Age-related macular degeneration (ARMD) is the leading cause of vision loss in aging Western societies, accounting for 45% of all visual disability in the United States. Increasing age is associated with increasing prevalence of ARMD. Atrophic ARMD constitutes 90% of all cases. It results in a chronic, painless, bilateral, asymmetric, paracentral, or central photoreceptor-retinal pigment epithelium (RPE) disturbance. ARMD has increased in prevalence in Great Britain in the last 60 years, suggesting that genetic predisposition is not the primary etiologic factor. In Japan, the prevalence of ARMD is increasing, possibly from a shift to a more-Westernized diet.

ARMD is a complex disorder that involves genetic, cardiovascular, environmental, and nutritional components. Recent identification of a locus on chromosome 1q31 associated with increased susceptibility to ARMD may some day allow testing of high-risk individuals. After aging, smoking remains the most significant risk factor for ARMD. Smoking is known to deplete serum antioxidants, alter blood viscosity, alter the auto regulation flow mechanism of blood vessels, and is associated with lower levels of macular xanthophylls pigments, such as lutein. Environmental risk factors include exposure to solar radiation/blue light and photosensitizing drugs. Low fruit and vegetable consumption increases the risk of ARMD. A population-based cross-sectional survey revealed that ARMD is lower in a self-sustained farming community than elsewhere in the industrial world. The long-term, large-population National Eye Institute Age-related Eye Disease Study (NIH AREDS, 2001) showed that in people with intermediate or moderately advanced ARMD...
in one eye (but not the opposite eye), the combination of vitamins C, E, beta-carotene, zinc, and copper reduced 5-year risk of severe visual loss by 25%. As with AREDS, we also found that broad-spectrum antioxidant/mineral supplements delayed the progression of the disease, but did not reverse visual loss.\textsuperscript{20,21}

Low intake of lutein, the primary dietary carotenoid xanthophyll pigment responsible for macular pigment optical density (MPOD) in primates, is a major risk factor for advanced ARMD.\textsuperscript{16,22-24} The eyes of the elderly, smokers, blue-eyed individuals, post-menopausal women, and the retinas of autopsied ARMD patients have reduced lutein.\textsuperscript{10,24-28} Lutein intake and high MPOD are hypothesized to play a preventive and therapeutic role in optimizing eye health.\textsuperscript{29-31} AREDS did not evaluate lutein nor its potential effects on MPOD and ARMD.\textsuperscript{18}

The objective of the lutein antioxidant supplementation trial (LAST study) is to evaluate the effect of lutein alone or a more complete nutritional supplement of lutein in combination with additional carotenoids, antioxidants, vitamins, and minerals (referred to as L/A), on MPOD and central vision outcome measures in atrophic ARMD.

**Methods**

The study was approved by the R&D and Human Subjects Committees at the Department of Veterans Affairs (DVA) North Chicago and Hines Hospitals and took place between August 1999 and May 2001. Eligibility included diagnosis of atrophic ARMD (ICD9 362.51) by stereo bio-ophthalmoscopy and at least one vision-degrading visual-psychophysical abnormality associated with ARMD in one or both eyes.\textsuperscript{32,33} The latter include depressed contrast sensitivity (CSF, discussed later) at one or more of four spatial frequencies [3, 6, 12, or 18 cc/degree] not attributable to cataract or ocular disease; an abnormal photo-stress glare recovery (GR) deficit or deficits of the Amsler grid (i.e., intermittent/permanent visual spots [scotomas]); or distortions of lines (metamorphopsia). Inclusion criteria also included clear non-lenticular ocular media [cornea, aqueous, and vitreous], free of advanced glaucoma and diabetes or any other ocular or systemic disease that could affect central or parafoveal macular visual function. Subjects were excluded if they had undergone recent (within 6 months) cataract or retinal surgery, were taking photosensitizing drugs [such as phenothiazines and chloroquine], or did not meet ophthalmic/visual entrance criteria. Subjects were excluded if they had taken lutein supplements within the previous six months.

