Dose-Ranging Study of Lutein Supplementation in Persons Aged 60 Years or Older

Julie M. Rosenthal,[1] Jonghyeon Kim,[2] Francisco de Monastario,[3] Darby J. S. Thompson,[2] Richard A. Bone,[4] John T. Landrum,[4] Fabiana F. de Moura,[5] Frederick Khachik,[5] Huiping Chen,[6] Rosemary L. Schleicher,[6] Frederick L. Ferris III,[1] and Emily Y. Chew[1]

Purpose. To examine the dose–response relationship between oral lutein supplementation and serum lutein concentrations in persons aged 60 years and older, with or without age-related macular degeneration (AMD).

Methods. Forty-five participants with no AMD, large drusen, or advanced AMD, were randomized to receive one of three doses (2.5, 5, or 10 mg) of lutein for 6 months and to be observed for 6 additional months after the cessation of lutein supplementation.

Results. The mean age of the participants (33 women) was 71 years (range: 60–91). The serum lutein concentrations of each dose group were similar before supplementation, increased at 1 month, and peaked by 3 months. Median serum concentrations of the 2.5-, 5-, and 10-mg groups from baseline to month 6 increased from 18.7 to 35.1 μg/dL (2-fold increase), from 17.8 to 59.2 μg/dL (2.9-fold increase), and from 15.1 to 66.8 μg/dL (4-fold increase), respectively (all $P < 0.001$). The increases in lutein serum concentrations did not vary with AMD disease severity ($P = 0.98$). No toxicity was observed with any dose of lutein. No significant changes were detected in visual acuity or visual field tests.

Conclusions. Increasing doses of lutein supplements significantly increased the serum levels of lutein and zeaxanthin, and doses up to 10 mg were safely administered. A long-term large clinical trial is necessary to investigate the safety and efficacy of lutein in reducing the risk of the development of advanced AMD. (*Invest Ophthalmol Vis Sci.* 2006;47:5227–5233) DOI: 10.1167/iovs.05-1513

Age-related macular degeneration (AMD) is a leading cause of legal blindness—specifically, central vision loss—in persons over the age of 50 years in developed countries.[1] A recent analysis estimated that approximately 1.75 million U.S. residents have advanced AMD (neovascular [NV] AMD and geographic atrophy [GA]), whereas more than 7 million have large drusen in one or both eyes, putting them at risk for the development of AMD. With increasing longevity, these numbers may increase by as much as 50% by 2030.[2]

Treatments for advanced AMD are limited in scope and efficacy. To date, there is no approved therapy that has been shown to improve visual acuity for more than a small proportion of persons with advanced AMD. Laser photocoagulation and photodynamic therapy with Visudyne (Novartis Pharmaceuticals, East Hanover, NJ) are proven treatments that are beneficial in reducing the risk of moderate or severe vision loss from neovascular AMD.[3–5] More recently, anti-vascular endothelial growth factor (VEGF) treatment with intravitreal pegaptanib, and ranibizumab has been demonstrated to reduce the risk of moderate and severe vision loss from neovascular AMD.[6,7] Other anti-VEGF compounds are currently being investigated, such as now FDA-approved bevacizumab,[8] for the treatment of neovascular AMD.

Although the pathogenesis of AMD is not known, damage caused by oxidative stress is one plausible mechanism.[9] Observational data from epidemiologic studies suggested a possible role for antioxidants in reducing the risk of AMD. Results from case–control studies, such as the Eye Disease Case Control Study (EDCCS), showed that higher serum levels and dietary intake of individual carotenoids, especially lutein, were associated with a statistically significant reduction in the risk of neovascular–exudative AMD.[10,11] Data from the National Health and Nutrition Examination Survey (NHANES) showed that higher levels of dietary lutein and zeaxanthin were associated with a reduction in advanced AMD.[12] Other studies have found similar results,[13,14] whereas still others have failed to find an association or the results have not reached statistical significance.[15–21]

The Age-Related Eye Disease Study (AREDS), a randomized controlled clinical trial of high-dose antioxidant vitamins (vitamins C, E, and β-carotene) and minerals (zinc and copper), demonstrated that the combination of antioxidant vitamins and zinc treatment reduce the risk of progression to advanced AMD by 25%.[22] The beneficial results of these antioxidant vitamins and zinc support the notion that oxidative stress may indeed be an important aspect of the pathogenesis of AMD.

