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Serum and macular responses to multiple xanthophyll supplements in patients with early age-related macular degeneration

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ABSTRACT

Objective: This randomized controlled trial examined serum and macular (in vivo measured macular pigment optical density [MPOD]) responses to supplemental lutein and zeaxanthin in Chinese subjects with early age-related macular degeneration.
Methods: One hundred and eight patients with early age-related macular degeneration older than 50 y were randomized to low lutein (LL; 10 mg/d), high lutein (HL; 20 mg/d), lutein plus zeaxanthin (LZ; each 10 mg/d), or placebo during a 48-wk intervention. Serum concentrations were quantified by C_{30} high-performance liquid chromatography (at baseline and 4, 12, 24, and 48 wk), and MPOD was measured by analysis of autofluorescence images (at baseline and 24 and 48 wk).
Results: Serum lutein levels in the LL, LZ, and HL groups increased significantly in the first 4 wk and then increased 4.24-, 4.66-, and 6.23-fold during the trial, respectively (all $P < 0.001$). The serum lutein level in the HL group was significantly higher than that in the LL or LZ group at 48 wk ($P < 0.05$). Similarly, the serum zeaxanthin concentration in the LZ group increased 3.11-fold at 48 wk. MPOD increased smoothly in all treated groups, and the increase from baseline was greatest in the HL group at 24 and 48 wk (both $P < 0.05$). MPOD and serum lutein levels increased linearly with the dosage and their increasing rates were statistically correlated (all $P < 0.05$). No notable changes were detected in the placebo group for MPOD and serum concentrations.
Conclusion: Xanthophyll supplementation significantly increased serum concentrations and MPOD in patients with early age-related macular degeneration, and a higher lutein supplementation (20 mg/d) might be more effective in increasing these two biochemical markers in Chinese patients without significant side effects.

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Introduction

Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness, with a prevalence of 30 to 50 million, causing more than 8 million cases of blindness worldwide [1]. It is also a major epidemic in Asian countries, with prevalences of 6.8% for early AMD and 0.56% for late AMD in Asians 40 to 79 y old [2].

Lutein (L) and its isomer zeaxanthin (Z; L&Z) are known as xanthophylls or macular pigments (MPs) for their selective dense concentration in the human retina [1]. They are thought to protect the retina against photo-oxidative damage and, hence, prevent the progression of AMD by functioning as antioxidants and blue-light filters [3]. Indeed, several large population studies have indicated that less L&Z in the serum and macula (in vivo measured as MP optical density [MPOD]) might lead to the progression of AMD [4,5].

Intervention studies have suggested supplemental L and/or Z could significantly increase their serum concentrations and improve visual function in patients with AMD [6], although the change of MPOD has varied among studies [7,8]. One explanation was that the distinct distribution of L&Z in the perifovea and parafovea might influence the pattern of MP deposition during supplementation [9]. Because Z is selectively higher than L in the foveal center, where the greatest protection is needed, and presents in approximately equal amounts of L in the central 3 mm of macula, an equal dose of mixed L&Z (10:10 mg), at

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a Z dose five times higher than that in the Age-Related Eye Disease Study (AREDS) II (10:2 mg), was used in this study to explore the dynamic distribution of supplemental Z together with L in serum and the macula for further guidance [10].

To date, treatments for late AMD are limited in scope and efficacy [11]. It is generally accepted that late AMD, which often means vision loss and depression, mostly arises from early AMD (tolerable symptoms including blurred, dark vision or visually asymptomatic) [12]. Given the possible preventive role of L&Z supplementation, interest in its preclinical treatment for early AMD has increased. However, mostly controversial information has derived from observational studies [13,14], and only two trials conducted in developed countries have shown the effects of L and Z on early AMD, although they had a small samples and limited dose groups or had no placebo group [10,15].

Therefore, an intervention study with a reasonable sample size on the effect of supplemental L&Z in patients with early AMD should be quite interesting. This double-blinded, randomized, placebo-controlled trial was designed to investigate the macular and serum responses to varied L dosages and a 1:1 combination with Z in Chinese patients with early AMD and ultimately to provide useful supplementation suggestions for patients with early AMD.

Materials and methods

Subject recruitment

Volunteers were recruited from local communities in Beijing by posters, newsletters, and recommendations. Inclusion criteria included an age older than 50 y, clear ocular media for fundus visualization and photography, corrected visual acuity above 0.25, no history of L and/or Z supplementation, good general health, and a diagnosis of early AMD. Only those who met the standard of category 2 (small drusen [$<$63 μm, $n \geq 10$], or some intermediate drusen [63–124 μm, $n < 15$], or AMD-related pigment abnormalities) and category 3 (many intermediate drusen [63–124 μm, $n \geq 15$], or at least one large drusen [$>$125 μm], or non-central geographic atrophy) in the AREDS system were defined as having early AMD in this study [16,17]. Those who had other ocular diseases or reported an abnormal digestive condition were excluded.

Of the 330 volunteers who were telephonically screened, 212 were examined by professional ophthalmologists using funduscopy and fundus photographs, and 108 of those who met all the recruitment criteria were enrolled.