**Study design**

This was a 12-month randomized, double-masked, placebo-controlled clinical trial. One hundred nine subjects were registered by an optometrist and ophthalmologist, with 19 excluded because they: were fundus-positive, but had no visual psychophysical abnormality ($n = 9$); voluntarily withdrew during baseline workup ($n = 6$); received ARMD laser treatment ($n = 2$), or had pre-retinal membrane ($n = 1$) or Alzheimer’s disease ($n = 1$). Following written informed consent, 90 subjects (86 men and 4 women) were randomly assigned to one of three capsule groups by consecutive random card—3-choice, allocation sequence.

Randomization was applied to the entire sample of 90 subjects, with 29 in Group 1 L, 30 in Group 2 L/A, and 31 in Group 3 P. Serial eye examinations were performed on 28, 28, and 30 subjects after 4 months of intervention; 26, 26, and 28 subjects after 8 months of intervention; 25, 24, and 27 subjects after 12 months of intervention (for Groups 1 L, 2 L/A, and 3 P, respectively). During the 12-months’ clinical trial, 1, 2, and 1 subjects were lost to followup; 1, 0, and 2 subjects died; and 2, 4, and 1 subjects had other reasons for withdrawal (for Groups 1 L, 2 L/A, and 3 P, respectively). Compliance was assessed by telephone at 1 week, 2 weeks, 4 weeks, 6 weeks, 3 months, and 12 months. During the one-year study, 96% of the subjects took approximately 92% of their assigned capsules. There were no differences in compliance among the three groups.

We selected a dose of 10-mg non-esterified lutein to approximate food-equivalent lutein intake from spinach in our pilot case series experiments.\textsuperscript{33-35} Group 1 L received only lutein [FloraGlo\textsuperscript{®} from Kemin Foods International, Des Moines, Iowa]; Group 2 L/A received lutein plus additional antioxidants and nutrients [OcuPower\textsuperscript{®} from Nutraceutical Sciences Institute [NSI] , Boynton Beach, Florida], and Group 3 P received maltodextrin. The L/A OcuPower\textsuperscript{®} supplement consists of 10-mg lutein [FloraGlo]; 2,500 IU vitamin A;
15,000 IU natural beta carotene {Betatene®}; 1,500-mg vitamin C [as calcium ascorbate–Ester C®]; 400 IU vitamin D3; 500 IU natural vitamin E (d-alpha tocopherol succinate); 50-mg vitamin B1; 10-mg vitamin B2; 70-mg vitamin B3; 50-mg vitamin B5; 50-mg vitamin B6; 500-mcg vitamin B12; 800-mcg folic acid; 300-mcg biotin; 500-mg calcium; 300-mg magnesium; 75-mcg iodine; 25-mg zinc [as zinc L-methionine—L-OptiZinc®]; 1-mg copper; 2-mg manganese; 200-mcg selenium; 200-mcg chromium; 75-mcg molybdenum; 600-mcg lycopene; 160-mg bilberry extract [standardized to 25% anthocyanosides]; 150-mg alpha lipoic acid; 200-mg N-acetyl cysteine; 100-mg quercetin; 100-mg rutin; 250-mg citrus bioflavonoids; 50-mg plant enzymes; 5-mg black pepper extract {Bioperine®}; 325-mg malic acid; 900-mcg taurine; 100-mg L-glycine; 10-mg L-glutathione; and 2-mg boron. Nutraceutical Sciences Institute prepared the lutein capsules, the L/A capsules, and the P capsules and also maintained and concealed the blinding and four-digit allocation codes. Bottles with masked four-digit allocation codes were sent to the assigned research pharmacist at V.A. Medical Center, North Chicago. All personnel at the V.A. Medical Center were unaware of the masked allocation codes during the 12-month clinical study. Subjects were provided with opaque capsules of identical appearance in numbered containers taken as three capsules twice per day with food. Independent verification of lutein content was performed via random sampling and high-performance liquid chromatography at Kemin Foods, Inc.

Nutritional status was assessed using Food Frequency Questionnaires (FFQs), which the subject and/or spouse completed at baseline and final 12-month visit. All FFQs were analyzed by Harvard University, School of Public Health. Subjects were encouraged not to alter their diets.

