Changes in Macular Pigment Optical Density among Pseudophakic Patients following Intake of a Lutein-Containing Supplement

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Keywords

Lutein · Macular pigment optical density · Pseudophakia · Clear intraocular lens · Gender differences

Abstract

Introduction: Cataract surgery has been reported as a long-term risk of reduced macular pigment optical density (MPOD). This study investigated changes in MPOD in pseudophakic patients after lutein supplementation. **Methods:** Fifty-seven patients who had no ocular diseases and underwent cataract surgery with concurrent implantation of clear intraocular lenses were included. MPOD was measured before lutein supplementation and every week during 6 weeks of supplementation. Two additional measurements were conducted after the end of supplementation. **Results:** Compared with baseline, MPOD was increased after 1 week of supplementation ($p < 0.01$) and remained elevated after cessation of supplementation. After 3 weeks of supplementation, MPOD in females was higher than that in males ($p < 0.05$). Compared with patients at the highest quintile baseline MPOD, patients of both genders at the lowest quintile had significant increases after 6 weeks of supplementation ($p < 0.05$). **Conclusion:** MPOD increased after lutein supplementation in patients who had undergone cataract surgery.

With the same amount of lutein supplementation, MPOD increased more in patients with low MPOD at baseline; it also increased more in females than in males. Lutein supplementation is presumed to support increased MPOD, which can reduce the risk of age-related macular degeneration, especially in females with low MPOD.

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Introduction

Lutein, zeaxanthin, and their metabolite, mesozeaxanthin, are carotenoids concentrated in the retina, which are used to form macular pigments (MPs) known as xanthophylls. These xanthophylls protect photoreceptor outer segments and the retinal pigment epithelium via absorbance of blue light and quenching of reactive oxygen species [1]. Throughout the retina, lutein and zeaxanthin might also protect against age-related macular degeneration (AMD) by reducing oxidative stress [2–4] and inflammation [4–6]. The presence of lutein and zeaxanthin has also been shown to reduce lipofuscin [7–9], which is considered a precursor of AMD. Lower lutein and zeaxanthin levels have been found in the inner and medial regions of the retina in cadaver donors with AMD [10].

There is also epidemiological evidence to indicate that higher lutein and zeaxanthin levels in the diet or blood are protective against advanced AMD [11].

MP protects the retina from light damage [11–13]. In the fovea, MP can absorb 40–90% of short-wavelength light [14] that could otherwise damage the retina [15, 16]. Patients with a confirmed family history of AMD have significantly lower MP optical density (MPOD) [17]. Reported, MPOD is significantly lower in AMD eyes [18–20]. MPOD has also been associated with dietary and serum lutein and zeaxanthin [21–23]. Furthermore, MP concentrations are readily impacted by oral supplementation through both diet and vitamin intake [24, 25].

Aged lenses, which exhibit cataracts, are considered to be natural filters that decrease the transmittance of short-wavelength light, thereby reducing retinal phototoxicity [26]. Cataract surgery involves implantation of clear intraocular lenses (IOLs), which increases the transmittance of light at approximately 410 nm [27]; this enables visible spectrum and short-wavelength light to reach the retina and potentially cause retinal pigment epithelial cell damage [28]. Cataract surgery has been reported as a factor associated with risk of reduced MPOD [29, 30]. Demirel et al. [31] reported that MPOD values were lower in patients who had undergone cataract surgery than in age-matched patients with clear lenses. Furthermore, inverse correlations have been observed between the duration of the postoperative period and MPOD values, as well as between the duration of the postoperative period and increased incidence of AMD [32, 33]. The possibilities of increases in MPOD [34] and retinal protection have been suggested with the implantation of blue light-filtering IOLs which contain yellow chromophores and attenuate the transmission short-wavelength light as aged lenses [35, 36]. However, longer-term effects of blue light-filtering IOLs on macular health or MPOD were inconclusive in the results of a meta-analysis [37]. It has been reported that MPOD positively correlated with oral intake of lutein from food and serum levels of lutein [38, 39]. Intake of lutein supplement is also a promising candidate for preventing the decreases in MPOD after cataract surgery.

