Lutein Supplementation over a One-Year Period in Early AMD Might Have a Mild Beneficial Effect on Visual Acuity: The CLEAR Study

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PURPOSE. We investigated the effect of daily supplementation with lutein (L) capsules on macular pigment optical density (MPOD) and visual acuity (VA) in patients with early age-related macular degeneration (AMD).

METHODS. A randomized, double-blind, placebo-controlled, two-center investigation of the effects of L supplementation in early AMD was conducted. The duration of the trial was 12 months. The centers were Manchester, United Kingdom and Maastricht, the Netherlands. L capsules (10 mg Ester) or a placebo (P) were taken daily. There were 72 patients (mean age 70.5 ± 8.7) assigned randomly to either L (n = 36) or P (n = 36) groups. MPOD using a flicker-based technique (MPS9000) and best corrected VA (LogMAR) were measured at the beginning and at 4-month intervals over the duration of the 12-month supplementation period. Blood serum samples were collected to monitor compliance.

RESULTS. At the end of the trial, an overall increase in the mean MPOD level was found for the L group from 0.38 ± 0.19 to 0.53 ± 0.22 optical density (OD) units. According to a mixed design ANOVA, this was statistically significant (P < 0.001). No change in MPOD was found for the P group. There was no significant change in VA in the L group (n = 36). The P group (n = 36) showed a statistically significant deterioration from 0.05 ± 0.13 to 0.09 ± 0.13 (P < 0.05). When comparing the change in VA over the supplementation period, there was a significant difference between the two groups (P < 0.05). To avoid ceiling effects, 2 subgroups of patients with VA worse than 0.06 at baseline were reanalyzed. In the L subgroup (n = 19) a mean improvement in VA from 0.23 ± 0.12 at baseline to 0.16 ± 0.10 at visit 4 was observed (P < 0.05). In the P subgroup (n = 14), there was a small deterioration from 0.18 ± 0.13 to 0.19 ± 0.12 (P = 0.70). The improvement in VA in the L subgroup was compared to the deterioration in VA in the P group and this effect reached statistical significance (P < 0.05).

CONCLUSIONS. L supplementation increases MPOD levels in early stage AMD patients. According to the VA measurements, the progress of the disease might be slowed in some patients with augmented levels of MP. (ClinicalTrials.gov number NCT01042860.) (Invest Ophthalmol Vis. Sci. 2013;54:1781–1788) DOI:10.1167/iovs.12-10715

There is substantial indirect evidence to support the idea that the retinal carotenoid, lutein (L), has a major role in maintaining the health of the retina in humans and higher primates. Lutein is a member of the xanthophyll family of carotenoids, a group of naturally-occurring pigments that provide coloration and protection from harmful, high energy short wave radiation in plants. They are powerful antioxidants, capable of quenching light-induced reactive oxygen species (ROS). It is thought they have this same dual role of photic screening and protection from free radical damage in the retina. Furthermore, there is increasing evidence that L has anti-inflammatory properties and that these may be of particular benefit in the aging retina.

The putative benefits of L and its stereoisomer zeaxanthin (Z), the main components of macular pigment (MP), are usually discussed in the context of the possible prevention or slowing of age-related macular degeneration (AMD) and other eye diseases. This hypothesis is supported by many observational studies. There is evidence of an inverse relationship between the presence of L and Z in the retina and the risk for AMD, although Kanis et al.,10 Chong et al.,11 and Berendschot et al.12 present an alternative viewpoint.

AMD is becoming a major health problem for industrialized countries. It is predicted that the number of cases in the United States will increase almost 2-fold between 2010 and 2050.13 AMD is by far the leading reason for inclusion in the blind registers in the United States, Europe, and Australasia. Approximately 30% of the Caucasian populations over 75 in the United States are thought to be affected by early stage macular disease.14,15 In the Netherlands, the incidence is slightly lower according to the Rotterdam study.16 In that study the investigators reported that a quarter of patients in the early stages of the disease showed progression to later stages in their 2-year follow-up period.