Lutein is one of the major dietary carotenoids found in human plasma and serum and ocular tissues. Approximately 25% of the total retinal carotenoids are found in the rod outer segments. Although the retinal carotenoids are found throughout the retina, both lutein and zeaxanthin are concentrated in the macula, and they are also called the macular xanthophylls.[23] In vitro studies have shown that both lutein and

From the [1]Clinical Trials Branch, Division of Epidemiology and Clinical Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland; the [2]EMMES Corporation, Rockville, Maryland; the [3]Office of the Clinical Director, National Eye Institute, National Institutes of Health, Bethesda, Maryland; the [4]Department of Chemistry and Biochemistry, Florida International University, Miami, FL; the [5]Joint Institute for Food Safety and Applied Nutrition, Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland; and the [6]Centers for Disease Control and Prevention, Atlanta, Georgia.

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Corresponding author: Emily Y. Chew, Building 10, CRC, Room 3-2531, 10 Center Drive, MSC 1204, Bethesda, MD 20892-1204; echew@nei.nih.gov.

zeaxanthin provide protection from oxidative damage induced either by exposure to UV radiation or by incubation with a peroxidation initiator.[24] Lutein acts in biological systems as (1) an important structural molecule within cell membranes; (2) a short-wavelength light filter; (3) a modulator of the intra- and extracellular reduction–oxidation (redox) balance; and (4) a modulator in signal-transduction pathways. It may also modulate processes or factors involved in the immune response. Humans do not have the capacity for de novo biosynthesis of lutein and are thus dependent on dietary sources.

The importance of lutein supplementation in the treatment of AMD has not yet been tested in a large-scale trial. Commercial preparations of lutein were not available at the start of the AREDS study, although it was considered a likely candidate for inclusion. The National Eye Institute is planning the AREDS 2, a controlled, clinical trial of lutein and other nutrients for preventing the development of advanced AMD. The present dose-ranging study was conducted to assess the association of three different oral doses of lutein with increases in serum levels, to determine the amount of lutein to be used in the AREDS 2. Other goals included evaluation of measurements of optical densities of the macular pigment, visual acuities, visual fields, and adverse events. The concentrations of the carotenoids in the serum were measured at both the Centers for Disease Control (CDC) and the University of Maryland, and the results from the two groups were similar. The present report summarizes the serum data from the CDC. The data from the laboratory at the University of Maryland will be presented in another report in which the concentration results of other metabolites from the carotenoids will be included.

METHODS

Study Objectives and Design

The primary objective of this dose-ranging study was to examine the effects of oral supplementation with three different doses of lutein (2.5, 5, and 10 mg) on the serum lutein concentration in patients with AMD of various severities. The secondary objective of this study was to investigate the relationship between lutein absorption, AMD severity, and macular pigment density.

Forty-five participants over age 60 were equally stratified at baseline into three categories based on the level of disease severity: small or no drusen; large drusen; and advanced AMD in at least one eye. Within each stratum, the 15 participants were randomized into three groups of 5 each, with each group receiving one of the three doses of lutein. Participants returned 1 week after the baseline visit, at which time the 6-month daily oral supplementation period began. Participants were observed for an additional 6 months after cessation of daily supplementation. Follow-up visits were scheduled for week 1 and months 1, 3, 6, 9, and 12. Fasting blood samples were drawn from participants and assessed in a masked fashion at the CDC for serum lutein and other fat-soluble micronutrients at each study visit. The present study also collected information of dietary sources of lutein from a food-frequency questionnaire (FFQ) that was focused on foods containing lutein at each visit based on the Minnesota Nutritional Coordinating Center. The questionnaire did not ask for information on other carotenoids and did not allow for adjustments for energy intakes. The FFQ informed us of any change in dietary intake of foods high in lutein since the last visit. Complete ophthalmic exams were performed at each visit, including manifest refraction, visual acuity measurements, and visual field (Humphrey 10-2; Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA). Optical densities of macular pigment within the central 1.5° were measured by heterochromatic flicker photometry (HFP; 460 vs. 540 nm), to evaluate macular pigment changes in response to lutein supplementation.[25] The optical density of the pigment (at 460 nm) was computed by the log ratio of the intensity of the 460-nm light in the foveal match to that of the 460-nm light in the extrafoveal match (8° superiorly). Each measurement was replicated five times in both retinal locations. Color vision testing (Panel D-15) was conducted before HFP.

