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Correlations among macular pigment optical density, central macular thickness and body mass index

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黄斑色素光学密度、中央黄斑厚度与体重指数的关系

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摘要

目的:评估黄斑色素光学密度(MPOD)、中央黄斑厚度与体重指数(BMI)的关系。

方法:这是一项在单一机构中进行比较的横断面研究。本研究共纳入210名符合入选标准的志愿者。使用黄斑色素筛选剂II对受试者MPOD进行测量。使用SD Cirrus OCT测量中央黄斑厚度。记录所有眼MPOD和OCT信息。使用Microsoft© Excel,SPSS和R进行数据分析。

结果:MPOD和中央黄斑厚度之间呈明显正相关($r=0.42$, $P<0.01$)。同时,MPOD和BMI之间呈明显负相关($r=-0.23$, $P<0.01$)。

结论:研究得出,MPOD和中央黄斑厚度之间呈明显正相关。还需要进一步研究中央凹的详细结构及其与MPOD的关系。研究发现了MPOD与BMI之间呈明显正相关,且得出BMI的降低可能会增加黄斑色素的密度,这有助于预防年龄相关性黄斑变性(ARMD)。

关键词:黄斑色素光学密度;体重指数;中央黄斑厚度

Abstract

• AIM: To determine the relationship among the macular pigment optical density (MPOD), central macular thickness and body mass index (BMI).

• METHODS: This is a comparative cross-sectional study performed in a single institution. Totally 210 volunteers who met the inclusion criteria were included in this study. The subject's MPOD was measured using Macula Pigment Screener II (MPS II, by Electron Technology). Central macular thickness was measured with Spectral Domain Cirrus Optical Coherence Tomography (OCT), Cirrus (Model 4000, Carl Zeiss Meditec). The information of both MPOD and OCT from both eyes were recorded. The data was analysed using Microsoft© Excel [Version 15.12.3 (150724) ℃ 2015 Microsoft], SPSS (IBM© SPSS© Statistics Version 2.2), and R (version 3.2.1; R Core Team 2015).

• RESULTS: There was significant positive correlation between MPOD and central macular thickness ($r=0.42$, $P<0.01$) and a significant negative correlation between MPOD and BMI ($r=-0.23$, $P<0.01$).

• CONCLUSION: Our study showed a significant positive correlation between MPOD and central macular thickness. Further study is needed to look at the detailed structure of the fovea and its relationship with MPOD. Our study also found a significant negative correlation between MPOD and BMI, suggesting that a reduction in BMI may increase the density of macula pigment, which can be helpful in preventing age-retinal pigment epitheliitis (ARMD).

• KEYWORDS: macular pigment optical density; body mass index; central macular thickness
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INTRODUCTION

Lutein and zeaxanthin are pigments that are classified as xanthophyll carotenoids[1-2], which can be found in the human blood and body tissues, especially in the macula. Lutein, Zeaxanthin and Mesozeaxanthin constitute to the macular pigments[3]. Macula pigment is measured in optical density unit (d.u.) and termed as macula pigment optical density (MPOD). The concentration of macula pigments is highest at the fovea and reduces exponentially towards periphery. Several studies on the correlation between macula pigment and central macular thickness have been published. Veen *et al*[4] found a significant correlation between MPOD and central retinal thickness, whereas Nolan *et al*[5] found no

such correlation.

The purpose of our study is to investigate the correlation between MPOD and central macular thickness in the healthy Malaysian individuals, aged 30-50 years old. Our study is the first study on the Malaysian population. The outcome of this study will contribute to the pool of the current scientific knowledge and may strengthen the outcome of the previous studies.

SUBJECTS AND METHODS

The study is adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional Review Board approval was obtained from the Medical Ethics Board of the University Malaya Medical Centre (UMMC). It is a comparative cross-sectional study, conducted from December 2014 to July 2015. The subjects included were aged 30-50 years old, fit and healthy with visual acuity of LogMar 0.0-0.30, equivalent to 6/6 - 6/12 on Snellen (aided and unaided). Exclusion criteria are those taking lipid lowering medication, with systemic and ocular diseases that may affect the study result (Ocular: glaucoma, age-retinal pigment epitheliitis, cataract, retinal diseases; Systemic: diabetes, any illness that has effect on retina), and taking supplement or diet which contain high level of lutein and zeaxanthin.

Informed consent was obtained, and a full systemic and ocular history were taken. The visual acuity was checked with the LogMar visual acuity chart. A thorough ocular examination was carried out. The date of birth, weight and height were also recorded. MPOD measurement was done using MPS II, followed by central macular thickness measurement using SD Cirrus OCT.

