant. *P<0.01, Group 1 versus Groups 2, 3, and 4. †P<0.01, Group 1 versus Groups 2, 3, and 4, CMT: Central macular thickness, MPOD: Macular pigment optical density.

eyes as well as hyperopic and emmetropic controls (p<0.001 for all) (Figs. 1 and 2). However, no significant differences were found in mean and maximum MPOD scores among the remaining three study groups (p=0.456). The mean MPOD level was found to be significantly correlated with the CMT score (r=−0.210, p=0.032) and logMAR visual acuity score (r=−0.440, p<0.001), whereas no significant correlation was found with age (p=0.970), SE of refractive errors (p=0.340), or AL (p=0.137). Pearson's test also revealed no correlation of max MPOD levels with age (p=0.664), SE of refractive errors (p=0.416), AL (p=0.396), or CMT scores (p=0.803). However, max MPOD level was found to be negatively correlated with logMAR visual acuity scores (r=−0.211, p=0.025).

Discussion

It is a well-known theory that amblyopia occurs during the development and maturation of neuronal network establishment between the retina and visual cortex (16-18). According to the long suppression period related to severe refractive errors, the visual cortex may inhibit the images transferred from the amblyopic eye, which is the main cause of the gradual decrease in visual acuity within the critical period lasting approximately 3–12 years (19). Moreover, the relationship between amblyopia and morphological changes in the retina has not been completely clarified yet. There has not been a consensus regarding the retinal structural difference between the eyes with anisometropic amblyopia and their normal fellow eyes.

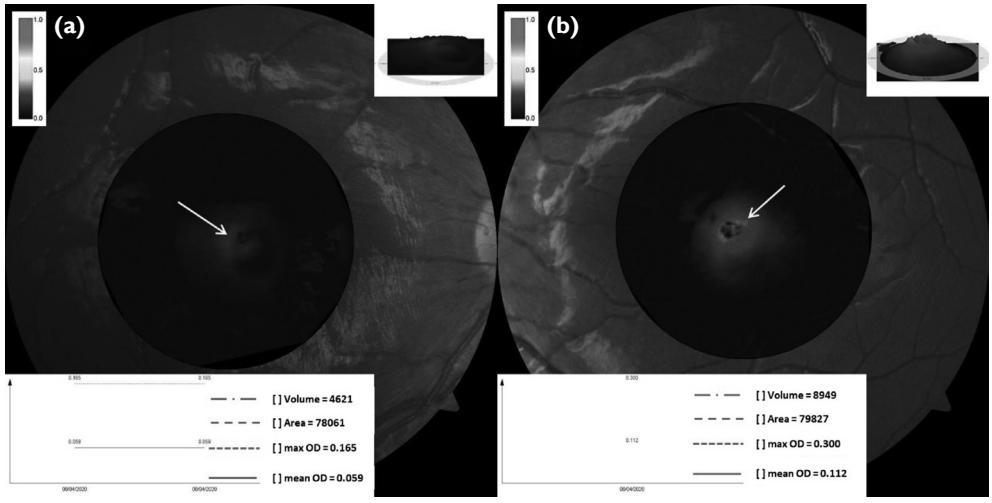

Figure 1. Macular pigment optical density (MPOD) is stated as maximum optical density and mean optical density. Right eye of a hyperopic anisometropic amblyopia **(a)** MPOD measurement: maximum optical density = 0.165, mean optical density = 0.059. Their fellow eye (lefte eye), **(b)** MPOD measurement: maximum optical density = 0.300, mean optical density = 0.112.

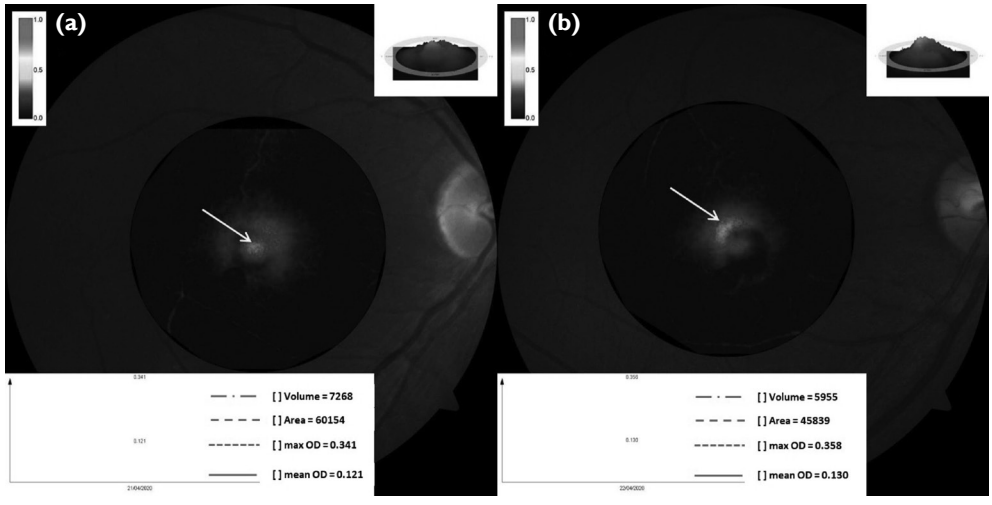

Figure 2. Measurement of mean and maximum (max) MPOD in a hyperopic and an emmetropic eye. Max MPOD = 0.341 and mean MPOD = 0.121 in the hyperopic eye. Max MPOD = 0.356 and mean MPOD = 0.130 in the emmetropic eye.