In addition to collecting information about adverse events, safety was assessed with the following: visual acuity, comprehensive ophthalmic examination, fundus photography, liver function tests, visual field tests, and the AREDS side-effect questionnaire.

This study protocol was approved by the Institutional Review Board of the National Eye Institute (NEI; National Institutes of Health, Bethesda, MD). The study design and data were reviewed and monitored by the NEI Data and Safety Monitoring Committee. Informed consent was obtained from each subject in accordance with the guidelines of the Declaration of Helsinki.

TABLE 1. Demographics and Baseline Serum Levels

	2.5 mg	5.0 mg	10 mg	*P*
n	15	15	15	
Age	71.4 ± 9.0	70.5 ± 10.4	71.5 ± 8.4	0.95
BMI	25.8 ± 3.5	25.3 ± 3.6	27.1 ± 5.4	0.50
Sex (female)	12	11	10	0.91
Race	14 White/1 Asian	11 White/2 Asian/2 Black	15 White	0.16
Alcohol	12 Occasionally/3 never	11 Occasionally/4 never	2 Daily/12 occasionally/1 Never	0.22
Ever smoked (yes)	8	9	9	1.00
Visual acuity (letters)	75.5 ± 18.0	68.7 ± 27.7	70.6 ± 28.4	0.56
FFQ estimates of lutein and zeaxanthin (μg/dL)	1.8 ± 1.0	3.5 ± 2.2	3.0 ± 2.2	0.04
Serum levels (μg/dL)				
Lutein	20.0 ± 5.8	19.0 ± 7.4	19.0 ± 9.2	0.92
Zeaxanthin	4.8 ± 1.3	4.5 ± 1.5	4.6 ± 1.7	0.89
α-Carotene	10.5 ± 10.3	6.1 ± 3.9	7.4 ± 5.7	0.23
β-Carotene	49.8 ± 46.6	39.6 ± 31.3	39.9 ± 39.4	0.73
cis-β-Carotene	3.3 ± 3.0	2.8 ± 2.1	2.4 ± 2.1	0.59
β-cryptoxanthin	13.1 ± 13.0	11.2 ± 5.8	11.1 ± 4.8	0.79
γ-Tocopherol	86.9 ± 49.5	104.3 ± 55.0	108.5 ± 60.9	0.53
Retinyl palmitate	2.5 ± 1.4	2.2 ± 1.2	2.2 ± 1.1	0.69
Retinyl stearate	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.4	0.58
Retinol	62.0 ± 9.7	61.6 ± 12.6	68.1 ± 10.6	0.21
α-Tocopherol	2174.3 ± 940.9	1893.9 ± 815.6	1996.0 ± 491.3	0.61

Data are the mean ± SD.