Heterochromatic flicker photometry is a commonly used technique for measuring MPOD, based on the principle of matching the luminance of flickering blue and green lights. Yellow coloring in the optic pathway, such as that demonstrated by cataractous lenses and yellow-tinted IOLs, absorbs blue light and may cause incorrect measurements. In this study, we examined patients who had undergone implantation of clear IOLs to investigate

Table 1. The composition of Ocuvite + Lutein®

Substance	Amount
Lutein	6.0 mg
Vitamin C	300.0 mg
Vitamin E	60.0 mg
Vitamin B ₂	3.0 mg
β-Carotene	1,200.0 µg
Niacin	12.0 mg
Zinc	9.0 mg
Selenium	45.0 µg
Copper	0.6 mg
Manganese	1.5 mg

the effects of lutein supplementation on changes in MPOD after cataract surgery. Gender differences were also investigated. This is the first investigation of MPOD in pseudophakic patients with clear IOLs.

Materials and Methods

Subjects

Patients who underwent bilateral cataract surgery at the Lively Eye Clinic from May 2016 to December 2016 and had postoperative visual acuity better than 1.0 in decimal scale measurements with the Landolt C chart were included in this study. Clear IOLs (TECNIS® One-piece ZCB00; USA) were implanted in all patients. Informed consent was obtained from all patients for inclusion before they participated in the study, and the study was performed in accordance with the tenets of the Declaration of Helsinki. Approval was granted by the institutional Human Experimentation Committee in Dokkyo Medical University. Patients with ocular complications (e.g., uveitis and retinopathy) were excluded from this study, as were patients with systemic disease (including diabetes) and those taking other supplements.

Excluding patients with visual acuity worse than 1.0 after cataract surgery, patients were continuously enrolled into the study group according to the surgery schedule of the Lively Eye Clinic. Fifty-seven patients (23 males, age range: 60–84 years; 34 females, age range: 62–83 years) were included in the study group. After the study group recruiting period, the control group was continuously enrolled from among patients who had the same surgical procedure with the same IOLs, according to the surgery schedule of the Lively Eye Clinic. Twenty patients (10 males, age range: 58–80 years; 10 females, age range: 60–85 years) were included in the control group. No patients in either group subsequently declined to participate in this study.

Measurements and Study Protocol

MPOD was measured with heterochromatic flicker photometry as the differences between sensitivities at 465 nm and 530 nm (MPSII; Elektron Technology, Switzerland). One week after cataract surgery, the baseline MPOD was measured in both the study and control groups. Three tablets (the recommended daily

Table 2. Characteristics of the study and control groups

	The study group	The control group
Males		
<i>N</i>	23	10
Age, y/o		
Mean $\pm$ SD (range)	72.9 $\pm$ 7.4 (60–84)	69.3 $\pm$ 9.2 (58–80)
MPOD at baseline		
Mean $\pm$ SD (range)	0.54 $\pm$ 0.19 (0.23–0.86)	0.53 $\pm$ 0.19 (0.29–0.86)
Females		
<i>N</i>	34	10
Age, y/o		
Mean $\pm$ SD (range)	71.2 $\pm$ 5.2 (62–83)	71.0 $\pm$ 3.7 (60–85)
MPOD at baseline		
Mean $\pm$ SD (range)	0.6 $\pm$ 0.2 (0.24–0.9)	0.59 $\pm$ 0.29 (0.24–0.91)

MPOD, macular pigment optical density.

Fig. 1. Changes in MPOD. Compared with baseline, MPOD significantly increased after 1 week of lutein supplementation and remained elevated for 2 weeks after the end of supplementation in both males and females. There were no differences in the MPOD between genders at baseline and after 2 weeks of supplementation. However, compared with the MPOD in males, the MPOD in females was significantly higher after 3 weeks of supplementation and remained higher until 2 weeks after the end of supplementation (analysis of variance, $*p < 0.01$). MPOD, macular pigment optical density.

dosage) of Ocuvite + Lutein[®] (Bausch + Lomb, Rochester, NY, USA), a lutein-containing antioxidant supplement with components similar to the AREDS formula which has been proven effective on preventing the progression of AMD [40], were administered orally each day, beginning the day after the first measurement in the study group. The composition of the Ocuvite + Lutein[®] supplement is described in Table 1. During the 6-week supplementation period, the MPOD was measured each week. Measurements continued 2 weeks after the end of supplementation in the study group. In the control group, MPOD was measured at baseline, 1 week after cataract surgery, and each subsequent week for 4 weeks.

