Lutein and Zeaxanthin Supplementation and Association With Visual Function in Age-Related Macular Degeneration

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RL, TW, and BZ contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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Purpose. To evaluate the effects of lutein and zeaxanthin on visual function in randomized controlled trials (RCTs) of AMD patients.

Methods. Relevant studies were identified by searches on PubMed, EMBASE, Web of Science, and Cochrane Library database up to April 2014. Three investigators independently determined the eligibility of RCTs, which compared lutein and zeaxanthin intervention with placebo. The adjusted weighted mean differences (WMDs) from each study were extracted to calculate a pooled estimate with its corresponding 95% confidence interval (CI). The main outcome measurements included visual acuity (VA), contrast sensitivity (CS), glare recovery time (GRT), and subjective perception of visual quality.

Results. Eight RCTs involving 1176 AMD patients were included in the meta-analysis. Xanthophyll carotenoids supplementation was associated with significant decrease in logMAR levels compared with the placebo group (WMD, −0.04; 95% CI, −0.06 to −0.03), and during intervention, each 1-mg/day increase in these carotenoids supplementation was related to a 0.003 reduction in logMAR level of VA. Remarkable benefit was also observed at all four spatial frequencies of CS (WMD ranging from 0.08–0.18; all P < 0.05) in contrast to placebo. Furthermore, association was observed between the postintervention increase in macular pigment optical density and improvements in VA (r = −0.58; P = 0.02), and in CS at 12 cycles/degree as well (r = 0.94; P < 0.001).

Conclusions. Lutein and zeaxanthin supplementation is a safe strategy for improving visual performance of AMD patients, which mainly showed in a dose-response relationship.

Keywords: lutein, zeaxanthin, age-related macular degeneration, visual function, meta-analysis

Age-related macular degeneration (AMD) is a progressively degenerative disease at the central area of the retina, which results in severe visual impairment.1 It is the leading cause of irreversible blindness among people aged over 65 in developed countries.2 With growing longevity, the number of AMD patients is likely to double in 2010 to 2050 in the United States, and this disease is becoming a crucial issue that threatens public health, especially the aging population.3 Although therapies using anti-VEGF agents benefit patients with certain types of neovascular AMD, so far no effective treatment strategies exist for early AMD and geographic atrophy.4,5 Therefore, it is urgent to find feasible interventions to decrease the visual impairment for AMD patients, and ultimately reduce the burden of this disease.

Although the exact pathogenesis of AMD remains incompletely understood, light-initiated oxidative damage and the reduction of macular pigment (MP) are hypothesized to be the putative mechanisms involved in the disease.6,7 The xanthophyll carotenoids, lutein (L) and zeaxanthin (Z), are concentrated at the central fovea of the macula and compose the MP.8 Furthermore, they are believed to protect the macular region from photo-oxidative injury by scavenging reactive oxygen species and filtering blue light, which indicates that these carotenoids may play a role in improving visual function, especially for AMD patients.9,10 Previous epidemiologic studies have shown that higher-level dietary intake of L and Z was associated with decreased AMD risk and less visual impairment.11,12 Meanwhile, several intervention studies suggested that visual function of AMD patients was improved by L or/and Z supplementation,13,14 but others still failed to find such results.15 Moreover, the efficacy of macular pigment optical density (MPOD) on visual function for AMD patients remained uncertain.16,17 In addition, it is necessary to ascertain the appropriate dosage of these carotenoids for maximally improving vision.

Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) to evaluate the visual performance in AMD with L and Z supplementation.

Methods

This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.18

Data Sources and Searches

Systematic literatures up to April 2014 on PubMed, EMBASE, Web of Science, and Cochrane Library database were searched, by using the items “lutein (L), zeaxanthin (Z), xanthophyll, carotenoids and visual function, visual performance, visual acuity (VA), vision, contrast sensitivity (CS), glare sensitivity...
Lutein and Zeaxanthin Supplementation on Visual Function

Study Selection

Only studies fulfilling the following criteria were included in the meta-analysis: (1) eligible studies were limited to RCTs, (2) patients were diagnosed as AMD and randomized to receive L or/and Z or placebo, and (3) the outcome of interest was visual function variables, including VA, CS, glare recovery time (GRT), and the score of Visual Function Questionnaire (VFQ). If multiple articles were published from the same study, only the last published report was selected for analysis, and the previous could be reviewed as supplementations for missing data where applicable. Three investigators (RL, TW, and BZ) independently conducted for inclusion independently, retrieved potentially relevant studies, and determined the eligibility of them, with disagreements resolved by group consensus.