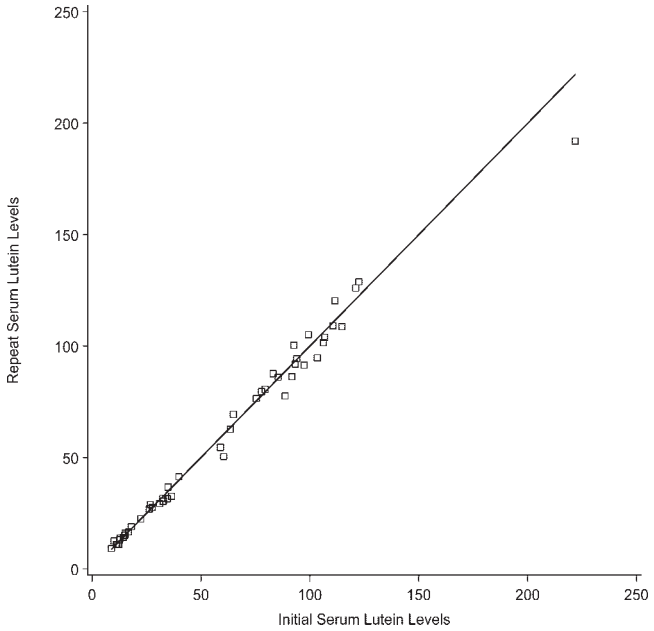

FIGURE 1. Reproducibility of serum lutein concentrations (micrograms/decaliter) of those participants who had extreme increases (approximately fivefold increase compared to baseline levels) after supplementation. Only data for those with extreme values at any visit before 6 months are shown (multiple data points shown per person).

Serum Assay Method

Carotenoids, including total lutein and total zeaxanthin, were measured by using a modification of a routine HPLC method, with the major changes being use of a smaller volume of serum, a different internal standard, and gradient elution on a high-carbon-load C18 column, to separate lutein from zeaxanthin.[26] Quantification was accomplished by comparing the peak height or area of the analyte in serum with the peak height or area of a known amount of standard in a calibrator solution. Calculations were corrected based on the peak height or peak area of the internal standard. Carotenoids were compared with apo-8′-carotenal at 450 nm. Values higher than NHANES III 99% reference ranges were recalculated and confirmed. In many cases, samples were diluted by a factor of 2 or 3, and/or different volumes (5, 10, 15, or 30 μL) were injected to assess linearity, and/or samples were processed using multiple extractions to enhance recovery.

Analysis Methods

The primary outcome measure in this study was serum lutein concentration (micrograms per decaliter). To assess the reproducibility of the assay, serum concentrations of two samples taken before oral supplementation (baseline and week 1) were compared by using a paired *t*-test. The generalized estimating equation method was applied to investigate the trends and variations of serum concentrations of lutein measured over the 6-month supplementation course of the study.[27] As the response variable, the change in serum concentrations from baseline in log units was chosen to reduce the influence of a small number of extreme serum concentrations, to adjust for participants' individual serum concentrations of lutein at baseline, and to have a stable variability of serum concentrations across dose groups within each disease level. Also, to study the association between macular pigment density and lutein, changes in pigment densities from baseline pigment density in log units were compared among the three dose groups. The analysis of variance model was used for testing whether mean changes in visual acuities differed among the three dose arms. Parsimonious and well-fitted models for each outcome was searched by a backward variable selection of the following variables: disease severity, age, gender, smoking history, alcohol status, other sources of lutein and zeaxanthin intakes (estimated from the responses to the FFQ), body mass index (BMI), and the first and the second order of duration (in weeks) of oral supplementation.

RESULTS

Baseline Characteristics

Thirty-three female and 12 male participants, ranging in age from 60 to 91 years (mean, 71), were enrolled (Table 1). Twenty-six participants had a history of smoking for ≥6 months, and three were active smokers at enrollment. All participants completed 1 year of follow-up except one, who underwent intracranial surgery for meningioma after his 3-month visit.