Rates of increase were defined as increases in MPOD measured at the end of each week, compared with measurement at baseline. Statistical analyses of the changes in MPOD were performed by using analysis of variance. Comparisons were analyzed by using the Mann-Whitney U test. Correlations were analyzed by using Spearman's rank correlation coefficient. Significant differences were regarded as those where $p < 0.05$.

Results

There was no significant difference in age between genders (mean $\pm$ SD): males = 72.9 $\pm$ 7.4 years, while females = 71.2 $\pm$ 5.2 years in the control group. The age distribution of the control group was not different from the study group: males = 69.3 $\pm$ 9.2 years and females = 71.0 $\pm$ 3.7 years. The MPOD at baseline was no different between the study group and the control group, either (Table 2).

In the control group, the MPOD was significantly increased after 1 week of supplementation (males: 0.59 $\pm$ 0.21; females: 0.69 $\pm$ 0.2), compared with baseline (males: 0.54 $\pm$ 0.19; females: 0.6 $\pm$ 0.2), and remained elevated for 2 weeks after the end of supplementation in both genders (males: 0.66 $\pm$ 0.18; females: 0.76 $\pm$ 0.17) (shown in Fig. 1,

Fig. 2. Increasing rates of MPOD at the end of each week. There were no changes in the rates of MPOD increase during supplementation in either males or females. Compared with the rates of MPOD increase in males, the rates in females were significantly higher during the first 3 weeks of supplementation (Mann-Whitney U test, * $p < 0.05$). MPOD, macular pigment optical density.

Fig. 3. The correlation between MPOD at baseline and after 6 weeks of supplementation. There were positive correlations between MPOD at baseline and after 6 weeks of supplementation in both genders. The correlations were analyzed by using Spearman's rank correlation coefficient, while the regression lines were added to show the direction of correlation. MPOD, macular pigment optical density.

$p < 0.01$). There were no differences in the MPOD between genders at baseline and after 2 weeks of supplementation. However, compared with the MPOD in males, the MPOD in females was significantly higher after 3 weeks of supplementation and remained higher until 2 weeks after the end of supplementation ($p < 0.05$). The rates of MPOD increase at the end of 6 weeks of supplementation were $28.6 \pm 23.75\%$ in males and $29.8 \pm 26.6\%$ in females (shown in Fig. 2). Compared with the rates of increase in males, the rates of MPOD increase were significantly higher in females for the first 3 weeks ($p < 0.05$). However, there were no significant differences between genders after 4 weeks of supplementation.

In both genders, the levels of MPOD at the end of 6-week supplementation were significantly correlated with the levels of MPOD at baseline in both genders (shown in Fig. 3). However, the rates of MPOD increase at the end of 6 weeks of supplementation were negatively correlated with the levels of MPOD at baseline (shown in Fig. 4). Considering the differences in rates of MPOD increase with respect to baseline, the rates of MPOD increase at the end of 6 weeks of supplementation were significantly higher in patients with the lowest quintile baseline MPOD than in those with the highest quintile baseline MPOD (shown in Fig. 5, $p < 0.05$). Although it did not reach statistical significance, among patients with the lowest quintile baseline MPOD, the rate of MPOD in-

Fig. 4. The correlation between MPOD at baseline and the increasing rates after 6 weeks of supplementation. After 6 weeks of supplementation, the rates of MPOD increase were negatively correlated with baseline MPOD in both genders. The correlations were analyzed by using Spearman's rank correlation coefficient, while the regression lines were added to show the direction of correlation. MPOD, macular pigment optical density.

crease tended to be higher in females than in males. Among the control group, the MPOD did not change 1 week later (males: 0.53 ± 0.19 ; females: 0.59 ± 0.29) compared with baseline (males: 0.55 ± 0.19 ; females: $0.59 \pm$

Fig. 5. The comparisons between patients who had the highest quintile and those who had the lowest quintile MPOD at baseline. Compared with patients who had the highest quintile MPOD at baseline, MPOD significantly increased after 6 weeks of supplementation in those who had the lowest quintile MPOD at baseline (* $p < 0.05$). MPOD, macular pigment optical density.