Objective measures

Ophthalmic testing was conducted at baseline and at 4 months, 8 months, and 12 months. Baseline and final ocular lens opacification (cataract) were evaluated subjectively by a single observer, using a Haag–Streit slit-lamp biomicroscope. A 7-increment validated Lens Opacity Cataract Scale (LOC-SIII) photographic transparency was placed on a 5000 K color temperature, 8-watt fluorescent photographic light box, according to standard procedures. Retinal images were taken with a Canon model CF-600 Vi Fundus camera at baseline and study completion, and were rated by a single retinologist, masked to image date or intervention group.

MPOD was measured by heterochromatic flicker photometry using a MacularMetrics® instrument [Rehoboth, Massachusetts], according to the manufacturers’ protocol. It was determined by subjects matching a one-degree 460/540 nanometer flickering stimulus for perceived brightness foveally and at a retinal location seven degrees extra-foveally, where the MPOD is virtually zero.

Refractive error was neutralized with lenses prior to acuity and glare testing at each visit, and resultant trial lenses were used for all vision tests. Glare recovery (GR) is a measure of both macular function and retinal health. Subjects monocularly viewed a 6500 lux, 5000 K color temperature light box held at 40 cm from their eye for one minute pre-adaptation. Following this visual stress, the subject was asked to attempt to read a threshold low-contrast line of print. Examiners monitored accuracy and time required for macular function to return to normal following the photo-stressed condition. One minute or less to recovery is normal.

Monocular visual acuity at distance was measured via random presentation of distance Snellen letters on a Mentor Ophthalmics BVAT–II® computer screen under mesopic lighting conditions. Low-vision patients with Snellen acuity less than 20/200 were tested with a Designs for Vision® Feinbloom distance acuity test for the partially sighted. In both cases, fractional Snellen acuity was converted to Log minimal angle of resolution (LogMAR). Visual acuity at near was measured for each eye using low- and high-contrast SKILL test targets.

Contrast sensitivity function (CSF) measures the least amount of contrast needed to detect visual stimuli at different spatial frequencies. It identifies selective retinal deficits in visual processing at an earlier stage than is possible with conventional visual acuity testing. The Vector Vision CSV 1000® contrast sensitivity test system was used. For low-vision patients, the CSV 1000L-V Pelli–Robson type single large letter chart of varying contrasts was used.

Activities of daily living, night driving, and glare recovery symptoms were evaluated on a 4- to
20-point VFQ–14 rating scale used by the National Eye Institute and described previously. Subjects were also provided an integrated instruction sheet/questionnaire/Amsler grid to monitor changes in vision over time. Subjects at each visit were asked if they felt their overall vision had worsened, remained the same, or improved, and the number of boxes missing (scotomas) or distorted (metamorphopsia) were counted. Reports of vision change were digitally videotaped.

### Statistical analysis

Repeated measures analysis of variance (ANOVA) assessed main ophthalmic outcome variables attributable to the time of measurement, treatment condition, and their interaction. Follow-up analyses for significant group differences were done by pair-wise comparisons between baseline and each time point (using pooled error terms) for unequal n’s, and a Bonferroni correction factor. The Friedman’s two-way ANOVA by rank test, a non-parametric test, was used in place of the repeated measures ANOVA when the assumptions for a parametric ANOVA were not satisfied [i.e., severity of disease comparisons with small sample sizes]. Finally, all analyses were conducted for each eye separately. At no time were results averaged across both eyes.

Power analysis was based on the guidelines put forth by Kirk. A minimum group size of 30 would be needed to detect a standard effect size of 1.0 at an error rate (Alpha) of 0.01, with a desired power (Beta) of 80 for three groups. Similarly, a minimum group size of 30 is considered adequate to detect a standard effect size of 1.0 with an error rate (Alpha) of 0.05.
and a desired power (Beta) of 0.90 for three groups. Repeated measures involve multiple instances of sampling the same subjects, thereby substituting for larger samples consisting of independent subjects.