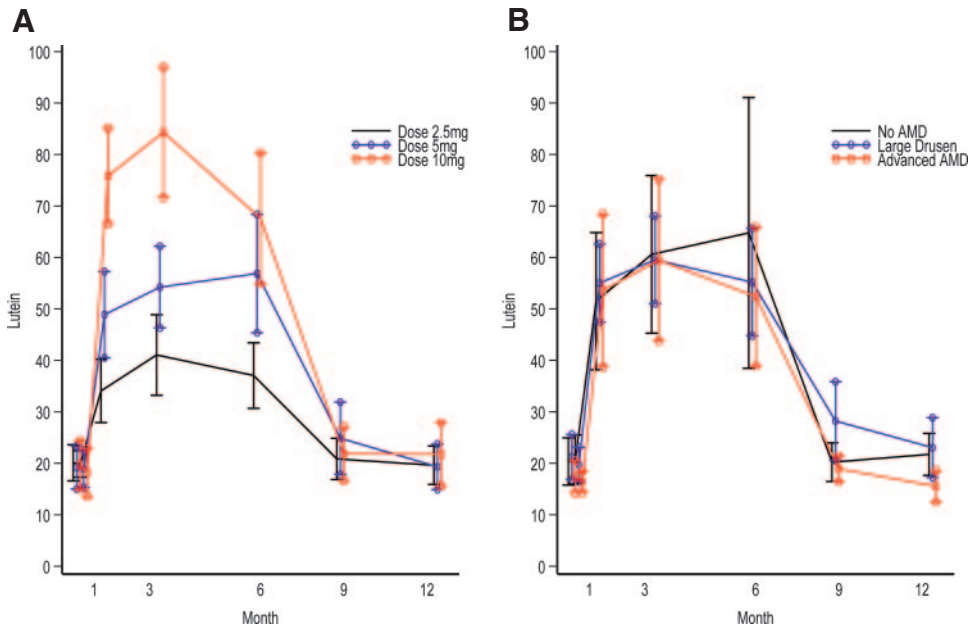

FIGURE 2. Average and 95% CI of serum lutein concentration by dose (**A**) and by AMD severity (**B**). The average serum lutein levels and the 95% CI during the course of the study according to the three doses, 2.5, 5, and 10 mg (**A**) and by AMD severity: no AMD, large drusen, or advanced AMD across all dose groups (**B**).

TABLE 2. Summary Statistics of Serum Concentrations of Lutein

	Dose			AMD		
	2.5 mg	5 mg	10 mg	Small or No Drusen	Large Drusen	Advanced AMD
Baseline*	20.0 ± 5.8	9.0 ± 7.4	19.0 ± 9.2	20.6 ± 9.0	20.5 ± 7.5	16.9 ± 5.0
Month 1	34.1 ± 11.8	48.9 ± 16.5	75.8 ± 18.	51.5 ± 26.3	55.0 ± 15.0	53.6 ± 28.4
Month 3	41.0 ± 15.5	54.2 ± 15.7	84.3 ± 25.0	60.6 ± 30.3	59.5 ± 16.8	59.5 ± 31.0
Month 6	37.1 ± 12.6	56.9 ± 22.7	80.3 ± 48.5	64.8 ± 52.0	55.2 ± 20.6	52.4 ± 25.8
Month 9	20.9 ± 7.9	24.9 ± 13.9	21.9 ± 10.0	20.2 ± 7.4	28.2 ± 15.1	18.9 ± 4.7
Year 1	19.6 ± 7.4	19.3 ± 8.	21.8 ± 11.7	21.7 ± 8.1	23.0 ± 11.5	15.5 ± 5.8

Data are the mean ± SD (μg/dL).

* $n = 15$ for each dose and each AMD severity level throughout the study, except for the loss of 1 participant due to a brain tumor that developed before his 6-month visit. He was randomly assigned to the 10-mg group, and he had advanced AMD in one eye.

Participant Adherence to Study Drugs

Study tablets were dispensed to participants at week 1. To assess adherence, participants were asked to bring the bottles to all subsequent visits. The bottles were weighed and compared to the baseline weights. The bottle weights were not different among the dose groups during the study ($P > 0.45$ at each postrandomization visit). Approximately 90% of the participants had less than 10% of the study medications remaining in the bottles at the end of the 6-month period.

Lutein Serum Concentrations

Baseline. Serum concentrations of lutein and other micronutrients were assessed twice before oral supplementation (baseline and week 1) and the two serum concentrations were found to be similar (mean difference in lutein serum concentrations of 0.68 μg/dL, 95% confidence interval (CI) for the mean difference was −0.41 to 1.77 ($P = 0.21$ by the paired *t*-test). The average of the two baseline lutein serum concentrations was used as the single baseline value in the repeated-measures analysis of lutein serum concentration.