The stratification of early stage macular degeneration is based on fundus appearance rather than its effects on vision, but it is well known that many patients with early stage disease have gradual progression to geographic atrophy, accounting for approximately 25% of patients with severe vision loss due to macular disease.13 Some studies have been concerned with the putative functional benefits of enhancing retinal carotenoids,
for example Dageneie et al.,17 Richer et al.,18,19 Weigert et al.,20 and, more recently, Ma et al.21

The aforementioned studies show rather modest effects, suggesting that whether there are real benefits is not established easily. The optimum approach is to use a randomized placebo-controlled design. The aim of the Combi-
nation of Lutein Effects in the Aging Retina (CLEAR) study was to determine how increasing the concentration of retinal carotenoids using a capsule containing L alone might affect a wide range of measures, including MP, visual acuity (VA), ocular scatter, and dark adaptation. In our study, we explored the link between increase in macular pigment optical density (MPOD) and changes in VA in two populations of participants based in Maastricht, the Netherlands and Manchester, United Kingdom.

METHODS

Study Design

We conducted a two-center, randomized, placebo-controlled intervention trial of the effect of the daily ingestion of 10 mg of L ester at The Faculty of Life Sciences, University of Manchester, United Kingdom and The University Hospital of Maastricht, the Netherlands. The placebo (P) capsule contained soya bean oil. We reported the effects on MPOD and VA. Other measurements conducted as part of the study were scanning laser ophthalmoscopy (SLO)–based MPOD, retinal reflectometry–based MPOD, dark adaptometry, optical coherence tomography (OCT), and ocular scatter. These data will be described in separate reports.

Uniform procedures and management strategies were used at each center. A management committee was composed of the PIs, a biophysicist, and a mathematician, and the researchers based at the two centers. Recruitment strategies were designed carefully to be compatible in the two locations and planned in advance of the start of the study.

The flow of participants through each stage of the project, including enrollment, randomization, treatment allocation, follow-up, and analysis, is presented in Figure 1. All participants signed a consent form after agreeing to take part in the project. The Manchester arm of the study was approved by the South Manchester Regional Ethical Committee and the Maastricht arm of the study was approved by the Medical Ethical Committee at the University Hospital of Maastricht. All aspects of the research followed the tenets of the Declaration of Helsinki on the treatment of human subjects in medical research.

Recruitment Strategies

An advertising campaign was conducted within the universities and in local newspapers at both centers. Responding potential participants were contacted by letter and telephone.

Eligibility Criteria

Male and female subjects aged from 50 to 80 years were included in the study according to the following criteria: AMD grade 0 to 4 in one eye according to the Rotterdam study,16,22 best corrected visual acuity (BCVA) of LogMAR = 0.5 or better, minimal cataract. A small number of patients with grade 4 were included provided they reached the BCVA criterion, so we refer to our patient cohort as AMD rather than ARM. Exclusion criteria were as follows: any ophthalmic disorder, such as diabetic retinopathy; optic atrophy; pigmented abnormalities considered by the investigating ophthalmologist to be less typical of AMD than of some other condition (e.g., myopia); history of glaucoma; and any dietary supplements containing L, Z, or meso-zeaxanthin within 3 months of the start of the study. Individuals who were unable to understand the study procedures or unable to give informed consent were not enrolled. A small payment was made to patients who were included in the trial to compensate for travel costs.

Follow-Up

Following the baseline measurements, participants attended after three, eight, and 12 months during the 12-month intervention period. Discontinuations because of patients’ preferences, health issues, or unplanned ophthalmic interventions or complications were recorded and are indicated in Figure 1.

Allocation of L and P Capsules

The supplementation was manufactured specifically for the study by Cognis GmbH, Monheim, Germany (now BASF SE), in accordance with good manufacturing practice (GMP). A randomization code was generated by the sample manufacturer. Treatment numbers were allocated in ascending order using the next available consecutive number and capsules distributed accordingly. If a discontinued patient was replaced, the next available treatment number was used. The P and L capsules and their packaging were completely indistinguishable. The code remained with the manufacturer until the end of the intervention trial. The experimenters were unaware of which patients were assigned to which groups. A second copy of the list was kept in the statistical monitor’s file. Retrospectively, following the code being released, participants were divided into two groups referred to as P (placebo) and L (lutein) based on the supplementation they received.