Measurement of Macular Pigment The measurement of macula pigments is termed as macula pigment optical density (MPOD). It is a measurement of blue light attenuation by macula pigment and is measured in DU. It has a range of 0 to 1. The technique used for macula pigments is Heterochromatic Flicker Photometry (HFP). It is minimally invasive, does not require dilatation of pupil, and uses low light level[6-7]. The method is based on the property of the macula pigments that absorbed a spectrum of blue to green wavelength (460 nm to 570 nm). The MPOD is determined by a test stimuli that alternates between a wavelength absorbed by the macular pigments at the fovea and eccentric fovea, and at the same time, the radiance of the blue light is adjusted by the subject until the perception of flicker is minimized or eliminated. It is base on the assumption that macula pigment is maximum at the fovea, and reduces exponentially towards eccentricity, with minimal or absent of the pigments at 6-8 degree of eccentricity. The Log ratio of the radiance of blue light needed at the fovea (Bf) compared to that at the parafovea (Bp) gives the measurement of MPOD [MPOD=Log 10 (Bf/Bp)]. In the MPS II, the subject responds when they first see a flicker[8-9]. The flicker sensitivity of each subject is determined by a pre-set test which takes only few seconds. The blue-green alternation flicker is then initiated and decreased in 6 Hz steps from 60 Hz, which is above the critical flicker fusion frequency. At the initial part of the test, the subject will not notice any flickers. The sequence of the different blue-green ratios are continued until a blue curve is seen, follows by the peripheral test. The minimum point of each curve is taken for calculation of MPOD using the same formula mentioned earlier. The minimum point at the curve indicates the moment where blue and green light achieve an iso-luminance.

Measurement of Central Macular Thickness Central macular thickness (CMT) is measured using OCT (SD Cirrus OCT Model 4000 from Carl Zeiss Meditec)[10]. The measurement of macular cube 512×128 scan was selected, to capture the central 6×6 mm central macula. Six radial scans (6 mm long) which centred on the fixation point were performed on each eye. This scan takes 2.4s to complete for each eye. The retinal thickness is calculated, which is the distance between the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE). The Early Treatment Diabetic Retinopathy Study (EDTRS) grid is centred at the fovea automatically by a fovea finder. This grid consists of one innermost circle which corresponds to the central area of 500 μm radius, follows by a consecutive inner and outer ring measuring 1500 μm and 3000 μm radius respectively. The average thickness of each designated section of the central macula is documented in the grid in micrometre. The volume cube (total volume cube of 6×6 mm diameter) and thickness-average cube (overall average thickness of the entire 6×6 mm diameter) are also measured.

Statistical Analysis Microsoft© Excel [Version 15.12.3 (150724) ℃ 2015 Microsoft], SPSS (IBM© SPSS© Statistics Version 2.2), and R (version 3.2.1; R Core Team 2015) were used for data processing and statistical analysis. Pearson correlation coefficient analysis was done to study the inter-ocular correlation for MPOD and CMT, and to study the correlation between MPOD, CMT, and body mass index (BMI). Two-sample t-test was used to compare the mean MPOD between male and female. Multiple linear regression analysis for MPOD against CMT and BMI was done to obtain regression coefficient models.

RESULTS

A total of 210 volunteers are recruited for this study (174 females, 36 males). The mean MPOD values were similar for both eyes (RE: mean 0.47, SD 0.16, range: 0.02-0.84, LE: mean 0.48, SD: 0.17, range: 0.05-0.94), and the inter-ocular correlation coefficient between subjects' fellow eyes was 0.68 ($P<0.01$). The mean central subfield thickness, which is the central 1000 μm diameter area of both eyes, were similar and showed high inter-ocular correlation with r value of 0.90 ($P<0.01$) (RE: mean 241 μm, SD: 19.79, range: 191-316; LE: mean 241, SD: 19.85, range: 178-319). Left eye values were used for all statistical analysis in our study. The MPOD and CMT showed normal distribution patterns (skew test -0.17 and 0.38 respectively). No significant difference in mean MPOD between male and female (0.53 and 0.46, $P=0.08$).

Table 1 Summary of the statistics for the subjects (n=210)

Parameters	Mean±SD	Range (min-max)
Age, a	38±6	30-50
Weight (kg)	66±14	35-124
Height (m)	1.58±0.07	1.40-1.83
BMI (kg/m^2)	26.5±4.9	15.4-49.7
Central subfield thickness (μm)	242±20	191-416
Thickness average cube (μm)	277±14	206-308
Volume cube (mm^3)	9.9±0.5	7.7-11

SD:Standard deviation; BMI: Body mass index.