The study complied with the tenets of the Declaration of Helsinki and was approved by the institutional review boards of Peking University. Written informed consent was obtained from each subject. The study was registered in the ClinicalTrials system (NCT01528605).

Study design

This was a 48-wk, double-blinded, randomized, placebo-controlled study. Subjects randomly received low L (LL; 10 mg/d), high L (HL; 20 mg/d), L plus Z (LZ; each 10 mg/d), or placebo. All supplements had the same appearance, were in identical coded bottles, and manufactured by Beijing Yuguang Bioscience Research Center Co., Ltd. (Beijing, China). Study staff, examiners, and subjects were unaware of the treatment allocation.

Subjects were instructed to maintain their ordinary dietary habits and finish a food-frequency questionnaire mainly focused on food containing L&Z at weeks 0 and 48. All subjects were required to bring the supplement bottles and compliance calendars every 4 wk when picking up new monthly supplements. Approximately 98% of the subjects took 95% of the supplements every month.

Characteristic information, including gender, age, smoking status, waist circumference, height, and weight, was collected at baseline from questionnaires and physical examinations. Fasting blood samples were collected at weeks 0, 4, 12, 24, and 48, immediately centrifuged for serum, and stored at −80°C until high-performance liquid chromatographic (HPLC) analysis. Total cholesterol, triacylglycerol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured at baseline by an autoanalyzer at the Beijing Lawke Health Laboratory. Autofluorescence (AF) images and fundus photographs were taken at baseline and 24 and 48 wk in the Beijing Third Hospital. Subjects were encouraged to report any adverse effects immediately and were asked specifically about adverse events every 4 wk.

HPLC analysis

Serum L, Z, and β-carotene were extracted and analyzed by a modified classic HPLC method [18,19]. Briefly, 0.5 mL of serum and 0.5 mL of an internal standard (β-Apo-8′-carotenal) were precipitated with 0.5 mL of ethanol and extracted into 0.7 mL of hexane. The supernatant hexane layer was removed, and the extraction procedure was repeated twice more. The combined supernatants were evaporated to dryness under nitrogen, solubilized in 0.2 mL of solvent A (see next paragraph), and 20 μL was injected for HPLC analysis.

The analysis was performed on a Hewlett-Packard/Agilent Technology model 1100 HPLC system with a C_{30} column (5 μm, 4.6 × 250 mm; Develosil, Seto, Japan). The mobile phase was acetonitrile:methanol (60:40 by volume; solvent A) and methyl-tert-butyl ether (solvent B). The gradient procedure, at a flow rate of 1 mL/min, began at 100% solvent A before proceeding to 58% solvent A over a 15-min linear gradient, followed by a 5-min linear gradient to 20% solvent A, a 10-min gradient back to 100% solvent A, and a 5-min hold for equilibration detected at 450 nm. All procedures were performed under dim light through HPLC analysis.

Lutein, Z, and β-carotene were adequately separated and quantified by comparing peak areas of the analyte on high-performance liquid chromatograms calibrated against known standard amounts. Concentrations were corrected by monitoring the recovery of the internal standard in case of extraction and handling losses.

MPOD measurement

This AF method for measuring MPOD has been described in detail elsewhere and has been used previously in clinical studies [20–22]. Briefly, quantitative images of the fundus AF were taken by two qualified ophthalmologists using a Heidelberg Retina Angiograph (HRA-II, Heidelberg Engineering, Inc., Heidelberg, Germany) under dim light. A pupillary diameter of 6 mm was required after dilation by drops containing tropicamide. Subjects were requested to look straight ahead, with a minimal amount of motion. Aligned images were analyzed by MATLAB (MathWorks, Inc., Natick, MA, USA). The attenuation of the AF in the center was presumed to be proportional to the amount of blue-light–absorbing MP. Only one eye of each subject was chosen following the selection sequence of AMD stage and the right eye. For example, if both eyes of the subject was classified as early AMD, the right eye will be chosen.

Statistical analysis

Statistical analysis was conducted with SPSS 13.0 (SPSS, Inc., Chicago, IL, USA). Comparisons of characteristics among groups or different intervals were analyzed using analysis of variance for continuous variables and the chi-square test for categorical variables. Differences between baseline and follow-up measurements within groups were explored with a paired t test and general linear regression analysis. Linear correlations were assessed for the association between dosage and L body levels (serum L and MPOD). Statistical significance was set at $P < 0.05$.

Results

Subject baselines

In total 108 subjects (46 men and 62 women, mean age 67 y, range 50–81 y) participated in this study, and 27 subjects were randomly assigned to each group. Only one male subject from the LL group was excluded because he failed to attend two follow-up visits. Baseline characteristics, serum L&Z concentrations, and the MPOD of subjects were comparable among the four groups (Table 1). Among all variables, baseline MPOD was inversely correlated with age ($R = -0.28$, $P = 0.04$) and positively correlated with baseline serum L concentration ($R = 0.21$, $P = 0.034$). In addition, individual dietary intakes of L&Z were not statistically different before and after the intervention ($P = 0.65$).

Serum concentrations

Serum concentrations of L&Z responded positively to supplementation, whereas no significant changes were observed in the placebo group for L and Z (Table 2). All serum L levels in the non-placebo groups increased significantly from baseline to

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