Oral Lutein Supplementation Enhances Macular Pigment Density and Contrast Sensitivity but Not in Combination With Polyunsaturated Fatty Acids

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Purpose. It has been shown that lutein and zeaxanthin accumulate in the macula where they enhance contrast sensitivity and may reduce the risk of progression to advanced age-related macular degeneration (AMD). Furthermore, omega-3 long-chain polyunsaturated fatty acids (PUFA) might further reduce this risk. However, controversy exists regarding whether PUFA may reduce the bioavailability of lutein.

Methods. This was a prospective 12-month, randomized, open label study evaluating the effect of supplementation with lutein, other antioxidants, and minerals on contrast sensitivity (CS) and macular pigment optical density (MPOD) in patients with age-related maculopathy. A total of 79 patients were randomized to either lutein (10 mg) and antioxidant supplement or lutein and antioxidant supplement in combination with PUFA. Patients received supplementation for a period of 6 months and were followed for a total of 12 months.

Results. Serum lutein and zeaxanthin increased significantly by the first follow-up visit at 1 month, and remained elevated throughout the intervention period of 6 months in the lutein-only group but not in the lutein+PUFA group. Macular pigment optical density and CS increased significantly in the lutein-only group ($P < 0.005$) but not in the lutein+PUFA group ($P = 0.059$) compared to baseline. Best-corrected visual acuity remained unchanged during the entire study period in both groups.

Conclusions. Addition of PUFA may reduce the bioavailability of lutein and therefore lessen the beneficial effect on macular pigment and CS. This needs to be considered when prescribing lutein supplements to patients with low lutein levels. (ClinicalTrials.gov number, NCT00563979.)

Keywords: macular pigment, macular pigment, lutein, lutein, contrast sensitivity, contrast sensitivity

Macular pigment (MP) is composed of several carotenoids, mainly the two hydroxy-l-xanthophylls lutein (L) and zeaxanthin (Z). It has been speculated that MP has a protective role in the development and progression of age related maculopathy (ARM). Macular pigment reaches its highest concentration in the photoreceptor axons in the center of the fovea, where zeaxanthin is concentrated 2-fold higher than lutein, but in the periphery this relationship is reversed. The properties of MP include a high capacity to absorb short-wavelength blue light, and it has therefore a protective function for the fovea. It works as a broadband filter for the macula, with an absorbance peak at 460 nm. Two advantages result: The macula’s optical accuracy is enhanced, and the damaging photo-oxidative influence of light on the neurosensory retina is reduced. Assuming that the formation of free radicals is one cause of development of age-related macular degeneration (AMD), a high concentration of MP in the macula might be protective against light-induced oxidative damage and a low concentration increase the risk of AMD.

Mammals are not able to synthesize carotenoids but have to ingest them in food or as food supplements. Studies have shown a significant association between MP optical density (MPOD) and lutein blood serum levels. Furthermore, there is a positive association between MPOD and dietary intake of carotenoids, either by dietary modification or by supplementation. Recently, the role of omega-3 polyunsaturated fatty acid (PUFA) for prevention of AMD has been discussed. High levels of docosahexaenoic acid (DHA), an omega-3 fatty acid, are present in the disc membranes of photoreceptor outer segments. The specific role of DHA in the rod outer segment membranes is yet unknown. However, it is believed that DHA and its precursor eicosapentaenoic acid (EPA) play an important role in the retina and may be involved in the development of retinal diseases. Several epidemiologic studies have investigated the effect of PUFA on the progression of AMD, but the results were inconclusive. Recently, the Age-Related Eye Disease Study 2 (AREDS2) demonstrated no beneficial effects of DHA + EPA on the progression of AMD.

Nevertheless, various supplements containing high doses of PUFA are available and are widely used to prevent and slow down AMD progression.
In the current study we have investigated the effects of lutein/zeaxanthin supplementation as well as supplementation with lutein/zeaxanthin in a fixed combination with PUFA.

**Materials and Methods**

**Study Participants**

Consecutive patients who were referred to the outpatient department of the Department of Ophthalmology, Inselspital, University Bern, for AMD were recruited between July 2007 and June 2008 for this prospective study. Inclusion criteria were age over 50 years with early or intermediate AMD. Exclusion criteria were other eye disease in the study eye and opacities of optical media precluding fundus photography. Only one eye of each patient was included in the study. If both eyes were eligible for the study, the eye with more advanced AMD changes was included.