Fig. 6. The measurements of MPOD among the control group. Among the control group, there were no statistical differences in age between genders. Compared with baseline, the MPOD did not change 1 week later and remained at the same level 4 weeks later. MPOD, macular pigment optical density.

0.24). The MPOD remained at the same levels 4 weeks after in the control group (males: 0.54 ± 0.23 ; females: 0.58 ± 0.24) (shown in Fig. 6).

Discussion

During 6 weeks of lutein supplementation, MPOD increased at the end of the first week in patients who had undergone cataract surgery; this increase persisted until 2 weeks after the end of supplementation. Notably, the increase was greater in females. In addition, the increases were inversely proportional to the baseline MPOD, which indicated that patients with lower MPOD at baseline exhibited a greater increase in MPOD than patients with a higher MPOD at baseline. However, MPOD of the control group kept the same levels through the 4-week measurement period.

The results of our previous study indicated the increasing levels of lutein in serum after 6-week intake of the same supplement [41]. After oral consumption, serum lutein concentrations rapidly reach a peak, within 16 h [42]. During continuous lutein administration, the serum levels increase and reach a plateau within the first 2 weeks [43]. Those prior findings are consistent with the early increase of MPOD observed in the present study. The process by which carotenoids and their degradation

products are removed from the retina is unclear. However, macular carotenoid levels are known to be remarkably stable. Slow turnover and maintenance of MP have been reported following long periods of supplementation with lutein [44]. The present study also revealed that MPOD remained stable over 2 weeks after the end of supplementation, consistent with the results of a previous study [45].

At baseline, there were no gender differences in MPOD. However, with a fixed dose of supplementation, the increase in MPOD was greater in females than in males. The mechanisms involved in gender differences in the increase of MPOD are unclear. Hormonal influences may induce gender differences in the behavior of proteins involved in the absorption and transportation of lutein and zeaxanthin. Several highly selective transport proteins are involved in the specific selection of lutein and zeaxanthin for incorporation in the retina and other ocular tissue [46]. Dietary carotenoids are released from food matrices through the action of esterases, cleaved by carotenoid cleavage enzymes, and solubilized into micelles [47]. A cell surface glycoprotein, scavenger receptor class B, located on intestinal mucosal cells, then facilitates uptake and transport of carotenoids to the portal circulation in the chylomicron fraction [48, 49]. Carotenoids are then secreted into the lymphatic and portal circulation for transport to the liver. Carotenoids are modified in the

liver before release into the bloodstream [50, 51]. Most hydrophobic carotenoids, such as lycopene and beta-carotene, are transported on low-density lipoprotein, whereas the more hydrophilic lutein and zeaxanthin are carried by high-density lipoprotein (HDL) [52]. The scavenger receptor class B facilitates uptake of lutein, zeaxanthin, and other carotenoids into retinal and intestinal cells [53]. Lutein and zeaxanthin are specifically uptaken by selective binding proteins on retinal pigment epithelial cells, such as glutathione S-transferase P1 [54] and steroidogenic acute regulatory domain protein 3 [55]. Individual differences with respect to increases in MPOD after supplementation may result from variations in proteins involved in the absorption and transportation of lutein.

Gender differences have been also reported with respect to the transport proteins described above. Females reportedly exhibit a less atherogenic lipid profile than males due to higher levels of HDL [56–58], which carries lutein and zeaxanthin to the retina. Serum HDL is significantly associated with serum lutein/zeaxanthin and MPOD [59]. Reportedly, estrogen affects plasma lipoprotein metabolism [60, 61]; this may affect carotenoid availability because of the role of lipoprotein in carotenoid transport. Gender differences in MPOD may thus be due to the hormonal influence on absorption and transportation of carotenoids. Although plasma concentrations of lutein and zeaxanthin were positively correlated with MPOD in both genders, dietary fat was correlated with MPOD in a disparate manner between genders: positively in males and negatively in females [62]. Additionally, adipose tissue lutein concentration was significantly negatively correlated with MPOD in females, but significantly positively correlated in males [63]. These gender-related differences suggest that lutein and zeaxanthin are dynamic tissue components and that lutein metabolism may differ between genders.