Reproducibility. The assays from the CDC indicated that some participants had extremely high serum lutein concentrations at months 3 and 6 compared with those seen in AREDS and the NHANES.[22,28] To confirm these high levels, split or duplicate blood samples of participants who had extremely high increases after supplementation were sent in a masked fashion to the CDC, and the lutein serum concentrations were found to be virtually identical between the original blood sample and the back-up sample (correlation coefficient = 0.99; Fig. 1).

Repeated-Measures Analysis for the Changes in Lutein Serum Concentrations. Serum lutein concentrations increased through the month-3 visit and then stabilized until the cessation of supplementation at month 6 (Fig. 2A). After oral supplementation stopped, lutein serum concentrations returned to the baseline level. There were no noticeable differences detected in the serum concentrations among the three AMD severity levels (Fig. 2B), possibly because of the large variations of serum concentrations of the individual participant or the small sample sizes in each of the AMD severity levels. The increasing magnitude of serum concentrations from baseline significantly correlated with the increase in the dose of lutein in each disease stratum. Variations in serum concentrations were higher during the oral supplementation period than those at baseline or after oral supplementation (Table 2). Increases in lutein serum concentrations at month 6 were approximately 2-, 2.9-, and 4-fold for the 2.5-, 5-, and 10-mg doses, respectively (Table 3). Because zeaxanthin made up 4% to 7% of the compound, its serum concentrations also increased by 1.3- to 1.5-fold increase. There was no significant suppression of the other serum antioxidant vitamin concentrations by the lutein supplementation, although the power to detect a difference is limited by the small sample size (Table 3).

Disease severity, age, gender, smoking history, alcohol status, other sources of lutein and zeaxanthin intakes (estimated from FFQ), and BMI were not significantly associated with the increase in serum lutein concentration. Only the effect of dose and the first- and the second-order duration (in weeks) were significant. Table 4 presents pair-wise comparisons of increases in serum concentrations (in log units) with adjustment for age

TABLE 3. Median Serum Concentrations at Baseline and Median Percent Changes at Follow-up Months 3, 6, and 9

	Baseline Median			Median % Change at Month 3			Median % Change at Month 6			Median % Change at Month 9		
Specimen (μg/dL)	2.5	5	10	2.5	5	10	2.5	5	10	2.5	5	10
Lutein	18.7	17.8	15.1	79	165	363	100	185	300	−4	4	10
Zeaxanthin	5.0	4.6	4.3	28	30	41	28	40	45	16	4	−1
α-Carotene	6.4	5.3	6.4	22	3	15	9	8	−21	36	−9	−2
β-Carotene	36.7	36.4	31.7	18	−6	13	24	−5	−1	21	2	7
cis-β-Carotene	2.5	2.73	2.1	4	2	21	14	−6	14	10	−11	−1
β-Cryptoxanthin	8.3	12.6	12.0	4	−3	10	25	7	−5	13	9	−1
γ-Tocopherol	70.4	88.5	89.3	−12	19	−13	−22	15	−21	−23	−1	−22
Retinyl palmitate	2.0	2.1	2.1	−4	−7	5	−3	−2	4	21	15	24
Retinyl stearate	0	0.2	0.2	—	—	—	—	—	—	—	—	—
Retinol	62.2	57.6	69.0	4	4	−4	2	−6	−8	3	5	−2
α-Tocopherol	1955.0	1645.4	1841.8	6	−1	−1	12	−2	−13	3	6	−4

Doses are in milligrams.

TABLE 4. Comparison of Increases in Serum Concentrations Adjusted to Age and Duration of Oral Supplementation

Relative Increase	Estimate	95% CI Lower Limit	95% CI Upper Limit	*P*
10 mg vs. 2.5 mg	2.366	1.877	2.984	<.0001
5 mg vs. 2.5 mg	1.554	1.232	1.959	0.0002
10 mg vs. 5 mg	1.523	1.177	1.971	0.0014

Data were acquired at the 6-month supplementation follow-up and are expressed in log units.

and duration. The 10- and 5-mg groups have 2.37 ($P < 0.0001$) and 1.55 ($P = 0.0002$) times higher increases in serum concentrations than the 2.5-mg group, respectively. The 10-mg group had a 1.52 times higher ($P = 0.0019$) increase in serum level than did the 5-mg group.