Likewise, it is not known whether there is a relation between MPOD and anisometropic amblyopia or not. To the best of our knowledge, this is the first report of MPOD evaluation in amblyopic eyes secondary to anisometropia. In the present study, all participants aged between 12 and 40 years were deliberately enrolled since the critical period for neural network maturation should be ceased after the age of 12 years and the impact of age-related macular degeneration over MPOD alterations would most probably be minimum before the age of 40 years. Our study revealed that the MPOD scores of the eyes with hyperopic anisometropic amblyopia were significantly lower than those of their fellow eyes as well as those of hyperopic and emetropic controls.

Although a slightly thicker macula was found in the eyes with hyperopic amblyopia when compared to their fellow eyes as well as hyperopic and emmetropic controls, there was no statistical significance in mean CMT scores among our four study groups. There are also many studies in the literature that found no statistically significant difference in CMT scores between the eyes with hyperopic anisometropic amblyopia and their fellow eyes (20-25). On the contrary, some authors have published increased CMT scores in hyperopic and amblyopic eyes compared to their fellow eyes (26-29). Demircan et al. (25) reported significantly shorter AL in eyes diagnosed with hyperopic amblyopia than their fellow eyes in a study population aged between 13 and 42 years. In our study, AL in hypermetropic amblyopic eyes was also significantly shorter when compared to their fellow eyes and control groups.

Histological studies have revealed that MP is especially distributed in the inner and outer plexiform layers according to the volume of neural networks and synapses within those retinal layers (30,31). Besides, fovea has been shown to have the highest MP density, which is especially located in the Henle fibers (2-10,30). Scanning of MPOD may give valuable data about MP levels, which are also known to be positively related to serum lutein levels and dietary uptake (8-10). Some authors published a positive correlation between MPOD and CMT scores in healthy subjects (32-34). On the contrary, Westrup et al. (35) reported a negative correlation between the juxtafoveal MPOD and retinal thickness. According to present knowledge, the impact of MPOD over retina thickness has still remained controversial (32-38).

We showed that mean MPOD levels in hyperopic anisometropic amblopia eyes have a significant and negative relationship with the difference in CFT as measured by SD-OCT. Moreover, visual acuity is positively correlated with MPOD. Future researchers should explore the relationship between patching or refraction correction and MPOD in amblyopic patients and whether dietary supplementation with lutein might improve the condition of patients with amblyopia.

In the present study, Visucam® 500, which is based on reflectometry and measures MPOD through the reflectance of a single 460 nm wavelength, was used to measure the MPOD level. The stability of fixation has been shown to be abnormal in amblyopia (39). It also has additional advantages because of the use of an eccentric reference point, and there is no strong requirement for transparency of the media in the anterior segment (14). Therefore, fundus reflectometry can be considered as a good choice among various methods.

Amblyopia is a multifactorial disease with some known risk factors. There is not enough data to show whether amblyopia has an effect on retinal morphology. We speculated on two potential hypotheses about the MPOD decrease in amblyopic eyes. The first possible mechanism is the disruption of foveal development and microarchitecture due to less visual stimulus in anisometropic amblyopic eyes. A second possible mechanism may be explained by the lack of MP production and/or insufficient absorption and transformation of MPs from the blood by photoreceptors in the central fovea. MP lutein is shown to have neuroprotective effects in animal models (8,9). With their vital role in visual performance, MPs are published to have protective effects over photoreceptor cells according to inhibition of visual pigment (rhodopsin) reduction and outer segment shortening as well as photoreceptor dysfunction during retinal inflammation (40). Greater MPOD may protect retinal neurons against dairy stress and improve connections between retinal neurons. Recently, the relationship between age-related macular degeneration and MPs has mostly been studied (14,38-41). However, there is no study investigating the density of MPs in amblyopic eyes.

The main limitation of this study is the relatively small sample size, which may affect over performed correlation analyses. Enrolling subjects aged between 12 and 40 years may also introduce an age bias. The lack of data about the dairy nutritional patterns of the participants is another limitation of our study. The results of this study could be more powerful if we compared the readings of the one wavelength reflectometry method with other methods such as heterochromatic flicker photometry and fundus autofluorescence.

Conclusion

To the best of our knowledge, this is the first article that reports MPOD scores in amblyopic eyes secondary to hyperopic anisometropia. Our current study demonstrates that the MPOD decreases in hyperopic anisometropic amblyopia. This reduction may be due to less visual stimulus-induced deterioration of foveal development and microarchitecture in anisometropic amblyopic eyes. The mean MPOD scores were found to be negatively correlated with CMT and logMAR visual acuity scores. The possible impact of nutritional supplement intake as well as eye patching with full correction of refractive errors in amblopic eyes over MPOD scores needs to be researched in future prospective studies with large cohorts.

Disclosures

Ethics Committee Approval: Approval was obtained from the Non-interventional Research Ethics Committee of Dokuz Eylül University (2015/08-10).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.K., T.O., Z.A.; Design – M.K., T.O.; Supervision – M.K.; Resource – F.A.; Materials – B.A.Y.; Data collection and/or processing – M.K., F.A., B.A.Y.; Analysis and/or interpretation –M.K., Z.A.; Literature search – F.A., B.A.Y.; Writing – M.K., T.O.; Critical review – M.K.

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