Packaging, Distribution, and Labeling of Supplements

Each participant was allocated a box (a treatment unit) containing the capsules. These were stored in plastic cartons that held enough capsules for one month. The boxes and cartons were labeled with all the information legally required by European GMP to appear on medication used in clinical studies. The supplementation products were stored at temperatures below 25°C and not exposed to light. The supplements were given to each participant at the end of each visit and the remainder were stored by the investigator. The capsules were counted when the plastic cartons were returned at every visit.

Study Aims

The main aim of the part of the study reported here was to investigate the effects of an esterified L supplement on MPOD and VA, and to monitor compliance using measurement of L serum concentration.

Statistical Analysis, Sample Size, and Power Calculations

Data from the study were analyzed using SPSS 16 (SPSS Inc., Chicago, IL) and Origin 8.5 (OriginLab Corporation, Northampton, MA). According to the inclusion criteria, a “test eye” was allocated to each patient and data from only this eye were analyzed. The study was designed and powered to detect either a 0.1 optical density (OD) unit increase in MPOD between baseline and visit 4, assuming an SD of differences of 0.2 OD units, or a 0.1 change in logMAR VA with an across-subject SD of differences of 0.14. The study sample size was estimated using alpha of 0.05 and a paired t-test. The required sample size based on the MP data for 80% power was 34 participants in each group. Accordingly, between 40 and 45 participants were recruited at each center to allow for attrition.

Blood Plasma

Blood plasma samples were collected from all observers during each visit. They were stored at −80°C before being analyzed for L and lipid concentrations using high performance liquid chromatography.
Samples were deproteinized by adding a 500 mL sample to 500 mL ethanol. The samples were mixed and allowed to stand for 15 minutes at room temperature to complete the precipitation of proteins. The carotenoids were subsequently extracted by adding 1.0 mL n-hexane. After centrifugation for 10 minutes at 4°C and 3000 g, 0.5 mL of the upper hexane layer was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 0.5 mL of a mixture of methanol, acetonitrile (1:1), and dichloromethane, and subsequently analyzed by HPLC. Separation was obtained on a C18 reverse-phase column, thermostatically controlled at 30°C. The samples were eluted by use of a mobile phase consisting of methanol, acetonitrile, 2-propanol, and water at a flow rate of 1.5 mL/min. Detection was performed with a diode array UV detector. Quantification was done by including commercially available L as a standard (Sigma-Aldrich, St. Louis, MO).

Visual Acuity

BCVA was measured with an internally illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart at 4 m. Illumination in the testing room was 200 lux. The luminance of the charts (180 cd/m²) was checked with a photometer (PR-650 SpectraScan Colorimeter; SpectraScan International, Inc., Colorado Springs, CO). The same protocol was followed at both centers. Observers were asked to read all the letters they could recognize, monocularly with the testing eye, starting from the top left letter in the first row. Different charts were used to avoid learning effects on different visits.

Photographic Grading and Classification

Fundus photographs were obtained using a Topcon TRC-NW6s nonmydriatic retinal camera in Manchester and a Topcon TRV-50VT fundus camera in Maastricht (Topcon Corporation, Tokyo, Japan). Images subtended 45°, centered on the fovea (768 × 512 pixels), and were magnified to approximately ×30. Pupils were dilated in cases where they were too small to allow adequate image quality. During this photography, we were able to establish that there was no change in the degree of lenticular opacities throughout the study. Grading was performed according to the Rotterdam Study on the test eye. At baseline, stratification was as set out in Table 1. There were small but nonsignificant differences between the participants’ AMD severity at the two centers.
Measurement of MPOD
At both centers, MPOD was measured psychophysically using a flicker-based technique, described in detail by van der Veen et al. Note that their study describes a data set of MP in over 5000 eyes. The method has been validated by comparing values obtained for a series of different eccentricities using a retinal reflectometry technique.

Repeatability for the technique was determined as part of a separate study. A total of 68 AMD patients above the age of 45 years (mean age 66.9 ± 9.9 years, 35 male and 33 female patients) was tested on two separate occasions. The average of the mean differences (bias) was −0.011 ± 0.0755, while the coefficient of repeatability (CR) was 0.148.