Serum Zeaxanthin Concentrations

Although the formulation used in this study consisted mainly of lutein, approximately 4% to 7% of the compound is zeaxanthin. This is reflected in the 28% to 45% increase in the serum zeaxanthin concentration with all three doses of lutein and three AMD levels (Fig. 3; Table 3). These increases were not statistically significant among all the three dose groups or the three AMD levels (all $P > 0.264$).

Food-Frequency Questionnaire

Dietary intakes of lutein and zeaxanthin were estimated from the FFQ at baseline and the 1-, 3-, 6-, and 9-month visits. Average dietary levels in each dose group remained unchanged during the follow-up (data not shown). Thus, the increase in serum lutein concentration was attributed to the supplement.

Use of the AREDS Type Formulation and Other Supplements

During the course of the study, the results of AREDS were announced. To the present study participants with large drusen or advanced AMD in at least one eye, we recommended the AREDS formulation, which consisted of vitamin C (500 mg), vitamin E (400 international units), β-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide). Nine participants took the AREDS formulation during the lutein oral supplementation phase, with five of them taking it from enrollment through study close-out. There was no significant reduction in the serum carotenoids or other antioxidant vitamin concentrations in the serum.

TABLE 5. Visual Acuity by Dose Groups

Dose	Dose Group 2.5 mg	5 mg	10 mg	*P*
Baseline (mean/median)	75.5/80	68.7/83	70.6/81	0.56
Changes (letters) from baseline				
Month 1	1.0/0	0.8/1	0.8/0	0.98
Month 6	0.5/2	0.9/1	1.7/1	0.65
Month 9	0.6/1	−1.2/0	0.4/0	0.37

Macular Pigment Densities

Because of abnormal color vision and poor visual acuity (worse than 20/80), most participants with end-stage AMD were not able to visualize the light well enough to perform the flicker photometry. Even when only those subjects with good visual acuity were analyzed, the data were not sufficiently reproducible (data not shown).

Visual Field

Most study participants had stable visual field measurements. Two participants with advanced AMD had some measured change; one participant taking 2.5 mg had an approximately 13-dB improvement, whereas one participant taking 5 mg lost 8 dB.

Visual Acuity

Best corrected visual acuity was obtained at each study visit (Table 5). No significant changes in mean visual acuity over the follow-up were found among the three dose groups ($P > 0.372$). Three participants with advanced AMD (two receiving

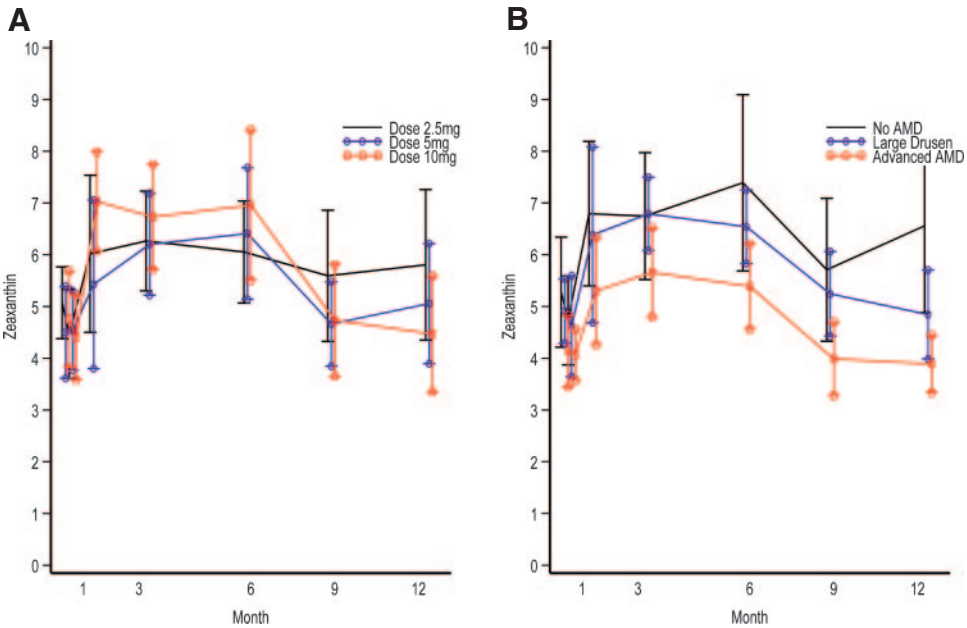

FIGURE 3. Average and 95% CI of serum zeaxanthin concentration by dose (**A**) and by AMD severity (**B**). Data are as described in Figure 2.