Correlation Between MPOD and Central Macular Thickness There was a significant positive correlation between MPOD and CMT (central 1000 μm diameter). Pearson correlation coefficient analysis showed r value of 0.42 (P<0.01). Regression coefficient between MPOD and CMT was statistically significant (P<0.01; 198 degrees of freedom, r^2=0.18). The regression is given by the equation MPOD = -0.4623-0.0039 CMT. Figure 1 showed the scatter plot and the regression line for MPOD and CMT.

Correlation Between MPOD and BMI There was a significant inverse correlation between MPOD and BMI (Pearson correlation, r = -0.23, P = 0.001). Regression coefficient between MPOD and BMI was statistically significant (P<0.001; 201 degrees of freedom, r^2 = 0.05). The regression is given by the equation MPOD = 0.6995 - 0.008 BMI. A further analysis into men and women groups showed a similar finding. There was a significant inverse correlation between MPOD and BMI, in men, r = -0.2294, P=0.003, and in women, r = -0.3447, P=0.0367.

Multiple linear Regression Multiple linear regression showed that CMT and BMI jointly explained about 25% variation in MPOD. The final regression model is given by the equation MPOD = -0.2705 - 0.0095 BMI + 0.0041 CMT. Table 2 gives the predicted mean MPOD values for particular combinations of BMI and CMT.

DISCUSSION

Our analysis showed a significant positive correlation of MPOD and central subfield thickness, volume cube and thickness area cube. Therefore, it can be suggested that MPOD is strongly correlated with macula thickness, up to 3 mm radius from central fovea, or 6 mm diameter of posterior pole. Our study agrees with the previous one done by Veen *et al*[4]. Liew *et al* did a study on 300 female patients, aged less than 50 years old in the UK. They used two different methods to measure MPOD, HFP (using maculometer) and autoflourescence (scanning laser ophthalmoscope). Both methods yielded a significant correlation between MPOD and central retinal thickness (average thickness of 1 mm central diameter of fovea). Veen *et al*[4] did a study on 40 Netherlands patients (age 18-58, 87.5% female). The MPOD was measured using Macula Pigment Screener, which was similar to our study. They found a significant positive correlation between MPOD and central foveal thickness. The central foveal thickness is defined as the average retinal thickness at the intersection point of six radial scans. However, they found no correlation between MPOD and central retinal thickness (1 mm diameter of fovea).

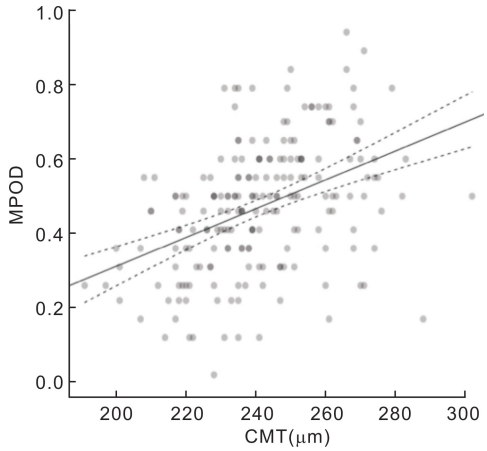

Figure 1 Scatter plot of MPOD against CMT, with fitted regression line (solid) and corresponding upper and lower limits of the 95% confidence interval of MPOD (dashed lines).

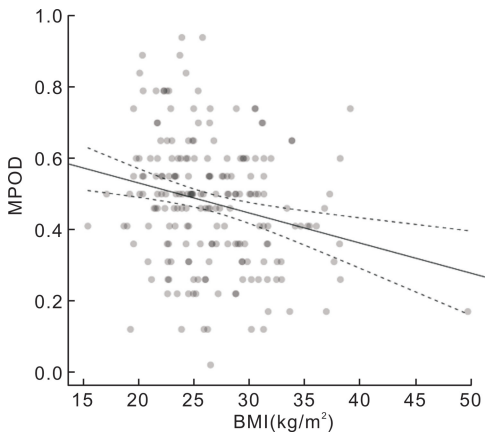

Figure 2 Scatter plot of MPOD against BMI, with fitted regression line (solid) and corresponding upper and lower limits of the 95% confidence interval of MPOD (dashed lines).