Data Extraction and Study Quality Assessment

Using a custom made standardized protocol, information from each article included were extracted by three investigators (RL, TW, and BZ). The study characteristics recorded were as followings: name of first author, year of publication, duration of intervention, characteristics of patients (age, sex), the mean dosage of L or/and Z supplements, outcome measurements, and corresponding assessment methods. For intervention and placebo groups in each trial, information for the number of patients in each group, the mean and corresponding SD changes were collected. When several means and SDs were present in a single study, we combined the data into a single group according to the Cochrane recommendation. If studies did not provide the data above, missing data would be calculated by widely used statistical techniques. When VA reported in studies was measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) scores, we converted those scores into logMARs.19 If the information of MPD was showed in studies, it was also extracted for further relevant analysis. The quality of each study included was assessed by the Jadad score, a 5-point study quality assessment instrument. The Jadad scale judged the quality of research from three aspects: the randomization method (three criteria), the adequacy of blinding (three criteria) and the reporting of patients lost to follow-up (two criteria). Studies that gained over a 3 Jadad score were considered to be categorized as high quality.20 Assessment of study quality for article selection was independently conducted by three investigators (RL, TW, and BZ). When discrepancies between investigators occurred, a final rating would be reached through consensus with a senior investigator (LM).

Statistical Analysis

The principal summary measures were the weighted mean differences (WMDs) and corresponding 95% confidence intervals (CIs). The presence of statistically significant heterogeneity was evaluated by conducting Q tests; and the extent of the observed heterogeneity was assessed by the I² statistic. The pooled effect size of each outcome measurement was calculated by the fixed- or random-effects model. Sensitivity analyses were conducted to determine the robustness of our conclusions by iteratively eliminating each research from the meta-analysis and comparing the point that estimated the including and excluding study. Stratified analyses were performed to explore the source of heterogeneity among variables, such as the dose of L or/and Z, supplement (>10 mg vs. <10 mg), duration of intervention (>12 months vs. ≤12 months), geographic area (Europe versus United States versus China), other antioxidants use (with other antioxidants versus without other antioxidants), the mean age of patients (>70 years vs. ≤70 years) and clinical stage (early AMD versus late AMD). Linear regression models were used to quantify the relationship between the dosages of L or/and Z supplements and corresponding changes of visual performance during intervention. Pearson correlation analysis was fitted to explore the association between the change in MPD and in visual function. Publication bias was investigated using visual assessment of the funnel plot, and further examined asymmetry by Egger and Begg regression test.21,22 All statistical analyses were performed by Stata version 10.0 (Stata Corp, College Station, TX, USA). P less than 0.05 was considered statistically significant.

Results

Literature Search

The search strategy yielded 496 citations in total. Among these citations, 441 were excluded after abstract review. The excluded studies contained duplicate publications, review articles, non-RCTs, and studies without original human research. On more detailed evaluation, 47 citations were excluded for the following reasons: duplicate publication, no outcomes suitable for the meta-analysis, lack of a placebo group, no means or SDs included in the publication. The remaining eight studies met the inclusion criteria and were included in this meta-analysis.13,14,23–28

Study Characteristics

The characteristics of RCTs included are presented in Table 1. Of these eight studies, six were conducted in Europe, one in the United States, and one in China. The number of subjects ranged from 30 to 433, comprised by a total of 1176 patients. The duration of intervention ranged from 6 to 36 months. Four trials were intervened with L versus placebo, one was supplemented combined L and Z versus placebo, and five had multiple arms (L or/and Z combined with other antioxidants, and placebo). The dosage of L and Z in the intervention groups varied from 6 to 20 mg/day, and from 0 to 10 mg/day, respectively. Visual acuity was used for assessing visual function in most of the studies; while CS, GRT, and VFQ were respectively measured in four, two, and two studies. The follow-up rates of the studies were substantially above 75.3%. All selected studies were considered as high quality.