RESULTS
Baseline Measurements
Baseline measurements between the two centers were analyzed for differences in age, MPOD, and VA. No statistical differences were found (Table 2). Baseline differences between the L and P groups, and corresponding significance levels also are included in Table 2. With the exception of MPOD, there were no differences between the two groups for the outcome measures before supplementation. These data represented the participants who completed all visits (Fig. 1), that is n = 35 for Maastricht and n = 37 for Manchester. The participants in the L group had slightly worse VA than those in the P group. This difference was not statistically significant.

Macular Pigment
A two-way, mixed design, repeated measures ANOVA was used to analyze the MPOD data. The data were stratified by group (L or P) and visit (n = 4). There was a highly significant main effect of visit (F[3,210] = 13.25, P < 0.001). There was a highly significant group*visit interaction (F[1,70] = 475.11, P < 0.001). A one-way repeated measures ANOVA of the L group only showed a highly significant effect (F[3,105] = 16.845, P < 0.001). As shown in Table 3, the (Bonferroni corrected) post hoc analysis showed no statistically significant differences between baseline and visit 1, but there were substantial effects when baseline was compared to visits 3 and 4. A one-way repeated measures ANOVA showed no change in MPOD for the P group (F[3,105] = 0.163, P = 0.921). See Table 2 for details.

Changes in Blood Plasma
Substantial increases in serum L concentrations were recorded in the L group at both centers. Baseline L levels were higher in Maastricht than in Manchester, and this meant a much larger overall increase in Manchester than Maastricht, as detailed below. At baseline, mean L concentration was 19.56 ng/mL and this increased to 78.75 ng/mL, representing an average increase of over 300%. A mixed model ANOVA showed that for the L group there was a strong main effect of visit’group (P < 0.001). There was no such effect for the P group. Patients in the L group at both centers showed a highly significant increase in serum L concentration; for Manchester there was an increase by ×7.6 and for Maastricht the increase was a factor of ×1.8. The data are presented in box and whisker format in Figure 2. It is clear that the blood plasma response varied markedly between individuals in the L group.

Visual Acuity
The VA data were analyzed with a two-way mixed design repeated measures ANOVA. There was no main effect of the repeated measures variable, visit (P = 0.34). There was a main group effect (P < 0.05), suggesting that the L and P groups responded differently to the supplementation. There was a small nonsignificant improvement in VA for the L group from 0.10 ± 0.17 to 0.09 ± 0.14. There was deterioration in VA in the P group over the intervention period from 0.05 ± 0.13 to 0.09 ± 0.13 and this reached statistical significance (P < 0.05). The data for baseline and final visits are illustrated in Figure 3 in

Table 1. Distribution of AMD in the CLEAR Study

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
<th>Man</th>
<th>Maas</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Any small drusen</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>Soft distinct drusen</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Indistinct drusen</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>Soft drusen/pigment changes</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Atrophic changes</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>37</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 2. VA and MPOD at Baseline for the Manchester (Man) and Maastricht (Maas) Participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>P Value</th>
<th>M</th>
<th>F</th>
<th>Mean VA</th>
<th>P Value</th>
<th>MPOD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>69.3 ± 9.4</td>
<td>0.2225</td>
<td>13</td>
<td>24</td>
<td>0.06 ± 0.14</td>
<td>0.4475</td>
<td>0.43 ± 0.19</td>
<td>0.7747</td>
</tr>
<tr>
<td>Maas</td>
<td>71.8 ± 7.8</td>
<td></td>
<td>15</td>
<td>20</td>
<td>0.09 ± 0.16</td>
<td>0.44 ± 0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>70.5 ± 8.7</td>
<td></td>
<td>28</td>
<td>44</td>
<td>0.07 ± 0.15</td>
<td>0.43 ± 0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutein</td>
<td>71.9 ± 8.7</td>
<td>0.1708</td>
<td>16</td>
<td>20</td>
<td>0.10 ± 0.17</td>
<td>0.1155</td>
<td>0.38 ± 0.19</td>
<td>0.0124</td>
</tr>
<tr>
<td>Placebo</td>
<td>69.1 ± 8.6</td>
<td></td>
<td>12</td>
<td>24</td>
<td>0.05 ± 0.13</td>
<td>0.49 ± 0.20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Student’s t-test was used to assess differences between means.
box plot format for L and P groups. We calculated the change in VA for the two groups and, as seen in Figure 3C, the L group improved by 0.01 logMAR units, whereas the P group deteriorated by 0.04 logMAR units. This difference reached statistical significance ($P < 0.05$).