2.5 mg and one, 5 mg) experienced a ≥10-letter decrease in visual acuity at month 6, compared with baseline. Three participants (two with large drusen and one with advanced AMD on 5 mg, and one participant with large drusen on 10 mg) experienced a gain of 10 or more letters. No other participants experienced a change of 10 letters or more in visual acuity, and all maintained stable visual acuity over the follow-up period.

Adverse Events

No adverse side effects were recorded on the AREDS side-effects questionnaire or in visual function (visual acuities and visual fields). Liver function test results remained unchanged. There was no suppression of the other antioxidant vitamin levels in the serum by the lutein supplementation (Table 3).

Discussion

In this small pilot study, we have evaluated how the serum concentration of lutein in persons with various degrees of AMD severity responded to oral supplementation with lutein by measuring their serum concentrations of lutein. During the 6-month period of lutein supplementation, serum concentrations of lutein in all participants rose with increasing doses of lutein, regardless of the AMD severity status. The highest dose of lutein (10 mg) was safe as a supplement in this 6-month period, as measured by the AREDS side-effects questionnaire, visual function tests, liver function testing, and the concentrations of other nutrients. The highest dose (10 mg) led to a fourfold increase in serum concentration. Of interest, even the serum zeaxanthin concentration increased despite the relatively small amount of zeaxanthin in this compound. There was no significant reduction in the serum carotenoids or other antioxidant vitamin concentrations. It is known that repeated serum measurements of many fat-soluble micronutrients in the same person on different occasions show substantial variation. Intraindividual coefficients of variation for carotenoids are typically between 18% and 26%.[29,30] Intraindividual variation for α-tocopherol is between 8% and 11%; similar information for γ-tocopherol is unavailable. The apparent changes in carotenoid and tocopherol concentrations over the course of this study are most likely attributable to normal biological variation. Given this variation, and our small sample size, our power to detect a difference in serum carotenoids may be severely limited. No adverse events related to the study medication were reported.

We were unable to demonstrate increases in macular pigment corresponding to increases in lutein serum concentrations, as the measurements of macular pigments were not reproducible. Administering HFP to patients with AMD was difficult because of their macular disease. This technique has been tested in only limited numbers of patients with AMD. It is a psychophysical test, and for some it is difficult to learn. In addition, the subjects are expected to fixate well. Those of advanced age (i.e., the population of interest in most AMD studies) are those who have the most difficulty with the task. The lack of reproducibility of this test may be due to difficulties with the testing and perhaps the lack of sufficient training before the start of the study. Other investigators, however, have used HFP (with an instrument of different design) and have favorable test–retest results in women 50 to 79 years of age.[31] Other methods of measuring macular pigment may have less of a subjective component and thus may be more easily applied to an elderly population, including Raman spectroscopy, autofluorescence imaging, or one of the various reflectance photometric methods.[32–35]

Further study is needed to elucidate the roles of lutein and zeaxanthin in macular degeneration. Currently, using the results of AREDS and the present study, the National Eye Institute is launching a large-scale randomized controlled trial of lutein and zeaxanthin supplements to evaluate the effects on the incidence and progression of AMD in the AREDS 2. The role of ω-3 long-chain polyunsaturated fatty acids, specifically docosahexanoic acid and eicosapentaenoic acid, will also be evaluated. This study will also provide an opportunity to refine the AREDS formulation by assessing formulations without β-carotene and lower doses of zinc. The data from AREDS 2 will provide valuable information regarding the role of these additional nutritional supplements on the development and progression of AMD, a disease of significant public health importance.

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