Baseline characteristics

The L, L/A, and P groups did not differ in age, years diagnosed with ARMD, smoking, caffeine/alcohol use, iris color, multivitamin use, and dietary lutein and iron intake (see Table 1). There were also no statistical differences among the three intervention groups in cataract or ocular lens opacification parameters, visual acuity, glare recovery ability, quality of vision as measured by CSF, or the presence or absence of scotomas/m metamorphopsias on Amsler grid testing. Right eyes Group 2 L/A have 0.7 log units less MPOD at baseline (P = 0.05) with a commensurate trend in increased lens color and decreased low spatial frequency CSF (P = 0.10), relationships reported previously.49,50 All of this is consistent with a higher body mass index which was found in Group 2 L/A (P = 0.06).

Nutritional characteristics at baseline and 12 months

Intervention groups were similar as to caloric and nutrient intake at baseline and 12 months, except
for higher supplemental zinc intake in Group 3 P \( (P = 0.04) \). There were no time-dependent dietary changes, or intra-group differences in consumption of total or individual bioflavonoids (apigenin, kaemferol, luteol, myricetin, or quercetin). There were no clinically significant time-dependent differences or intra-group differences in dietary consumption of five major carotenoids (lutein, alpha carotene, beta-carotene, lycopene, and cryptoxanthin), except for dietary lutein in Group 2 L/A, increasing from 2.1 mg to 3.3 mg by 12 months \( (t\text{ test}, \ P = 0.04) \).

Primary outcome intervention data and significance

Repeated measures (RM ANOVA) were conducted on macular pigment optical density, near and distance visual acuity, glare recovery, quality of vision as measured by CSF at multiple spatial frequencies, and ARMD retinopathy differences. The analyses revealed significant between-group differences, as well as significant within-group differences over time.

Between-group differences

The RM ANOVA on right eye MPOD showed a significant group by time of measurement interaction \( [F(2,70) = 4.3, \ P < 0.02] \). Group means (average of right and left eyes) showed a mean MPOD increase of 0.09 log units for Group 1 L, a 0.08 log unit increase for Group 2 L/A, but a small 0.03 log unit decrease for Group 3 P. Follow-up pair-wise comparisons (using the pooled error) between baseline and each time point for each of the three groups was conducted. Changes in right-eyes MPOD indicated a significant difference between Group 2 L/A and Group 3 P (mean MPOD difference = 0.15, Bonferroni corrected \( P = 0.02 \)). A trend was noted for the difference between Group 1 L and Group 3 P (mean MPOD difference = 0.11, Bonferroni corrected \( P = 0.10 \)). A marginally significant interaction was noted for left-eyes MPOD change over time \( [F(2,77) = 2.8, \ P = 0.068] \). To test for overall effects, the difference between mean eye MPOD at baseline and final study visit was calculated. The ANOVA on this difference was significant \( [F(2,80) = 3.7, \ P = 0.03] \). Mean (average of right- and left-eyes) MPOD increased approximately 36% in Group 1 L (0.09 log units) and 43% in Group 2 L/A (0.08 log units), while Group 3 P showed a mean MPOD decrease of 0.03 log units over the duration of the study.

Primary Outcome Intervention Data: mean (SD) macular pigment ocular density (MPOD) by intervention group at baseline and final study visit. Mean eye MPOD improved 36% in the lutein group, 43% in the lutein/antioxidant group, and mildly decreased in the placebo group. Paired \( t \) test \( P \) values shown: \( n \) = number of eyes.
The MPOD increased in Group 1 L, independent of the severity of disease (see Figure 2).