Of our total of 72 participants, 54.2% ($n = 39$) had normal or close-to-normal VA (i.e., logMAR $> 0.06$). It was argued that a ceiling effect could be anticipated if those patients with normal VA were included in the analysis. Accordingly, a subpopulation (33/72, 45.8%) whose VA was $> 0.06$ at baseline was analyzed separately. The details of this subgroup are provided in Table 4.

As can be seen, there were no statistically different differences between the L and P subgroups for age or sex before the supplementation.

A two-way, mixed design, repeated measures ANOVA was used to analyze these subgroups. There was a significant effect of group ($P < 0.001$), indicating that the visual acuities were different in the two subgroups when baseline and final visits were compared. This justified further post hoc analysis using separate one-way repeated measures ANOVA for the L and P groups. In this case, there was a statistically significant improvement in VA ($P < 0.01$) for the L group. Post hoc pair-wise comparisons for this group revealed no effect on VA comparing visit 1 with visit 2 or with visit 3, but a significant effect when visit 1 was compared to visit 4 ($P < 0.05$). These data are presented in detail in Table 5.

The data comparing baseline with final visits for the two subgroups are presented in Figure 4. As seen in Figure 4A, there was an overall improvement in VA in the L subgroup resulting in a mean improvement in VA from $0.23 \pm 0.12$ to $0.16 \pm 0.10$ when baseline is compared to visit 4. There was a corresponding slight but nonsignificant deterioration in mean VA in the P subgroup from $0.16 \pm 0.11$ to $0.19 \pm 0.12$, as illustrated in Figure 4B.

In Figure 4C, we show the change in VA between baseline and visit 4 for the two subgroups. An independent means $t$-test showed a significant difference; P group reduced by $0.03 \pm 0.12$ and L group improved by $0.07 \pm 0.10$ ($P < 0.05$).

**DISCUSSION**

In our study a clear link between the L supplement, L blood serum levels, and changes in MPOD was established. There were small but significant changes in VA between the P and L groups. The CLEAR study is novel in two ways. First, it is a dual center investigation based in two Northern European countries, and second, it tests a dietary supplement composed only of L. Most such trials have used proprietal products that have the advantage of being widely available, but necessarily contain a cocktail of nutrients. This introduces added complexity to the interpretation of the data. It is well known that L and Z have a characteristic distribution in the macula and it is likely that the pattern of normal deposition of MP, dictated by an individual diet, is disrupted by a particular mix of carotenoids. The CLEAR study shows, for the first time to our knowledge, functional and MPOD effects of one-year supplementation with L only.
Macular Pigment Optical Density

The increase in MPOD in the L group was broadly consistent with previous reports. It is now accepted widely that levels of enhancement following supplementation vary substantially between individuals, as reviewed by Bernstein et al. and Berendschot et al. Koh et al. also supplemented early AMD patients with a 10 mg L-only tablet and found an overall increase of 29% in MPOD over a 12-week period. More recently, many other studies have shown an increase in MPOD following supplementation with different concentrations and combinations of L and Z.

As illustrated in Table 3, typical increases in MPOD in the L group in our investigation were between 0.1 and 0.2 OD units. There were compatible changes at the two centers. We found a mild positive correlation between those patients with lower baseline levels and the degree of increase in MPOD. It has been reported that patients with low baseline MPOD were more likely to show either no response or maximal increase in their MPOD.

In our study there were 5 patients in the L group (approximately 13%) in whom there was either a decrease or no increase in MPOD. This is similar to previous reports. Although the numbers are limited, the findings agree with those of Trieschmann et al. Three of our nonresponding participants had abnormally high baseline MPOD and one had a low baseline of 0.07, which did not change throughout the supplementation period. The other “nonresponder” in our population had a slightly below average baseline MPOD of 0.22. We might speculate that those with high baseline values already had reached saturated levels of MPOD. As seen in Table 3, the overall increase in MP after the 4-month visit was only approximately 8% and this did not reach statistical significance. As reported in many other studies, the effects of the supplementation on MP were substantial after 8 months (approximately 24%) and at the final visit there was an overall increase of nearly 40%, a value that is slightly higher than reported typically for this level of supplementation.