Nolan *et al*[5] did a similar study in Georgia, US on 59 patients (age range 18-60, 59.3% female), and found a significant correlation between MPOD and MFT (minimal foveal thickness - the average retinal thickness at point intersection point of six radial scans), only in their non-white population (n = 18, 31%) which consisted of 5 Indians, 6 Asians, 3 Hispanics and 4 Blacks. No correlation was found between MPOD and CFT (central foveal thickness, 1 mm diameter) or MFT when the whole population, including the white population, was taken into account. In their study, macula densitometer (customized HFP) was used. This technique yielded higher MPOD values compared to MPS. Their study also did not find a similar correlation to ours. The differences can be explained by two factors: the distribution of macula pigments and the size of study population. It is known that the peak distribution of macula pigment is at the centremost of the fovea and decrease exponentially to

Table 2 Predicted mean MPOD values for particular combinations of CMT and BMI

CMT (μm)	BMI (kg/m^2)			
	20	25	30	35
200	0.36(0.32, 0.39)	0.32(0.27, 0.37)	0.27(0.21, 0.34)	0.22(0.16, 0.30)
240	0.53(0.50, 0.56)	0.48(0.46, 0.50)	0.43(0.41, 0.45)	0.39(0.36, 0.42)
280	0.69(0.62, 0.74)	0.65(0.60, 0.69)	0.60(0.56, 0.64)	0.55(0.51, 0.60)

The 95% confidence interval for mean MPOD is given in brackets. MPOD: Macula pigment optical density; CMT: Central macular thickness; BMI: Body mass index.

undetectable levels at 6 to 8° eccentricity[1,3-4]. Note that in Veen *et al*[4] and Nolan *et al*[5] studies, the sample sizes were small. They could only find a significant correlation between MPOD and central foveal thickness at the centremost point of the fovea, where the 6 radial scans intersect with each other and not at the central 1 mm of foveal thickness. Zheng *et al*[11] found that MPOD in examined Chinese school age children, showed no significant association with the minimum and central foveal thickness. A similar finding was found by Abell *et al*[12], in which no significant correlation between macular OCT profile and MPOD.

From our findings on the correlation of MPOD and foveal thickness, we could suggest that the volume of retinal tissue may influence the amount of macula pigment accumulated in the retina. The relationship is linear, and we suggest that central subfield thickness may explain about 18% variations of MPOD ($r^2=0.18$).

In our study on the further analysis on the correlation between MPOD and BMI, we found a significant inverse correlation between MPOD and BMI. The trend is the same from a low to a high BMI as in a study by Dietzel *et al*[13] and Raman *et al*[14]. In the study done by Bovier *et al*[15], the MPOD at each retinal eccentricity was related to body fat mass, which is statistically significant for men. However, in a study by Ji *et al*[16], there was no relationships found between MPOD and BMI.

It is possible that there is a competitive factor in uptake of macular pigments into the body fat and the retinal tissue and this postulation is supported by a study done by Johnson *et al*[17]. The study measured the amount of pigments in the serum, adipose tissue and the macula of subjects who were supplemented with spinach and corn for 15wk. The diet contained about 5 times as much lutein and 2 times of zeaxanthin in a usual healthy diet. Subcutaneous adipose tissue sample was taken for adipose tissue pigments measurements. They found that the adipose tissue lutein concentration was inverse to the pattern of MPOD. They also noted that at 4wk supplement, there was a significant decrease in adipose tissue lutein and significant increase of MPOD compared to baseline. At the 8wk of supplement, the pattern reversed. Note that in this study, only lutein had significant correlations whereas zeaxanthin correlations were modest. This was due to the small amount of zeaxanthin content in the supplemented diet. The LUTEGA study also found that the supplementation of Lutein, zeaxanthin and omega-3-longchain-polyunsaturated-fatty-acids resulted in considerable increase in MPOD[18-19]. In the PIMAVOSA study has showed an association of MPOD level with plasma lutein, zeaxanthin and omega-3 long chain polyunsaturated fatty acids[20]. The serum xanthophylls, retinal xanthophylls and lipoproteins concentration are significantly related. The changing of the lipoprotein levels may impact the retinal xanthophylls level[21].

The animalstudy done by Thomson *et al*[22] analysed the amount of pigments from the sacrificed carotenoid-deficient quails after supplementation with lutein/zeaxanthin. Serum sample, liver, fat and retina tissue biopsies were taken and analysed using a HPLC method. They found a significant inverse correlation between lutein in the fat and in the retina. A study done in spain over 108 subjects, have found a significant correlations in dietary intake and MPOD in the older subjects[23-24].

The findings above, both on human and animal studies, suggest that adipose tissue acts as a reservoir and also compete for the macular pigments. Thereare evidence that adipose tissue has preference on lutein over zeaxanthin[2].

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