The RM ANOVA on left-eyes near visual acuity showed a significant group by time of measurement interaction $[F(2,81) = 4.7, P = 0.01]$. Between baseline and final study measurement, Group 1 L showed a mean eye 5.4 Snellen letter equivalent improvement (95% CI = 2.7 – 9.0, $P = 0.01$); Group 2 L/A showed a mean eye 3.5 Snellen letter equivalent improvement (95% CI = 0.8 – 6.1, $P = 0.04$), while Group 3 P showed a 2.1 Snellen letter equivalent decrease (95% CI = −6.7 to 2.4). Follow-up pair-wise comparisons (using a pooled error term) on changes in near visual acuity over time showed a significant difference between Group 1 L and Group 3 P (Bonferroni corrected $P = 0.01$) and a marginally significant difference between Group 2 L/A and Group 3 P (Bonferroni corrected $P = 0.08$). The RM ANOVA for right-eyes near visual acuity was non-significant $[F(2,65) = 0.3]$. To test for overall effects, an ANOVA on the difference between mean right-/left-eyes near visual acuity ratings at baseline and final study visit was performed and found to be significant $[F(2,83) = 4.7, P = 0.013]$. These results reveal that near visual acuity averaged over both eyes increased a mean of 5.4 Snellen equivalent letters (about 1 line of visual acuity) in Group 1 L (95% CI = 2.5 – 8.2), and 3.5 Snellen equivalent letters in Group 2 L/A (95% CI = 1.2 – 5.8), but decreased 0.2 Snellen equivalent letters in Group 3 P (95% CI = −3.0 – 2.7).

**Within-group differences**

RM ANOVAS indicated significant main effects for time of measurement on glare recovery, quality of vision, and distance acuity measurements. Between baseline and final study visit, photo-stress recovery (in seconds) quickened by 25.9 seconds (SD = 64.6) in the right eyes and 29.5 seconds (SD = 61.3) in left eyes, regardless of group membership. Descriptive statistics within each group for each eye showed that photo-stress-recovery quickened by approximately 34.8 seconds in Group 1 L right-eyes (95% confidence interval [CI] 2.9 – 66.8) and 20.3 seconds in group
1 left-eyes (95% CI –0.3 – 40.9). In Group 2 L/A, there was a 30.2-second improvement in right-eyes (95% CI 1.0 – 59.4) and a 37.0-second change in left-eyes (95% CI 5.4 – 68.7). In Group 3 P, there was a 15.4-second improvement in right-eyes (95% CI –7.0 – 38.3) and 20.4 seconds for left-eyes (95% CI –12.5 – 53.2).

Averaging the data from the right and left photostress-recovery times, it can be seen that there was a mean improvement in recovery time of 27.3 seconds (SD = 52.7). Within the separate treatment groups, this is seen as a 23.7 second more rapid glare recovery for Group 1 L, a 34.7 second mean eye quicker glare recovery for Group 2 L/A, and a 22.7 second more rapid recovery for Group 3 P from the baseline values shown in Table 1.

Lutein also improved glare recovery, independent of AREDS retinal stage, at baseline and after 12 months of lutein: stage II, $n = 10$, median 135 sec (range, 15 to 180) versus 35 (15 to 140), $P = 0.02$; stage III, $n = 11$, 75 (15 to 180) versus 30 (12 to 90), $P = 0.28$; and stage IV, $n = 9$, median 90 and mean 102 (20 to 180) versus median 90 and mean 80 (5 to 135), $P = 0.05$; Friedman’s non-parametric statistics.

RM ANOVAs on quality of vision, as measured by CSF at multiple spatial frequencies over time, indicated significant within-group differences over time for the right eyes, measured at 3, 6, and 12 cycles(cc)/degree, and for the left eye, measured at 6 and 12 cc/degree. For each of these effects, within-group $t$-tests comparing baseline to final study visit showed the quality of vision improved significantly in both Group 1 L, and especially with a greater effect in Group 2 L/A (see Figure 3). Repeated factors ANOVA of VFQ–14 questionnaires concerning night driving were not significant for any group. However, glare recovery VFQ–14 ANOVA subscale data, from baseline (score $15.4 \pm 4.0$, $n = 30$), over time, showed a trend toward significance by 4 months ($15.7 \pm$
Lutein supplementation had no significant effect on CSF for AREDS retinal stage II or III. For exploratory purposes, we reviewed whether lutein significantly improved contrast sensitivity in patients with advanced AREDS stage IV disease. At three of four spatial frequencies, this small group of patients with advanced AREDS stage IV disease—who were also taking lutein (n = 5)—showed mean contrast sensitivity improvements at 6, 12, and 18 cc/degree (all P’s < 0.05) as follows:

**Table 2. Video-documented change in Amsler grid findings (scotomas and/or metamorphopsias)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Improve (no. of eyes)</th>
<th>Worsen (no. of eyes)</th>
<th>Net effect</th>
<th>Improve (no. of veterans)</th>
<th>Worsen (no. of veterans)</th>
<th>Net effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months</td>
<td>Lutein</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Lutein/A</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>8 months</td>
<td>Lutein</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Lutein/A</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2</td>
<td>3</td>
<td>–1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>12 months</td>
<td>Lutein</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Lutein/A</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>Lutein</td>
<td>26</td>
<td>9</td>
<td>17</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Lutein/A</td>
<td>25</td>
<td>14</td>
<td>11</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12</td>
<td>7</td>
<td>5</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2 presents the number of single eyes and veterans, by intervention group, self-reporting improvement or worsening in the Amsler grid in terms of scotoma(s) or metamorphopsia(s) at 4, 8, and 12 months, as compared to the previous visit. Only veterans having a change in Amsler grid status are listed. Six veterans in Group 3 placebo confounded the results by mean dietary intake of lutein of 9.9 mg/day, with improvement in three of these veterans for scotomas/metamorphopsias. For this post hoc analysis, these six veterans were removed from the data analysis. The net changes over time (gray highlighted)—taking into account both improvement and worsening of the Amsler grid, by eyes or by number of reporting veterans—was significant for Group 1 Lutein, Chi-square; P = 0.01).

3.7, n = 28, P = 0.06, repeated factors ANOVA) and 8 months (16.3 ± 3.3, n = 26, P = 0.09) for Group 2 L/A.

Descriptive statistics within each group showed Group 1 L right-eyes change of neg 0.10 LogMAR (95% CI neg 0.19 – neg 0.01) and left-eyes change of neg 0.03 (95% CI neg 0.09 – pos 0.03). Group 2 L/A showed a LogMAR change of neg 0.03 in right-eyes (95% CI neg 0.12 – pos 0.07) and neg 0.06 in left-eyes (95% CI neg 0.14 – pos 0.03). Group 3 P showed a neg 0.14 right-eyes improvement (95% CI neg 0.30 – pos 0.03), but a left-eyes worsening of pos 0.05 (95% CI neg 0.14 – pos 0.23).

Retinopathy and lens change

There was no progression in ARMD retinopathy for either eye in any group over the course of the study. Across all participants, right-eyes baseline AREDS stage was 3.06 (SD = 0.87) and right-eyes final AREDS stage was 3.10 (SD = 0.89); left-eyes baseline AREDS stage was 2.98 (SD = 0.92) and left-eyes final AREDS stage was 3.04 (SD = 0.90). Descriptive statistics within each group showed that Group 1 L had no change in right-eyes, but an average 0.07 increase in AREDS stage for left-eyes; Group 2 L/A showed no changes in AREDS stage for either eye; and Group 3 P showed a 0.09 increase in AREDS stage for right-eyes and a 0.07 increase in AREDS stage in left-
eyes. Nonetheless, there were no between-group differences in retinopathy during the study [univariate RM ANOVA, R eyes, \( P = 0.35 \); L eyes, \( P = 0.13 \)]. Statistical analysis also revealed no significant within- and between-group changes in lens opacification.

Post-hoc analysis of subjective visual change and Amsler grid

After analyses were completed, we reviewed dietary lutein intake and found that six participants in the placebo group ingested a higher-than-average amount. In fact, the amount they consumed (9.9 mg/d by food frequency analysis) was similar to what was included in the other two treatment groups. To examine how this may have influenced results, we removed these six subjects. Subjects at the final visit were asked whether their vision had improved, remained the same, or worsened. Though not statistically significant, there was a trend in subjective visual improvement in Groups L and L/A by Chi-square analysis \( (P = 0.10) \) following elimination of these six subjects from the placebo group (data not shown).