As is well known, the increase in the serum levels in the L group is relatively rapid compared to MP enhancement, but the magnitude of the effect is variable across subjects. There are many dietary and lifestyle reasons for this. One of the main factors in serum response seems to be the fat content of the meal with which the supplement is taken. Other issues, such as obesity and smoking, have also been shown to affect serum absorption of retinal carotenoids.

Visual Acuity

As seen in Figure 3c, there was a significant difference between the change in VA for the L and P groups over the course of the supplementation. The latter exhibited a deterioration, while the L group remained largely unchanged. This observation is important. It invites the speculation that the enhanced levels of MP tended to stabilize VA in patients who otherwise would have deteriorated.

Approximately 50% of our patients had normal or above normal VA. We argue that these participants were unlikely to show an improvement in their vision. To test this, a subgroup of patients whose VA was abnormal at the start of the study was analyzed. The criterion for defining this group was logMAR VA > 0.06 (Snellen ~6/7). This cutoff was chosen as being the next line above the 6/6 meter-based system of VA measurement used in the United Kingdom. There were no differences between these groups before the supplementation, as illustrated in Table 4. Notwithstanding the relatively small numbers in these subgroups, the visit-by-visit change in VA, presented in detail in Table 5, and the data comparing baseline and final visit in Figure 4, suggest that there are benefits in terms of VA, of enhancing MPOD. Such effects have been described before in a population of patients who had more severe levels of disease than our participants. Richer et al. reported slight improvements in VA and contrast sensitivity in two groups of AMD patients who had enhanced MPOD levels. In a later study comparing the effects of L and Z supplementation, Richer et al. reported an increase in MPOD from 0.53 to 0.51 in a population of 60 patients with mild to moderate AMD. They found statistically significant improvements in VA and shape discrimination in L- and Z-supplemented groups. Weigert et al. described findings compatible to those reported here in a substantially larger patient group over a shorter supplementation period. Their effects did not reach statistical significance and this is exactly comparable to our observations in that any significant improvements in VA were not seen until the later stages of the intervention period (Table 5).

Our data reported here suggest that increasing MP, either by diet alone or by dietary supplementation, can be expected to provide the basis for a viable management strategy for early stage AMD. Although we await further independent confirmation, the results imply that increasing MP in early stage AMD patients could be justified easily in health economics terms. If more than half of patients can be expected either to improve or maintain VA as a result of enhancing their MP over a period of one year, the net benefits would far outweigh the very high costs to society when patients' disease is allowed to progress to the late stages.

Finally, the small changes in VA in the L group are particularly compelling when compared to those for the P group who experienced a reduction in VA, which, in some cases, was quite marked. Note that there were no particular changes in the ocular status of our patients during the study.
for example, none had surgery, vitrectomy, or vascular accidents, and there was little or no change in lenticular opacity. Coincidentally, there were only a handful of smokers in each group. Of course the placebo-control design is supposed to balance these effects, but even if they were present they would not be expected to cause an artifactual increase in VA.

The suggestion of real benefits for increasing the levels of retinal L and Z made here is contrary to the conclusion reached by Chong et al., who conducted a meta-analysis of studies investigating the benefits of dietary antioxidants. They included only studies that had investigated individuals who at baseline had no signs of AMD and who had a duration of one year. A relatively small number of reports met these criteria. They concluded that they could find no evidence that taking antioxidants was beneficial in primary AMD. On the other hand, a recent report from the AREDS trial found a high dietary intake of L and Z to be associated with reduced chance of having AMD, and a similar observation was made from a recent report from the AREDS trial found a high dietary intake of L and Z to be associated with reduced chance of having AMD.

**Concluding Comments**

The data presented suggest clear benefits of enhancing MP in the L group compared to the P group. These effects are largely similar at both centers, testifying to the veracity of the findings. The putative ocular advantages of dietary supplementation have been overemphasized by some and too easily dismissed by others. We present a balanced view and argue that the data support the persistent anecdotal reports of patients’ describing the benefits of increasing MPD. The role of L in maintaining, and perhaps restoring, retinal health in the early stages of macular degeneration deserves further investigation.

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**References**