The preservation of visual sensitivity has been associated with higher MP density in patients over 60 years of age [64]. Obana and coworkers [65] reported that MPOD levels decline by >10% with every 10-year increase in age. A reduction in MPOD after cataract surgery was also reported [29, 66]. Among elderly patients over 60 years of age in the present study, 6 weeks of lutein supplementation induced an increase in MPOD of nearly 30%; these increases were more significant in patients with lower baseline MPOD. These findings suggest that lutein supplementation may increase MPOD, thereby counteracting the aging-related decrease in MPOD and protecting photoreceptors; this may improve visual sensitivity in el-

derly individuals, especially those with lower MPOD and those who have undergone cataract surgery. Lutein supplementation may further prevent the onset and progression of AMD in those patients.

It has been reported that the individual intake of lutein might not be sufficient to increase the MPOD levels [67]. The supplement used in this study also included vitamin C (Vit C), vitamin E (Vit E), β -carotene, selenium (Se), and Zinc (Zn). Several investigations have demonstrated the protective effects of Vit C, Vit E, and Zn against the risk of AMD [68–70]. In addition, the Age-Related Eye Disease Study Research Group reported reduced development of advanced AMD among patients who received Vit C and Vit E plus Zn [71, 72]. The combination of Vit E, Vit C, and Se has been also reported to reduce the risk of AMD, although no significant protective effects were found with respect to separate supplementation with each individual component [73]. Lutein and zeaxanthin supplements alone did not influence AMD progression over 3 years [74], although lutein and zeaxanthin supplements did influence this progression when used in combination with other antioxidant supplements [75, 76]. The increases in MPOD observed in this study may thus be due to the synergistic effects of Vit E, Vit C, Zn, Se, and lutein included in the supplement used in this study.

In addition to dietary and supplement intake, several factors may influence MPOD; these include genotype [77], lifestyle characteristics (e.g., increased body fat [78, 79]), and sunlight exposure [80–82]. An important limitation of this study is that those factors were not evaluated. However, the following potential confounders were considered. With respect to metabolic health status, no patients with systemic diseases (e.g., diabetes) were included. Concerning nutritional status, questionnaires regarding dietary details were administered at baseline and 2 weeks later; there were no remarkable changes in either group. Because both study and control groups were continuously enrolled according to the surgery schedule, it is unlikely that patients in the study group had different nutritional awareness, compared with patients in the control group. Although we did not extensively investigate lifestyle factors, phenotypes, and sunlight exposure that could also influence MPOD, it is unlikely that those factors considerably differed between patients in the study and control groups because both groups were continuously enrolled according to the surgery schedule. Furthermore, there were no differences in baseline MPOD between the study and control groups.

MPOD can also be measured with physical techniques, such as fundus reflectometry [83] and autofluorescence

[84]. Although these methods may be more objective, they require expensive equipment and time-consuming procedures that are difficult for both the examiner and examinee. To the best of our knowledge, no reference method has been established for MP quantification [85, 86]. In this study, the MPOD was measured with heterochromatic flicker photometry, which is a psychophysical method broadly used for MPOD assessment [87, 88]. However, heterochromatic flicker photometry has several limitations, mainly with respect to patient compliance and usage in patients with low visual acuity. Nonetheless, it is rapid and easy to use. Strong correlations with the objective measurements obtained using fundus reflectometry [89] indicate that heterochromatic flicker photometry results are reliable.

Conclusions

MPOD increased after lutein supplementation in pseudophakic patients. Lutein supplementation is presumed to increase MPOD and could delay the onset of AMD after cataract surgery, especially in patients with lower MPOD. With a fixed amount of lutein supplementation, MPOD increased more in females than in males. These findings suggest that there are gender differences in absorption and transportation of carotenoids, which need further investigation.

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Statement of Ethics

Informed consent was obtained from all patients for inclusion before they participated in the study, and the study was performed in accordance with the tenets of the Declaration of Helsinki. Approval was granted by the Human Experimentation Committee of the Saitama Medical Center in Dokkyo Medical University (Dokkyo Ikadaigaku Saitama Iryousenta Seimei Rinri linkai) (No. 22025).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.H. and S.H. conceived, designed, and performed the experiments; R.H. analyzed the data; S.H. contributed to materials and analysis tools; R.H. and S.M. wrote the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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