Serial evaluation of the Amsler grid at each 4-month study visit indicated net improvements in both Group 1 L and 2 L/A. Following elimination of these six subjects, the net change—based on these reports of improvement or worsening of the Amsler grid—was significant for Group 1 L [Chi-square, \( P = 0.01 \)], but not for Group 2 L/A [see Table 2].

Adverse effects

There were no significant between-group differences in minor side effects among Groups L, L/A, and P [data not shown]. None of the 30 patients assigned to Group 2 L/A had a major cardiovascular event [myocardial infarction, sudden death, angioplasty, coronary artery bypass surgery, or stroke] or death from any cause. In contrast, in the 31 patients assigned to Group 3 P, one patient had angioplasty, one patient died from cardiac disease, and one patient died from metastatic adenocarcinoma. In the 29 patients assigned to Group 1 L, two patients had angioplasty, one patient had a stroke, and one patient died from cerebrovascular disease and pneumonia. Thus, there was a non-significant trend for fewer major cardiovascular events or death in Group L/A (0/30) as compared to Groups L and P combined (7/60) [see Appendix].

Comment

Nutritional treatment of retinal disease has proved at least partially successful in common retinitis pigmentosa [vitamin A], Bassen–Kowzweig disease [vitamins A, E, and K], gyrate atrophy [low protein, low arginine diet, and/or vitamin B6], Refsum disease [low phytol, low phytic acid], and Sorsby fundus dystrophy [vitamin A]. Small-scale, prospective, double-masked, randomized, placebo-controlled studies have demonstrated that the progression of ARMD can be slowed with either zinc alone, or the combination of beta carotene, vitamin C, vitamin E, and zinc. AREDS confirmed these findings.

We constructed LAST to evaluate the effect of lutein alone or lutein combined with additional carotenoids and antioxidants/minerals (including zinc, beta carotene, and vitamins C and E) on MPOD and objective visual outcome measures in atrophic ARMD. This study demonstrates that lutein alone or lutein combined with additional carotenoids and antioxidants/minerals (including zinc) significantly improved macular pigment optical density and glare recovery, improved near visual acuity, and significantly improved most measures of quality of vision [contrast sensitivity function], with L/A having a broader effect. L alone resulted in a net improvement in Amsler grid scotomas and metamorphopsia. These results are important because lutein is an essential carotenoid not produced by the body. Therapeutic loading and maintenance dosing of lutein and other nutrients may be required to treat atrophic ARMD.

The observation of no progression of ARMD retinopathy in patients receiving L/A must be considered a preliminary result, given the small number of patients studied, the short time period of observation—one year, and the lack of statistical significance among the three groups. The increased macular pigment and improved visual function with lutein and lutein together with antioxidants in the present LAST study—together with previous studies showing the importance of zinc and several vitamins in slowing the progression of ARMD retinopathy and visual loss—raise the possibility that lutein, together with a broad spectrum of antioxidants, vitamins, and minerals, may be a more effective nutritional supplement for treatment of ARMD.

There are major population, methodological, and outcome differences to consider in comparing the
results of this small, brief study with the NIH AREDS. Both studies evaluate white populations with a similar percentage of smokers, patients with diabetes, and patients on pre-existing multivitamin and mineral formulations. However, the 90 patients in the one-year LAST study were primarily male subjects with a mean age about 6 years older, compared to the 4,757 mixed gender patients enrolled in the multicenter, seven-year AREDS trial. Fully a third of the subjects had vision worse than 20/32 in the better-functioning eye and would not have qualified for AREDS. Indeed, the mean eye retinal stage for veterans in our LAST study is an AREDS moderately advanced “category 3.” Our study evaluated distinctly different outcome measures. In AREDS, progression to advanced ARMD was based on retinal photographs and visual acuity. In contrast, LAST used a battery of low-contrast visual psychophysical tests known to be more sensitive to clinical concerns of patients, compared to retinal appearance and traditional visual acuity tests used in AREDS and most ophthalmology offices (i.e., Snellen acuity measurement). We believe the strength of our methodological approach lies in the use of basic measurements of functional macular integrity related to ARMD symptoms.