**Study Design and Procedures**

This was a 12-month, randomized, open label study evaluating the effect of supplementation with lutein and other antioxidants and minerals on contrast sensitivity (CS) and MPOD in patients with AMD. Eligible patients were randomized in a 1:1 ratio to either lutein and other vitamins (VitaluxPlus; Novartis, Basel, Switzerland) or lutein, omega-3, and other vitamins (VitaluxOmega, Novartis). The antioxidants and minerals in VitaluxPlus and VitaluxOmega are shown in Table 1. Both drugs were commercially available at the time of the study.

All patients received supplementation for a period of 6 months and were followed for a total of 12 months. Examinations were scheduled at baseline, month 1, and months 3, 6, 7, 8, 9, and 12. At each visit a comprehensive ocular examination with best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, CS using the Pelli-Robson charts, dilated binocularophthalmoscopy, color fundus photography (FF 450 plus; Carl Zeiss Meditec, Jena, Germany), and MPOD measurement were performed. At each visit the empty blisters from the study medication were collected and a pill count was performed to ensure compliance with the study medication.

Additionally, serum concentrations of lutein and zeaxanthin were measured. Contrast sensitivity was assessed using the total contrast sensitivity score (CS score) ([number of letters–3] × 0.05). Macular pigment optical density measurements were obtained with the modified confocal scanning laser ophthalmoscope (mpHRA; Heidelberg Engineering, Heidelberg, Germany) using autofluorescence images obtained at two wavelengths based on pioneering work of Delori et al. According to previous work, we quantified MP densities by calculating a macular pigment density (MPD) map and comparing foveal and parafoveal autofluorescence at 488 and 514 nm. Density maps were obtained by subtracting the log images digitally. The central MPD (MPDc) is indicated in optical density units (D.U.) and was calculated within a 1° diameter circle centered on the fovea. All quantitative analyses were done by the software provided by the manufacturer of the scanning laser ophthalmoscope. Assessment and evaluation of respective imaging technique have previously been described in detail.

The primary objective of the study was to evaluate the effect of supplementation on CS and MPOD after 6 months. Secondary outcome measures were the change of CS, MPOD, BCVA, and serum concentrations of lutein and zeaxanthin over the time period of 12 months. Statistical analyses were conducted with SPSS software (SPSS, Inc., Chicago, IL, USA). In order to compare both treatment arms, data were analyzed using repeated measures ANOVA. Paired t-test was used to evaluate changes from baseline to the primary endpoint within one treatment arm. The level of significance was set at 0.05.

Prior to any study procedures, written informed consent was obtained from each patient after an extensive discussion about the purpose of the study and all the risks associated with participation. The research followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. This study is registered at ClinicalTrials.gov (NCT00563979).

**Results**

A total of 79 patients were randomized to the two treatment groups (lutein, n = 40; lutein+omega, n = 39). Demographics of included patients are summarized in Table 2. Six subjects were smokers, 25 subjects were ex-smokers, and 50 subjects had never smoked. All patients had medium or large drusen or AMD pigmentary abnormalities. The two treatment arms were
Comparably with respect to baseline characteristics (Table 2). The first patient visit took place in July 2007, and the last study visit took place in June 2009.

During the first 6 months of the study, all patients took daily supplementation of 10 mg of lutein with or without omega-3 fatty acids. No subject developed any systemic or ocular disorders during the study period.

The MPOD levels were 0.54 ± 0.19 D.U. for the lutein group (L) and 0.56 ± 0.21 D.U. for the lutein+omega group (L+O) at baseline. The MPOD levels increased after 6 months of supplementation to 0.66 ± 0.18 and 0.60 ± 0.22 D.U., respectively. The increase in the lutein group was highly significant (P < 0.005), whereas the change in the lutein+omega group failed to be significant (P = 0.059). ANOVA for repeated measurements revealed a significant difference between the two groups (P < 0.01) at the primary endpoint. The MPOD levels over the entire study period of 1 year showed a relatively slow decrease (Fig. 1). The differences between the groups were significant (ANOVA, P < 0.01).

The CS score was 1.29 ± 0.25 for the lutein group and 1.23 ± 0.27 for the lutein+omega group at baseline. Contrast sensitivity increased to 1.60 ± 0.22 in the lutein group (P < 0.01) and remained unchanged in the lutein+omega group after 6 months (1.30 ± 0.25; P = 0.086). ANOVA for repeated measurements revealed a significant difference between the two groups (P < 0.01) at the primary endpoint. The CS score drastically decreased after cessation of the supplementation after 6 months in the lutein group, whereas no changes were observed in CS in the lutein+omega group (Fig. 2). The differences between the groups were significant (ANOVA, P < 0.01).