Analogous to the findings in AREDS of antioxidants adding to zinc’s effect, subjects in our trial receiving L/A did better in overall visual quality (CSF) than those who received L alone. Previously, using a non–lutein-containing formulation, we observed a tendency for cataracts to develop in subjects over time. In contrast, no statistically significant lens opacification occurred in the one-year LAST study. In AREDS, use of isolated beta-carotene was associated with declines in serum concentration of other carotenoids, including lutein (as well as lycopene and beta-cryptoxanthin). Beta-carotene may compete with nutritional or supplemental lutein in both duodenum transport/absorption and hepatic lipoprotein segregation and fractionization. In contrast, the lutein/antioxidant formulation used in LAST contains a broader array of dietary carotenoids that may, in part, explain improvements in the visual outcome, compared with AREDS. These improvements occurred despite subjects being older—and with more severe disease—than patients enrolled in AREDS.

Increased MPOD is weakly correlated with quicker glare recovery in healthy women, which suggests that macular pigment may be important in visual function. In our LAST study, the improvement of visual function by lutein and lutein/antioxidant supplementation may, in part, be due to the increased MPOD. Part of the salutary effect of lutein or lutein/antioxidant intervention might result from two additional biophysical factors: reduction in chromatic aberration and reduction in glare sensitivity. Macular pigment, primarily positioned between incoming light and the photoreceptor outer segments, filters blue light, which is particularly degrading to image quality as well as damaging to photoreceptors and retinal pigment epithelium. Contrast sensitivity is enhanced by patients using simple yellow, amber, and orange filters. Nonetheless, this would not explain resolution of distortions and blind spots, which are distinct visual phenomena and represent healing. These events may relate to free oxyradical quenching and the rescue of cells undergoing apoptosis. Lutein is a powerful antioxidant, able to quench the triplet state of photosensitizers and singlet oxygen. Increased MPOD would be expected to limit oxidant stress from light in the low pO2 environment of the anterior retina. In LAST, resources limited patient enrollment. The sample was comprised mostly of male subjects, while the prevalence of ARMD is higher in older women. In addition to higher risk for arteriosclerosis, female post-menopausal hormonal shifts affect fat-soluble nutrients, like lutein, that are carried on lipoprotein molecules, from the liver to ocular tissues, and sequestered in adipose tissue. We also did not look for gene mutations in these subjects. Trying to increase lutein or reti-
nal antioxidants does not address the physiological dysfunction of a gene mutation.

In the future, development and refinement of meaningful atrophic ARMD severity scales, related to visual impairment, will be needed to evaluate nutritional or pharmaceutical intervention. We believe LAST supports this idea—that subtle signs of photoreceptor–retinal pigment epithelium disturbance characteristic of ARMD, such as glare recovery difficulty, degraded contrast sensitivity, scotomas/metamorphopsias, and possibly reading speed and comprehension difficulties—often occur, long before the appearance of obvious ophthalmoscopic signs, when up to 80% of photoreceptor–retinal pigment epithelium complexes are already gone.63

The past 20 years has produced many advances in the understanding of the pathophysiology and treatment of ARMD. Despite these advances, the number of patients worldwide with ARMD—particularly, atrophic ARMD—continues to grow. The negative psychosocial impact of ARMD is great, with diminishing vision, increasing emotional distress, and loss of independent activity of daily living.64 In the absence of cure, any therapeutic intervention that extends the time an affected individual retains good central vision can have a significant impact on quality of life. The results of our LAST study support the results of our pilot spinach data,33,35 that lutein may be useful in the nutritional intervention of atrophic ARMD in midwestern male subjects. In LAST, lutein enhanced macular pigment and visual function with AREDS stages II, III, and IV. Thus lutein supplementation may be beneficial at all stages of ARMD. Further studies with more patients of both genders are needed to determine the long-term effect of lutein alone or lutein together with a broad spectrum of antioxidants, vitamins, and minerals on patients with atrophic age-related macular degeneration.

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## Appendix

<table>
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<th>Group 2 (Lutein/A)</th>
<th>Group 3 (Placebo)</th>
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