Plasma levels of lutein (Fig. 3) and zeaxanthin (Fig. 4) showed changes only in the lutein group. Values in the lutein+omega group remained unchanged during the study period. The differences between the groups were significant for the plasma concentrations of lutein as well as for zeaxanthin (ANOVA, P < 0.01). The BCVA letter score remained unchanged during the entire study period in both groups (baseline L: 80 ± 7 ETDRS letters, L+O: 79 ± 11 ETDRS letters; 6 months L: 79 ± 7 ETDRS letters, L+O: 80 ± 11 ETDRS letters; 12 months L: 81 ± 5 ETDRS letters, L+O: 80 ± 10 ETDRS letters).

**DISCUSSION**

Lutein and zeaxanthin as nutritional supplements have been extensively investigated in biomedical and nutritional research, as they selectively accumulate in the macula. The characteristic yellow aspect of the macula is due to the presence of MP composed of lutein and zeaxanthin, which absorb blue light and prevent peroxidation of lipids in the retina. 17 Beside other factors, MP density is currently under investigation as a predictive factor in the development of AMD. 18–25 Although there is growing evidence that oxidative damage contributes to the development of AMD, 12,22,23 and that MP is protective against ARM, 18,24,25 this still remains unproven and considerable controversy exists. 26 Previous studies have shown a positive correlation between lutein intake and MPOD. 27–30 Substitution of lutein with a lutein dose of 10 mg or above resulted in a significant increase in serum levels of lutein and MPOD. 31

Recently, the role of PUFA in the pathophysiology of AMD has been discussed. Since the retina contains high concentrations of DHA, it has been speculated that supplementation with PUFA may help to prevent progression of AMD. 5,10,32,33 However, these epidemiologic studies have been used only to generate hypothesis and cannot show whether supplementation of PUFA leads to a significant effect on the progression of AMD. For this, prospective randomized clinical trials would be necessary.

Here, we show that supplementation of omega-3 PUFA with lutein leads to significantly lower plasma lutein levels when
Although the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD, there is generally no need for supplementation with lutein. However, the study population in AREDS2 has been reported to be a well-nourished cohort, and in subgroup analysis of subjects with the lowest dietary intake of lutein + zeaxanthin, lutein + zeaxanthin demonstrated a protective effect for progression to advanced AMD. And although the primary analyses demonstrated no beneficial effect of lutein/zeaxanthin in the treatment of advanced AMD in AREDS2, the post hoc analyses suggested that lutein and zeaxanthin may well play a role to reduce the risk of AMD progression, whether given with or without beta-carotene.46 Furthermore, it has been shown that lutein leads to improved CS, however, without increase in visual acuity, and thus may improve patients’ quality of life.57 As such, lutein supplementation may still be beneficial for a subgroup of patients suffering from ARM.

Our study has some limitations that need to be considered. Firstly, although we found a striking difference in lutein level between patients supplemented with VitaluxPlus and VitaluxOmega, we cannot conclusively define which lipid components may have led to decreased serum lutein levels in the omega group. Another limitation is that we have not measured serum levels of PUFA in our study. We have no data on bioavailability of the ingredients of either drug; therefore we cannot exclude that the bioavailability of lutein and zeaxanthin in the VitaluxOmega is reduced. However, since Vitalux with a combination of lutein + zeaxanthin and DHA + EPA is commercially available, the information on the reduced effect on MP changes may be important. Further investigations are necessary to clarify the interaction of lipid supplementation with intestinal lutein uptake. Additionally, further studies are needed to investigate the serum levels of the PUFA. Also, genetic polymorphisms may be another influencing factor worth studying in this context. Furthermore, because of the lack of placebo control there are no data with which to compare the active treatments. Taken together, serum lutein levels and MPOD are increased after supplementary intake of lutein. However, strikingly, serum lutein levels and MPOD were not increased after supplementation of lutein with concentrated fish oil containing DHA and EPA. This suggests that supplementation with specific fatty acids in lipids may largely prevent intestinal lutein uptake and therefore abolish the positive effects of lutein supplementation. This needs to be
taken into account when prescribing lutein supplementation for patients with AMD. Our findings further support the outcome of AREDS2 showing that intake of DHA + EPA has no beneficial effect for treatment of AMD. Therefore, we see very little reason to add DHA + EPA to the AREDS or other supplement formulations.

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