The Effect of L or/and Z Supplementation on VA

Seven studies reported the effect of supplementation with these carotenoids on VA.13,14,24–28 Within these studies, four showed significant improvement in VA. Studies showed the existence of statistically significant heterogeneity (I² = 71.5%; P = 0.002), and comparing with placebo group, xanthophyll carotenoids intervention was associated with more remarkable decrease in logMAR levels of VA (WMD, −0.04; 95% CI, −0.06 to −0.03; Fig. 1). Subgroup analysis was performed based on the dose of xanthophyll carotenoids supplement, and comparing with those with lower doses (WMD, −0.05; 95% CI, −0.05 to −0.01), a slightly stronger effect was noted for the studies.
with higher doses supplement (WMD, −0.04; 95% CI, −0.06 to −0.03), although little evidence of noteworthy difference was found between the subgroups (P = 0.31). The regression models showed that a linear improvement in VA was related to the increase in the dosage of these carotenoids supplement (r = −0.52, P = 0.03; Fig. 2). In the dose-response meta-analysis, each 1-mg/day increase in these carotenoids supplementation was associated with a 0.003 statistically significant reduction in logMAR levels. The results of meta-regression analysis showed, a slightly greater WMD decrease in logMAR was found in studies of longer duration (>12 months). Compared with early AMD patients, the magnitude of WMD decrease in logMAR for late AMD patients tended to be smaller. However, inconsistency in other variables did not significantly effect the supplementation on VA change (Table 2). The sensitivity analysis identified little influence on a protective effect of these carotenoids on VA for AMD, after excluding any single included study from the analysis. The Begg test (P = 0.45) and Egger test (P = 0.25) suggested no significant asymmetry of the funnel plot, indicating the absence of substantial publication bias.

### The Effect of L or/and Z Supplementation on CS

Two studies that measured CS by CSV-1000 in this meta-analysis showed decreasing tendency after these carotenoids supplementation.14,24 In the CS comparisons between the intervention groups and placebo groups, significant postintervention

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**Table 1. Characteristics of the Eligible RCTs**

<table>
<thead>
<tr>
<th>Authors (y)</th>
<th>Study Participants</th>
<th>Trial Duration</th>
<th>N of Groups</th>
<th>Interventions</th>
<th>Measurement Index</th>
<th>Follow-Up Rates (%)</th>
<th>Jadad Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piermarocchi et al.13</td>
<td>145 patients aged (72.5 ± 7.0) y in Italy</td>
<td>24 mo</td>
<td>2</td>
<td>10 mg lutein, 1 mg zeaxanthin combined with other antioxidants daily; Placebo</td>
<td>VA, CS, VFQ</td>
<td>75.9</td>
<td>4</td>
</tr>
<tr>
<td>Richer et al.14</td>
<td>90 patients aged (74.1 ± 7.5) y in the USA</td>
<td>12 mo</td>
<td>3</td>
<td>10 mg lutein daily; 10 mg lutein combined with other antioxidants daily; Placebo</td>
<td>VA, CS, MPOD, GRT</td>
<td>84.4</td>
<td>5</td>
</tr>
<tr>
<td>Bartlett et al.23</td>
<td>90 patients aged (69.2 ± 7.8) y in UK</td>
<td>9 mo</td>
<td>2</td>
<td>6 mg lutein combined with other antioxidants daily; Placebo</td>
<td>CS</td>
<td>83.5</td>
<td>4</td>
</tr>
<tr>
<td>Ma et al.24</td>
<td>108 patients aged (69.0 ± 7.4) y in China</td>
<td>48 wk</td>
<td>4</td>
<td>10 mg lutein daily; 20 mg lutein daily; 10 mg lutein plus 10 mg zeaxanthin daily; Placebo</td>
<td>VA, CS, MPOD, GRT, VFQ</td>
<td>99.1</td>
<td>5</td>
</tr>
<tr>
<td>Weigert et al.25</td>
<td>126 patients aged (71.6 ± 8.6) y in Austria</td>
<td>6 mo</td>
<td>2</td>
<td>20 mg lutein daily in mo 1-3 and 10 mg lutein daily in mo 4–6; Placebo</td>
<td>VA, MPOD</td>
<td>87.5</td>
<td>3</td>
</tr>
<tr>
<td>Dawczynski et al.26</td>
<td>172 patients aged (70.0 ± 10.0) y in Germany</td>
<td>12 mo</td>
<td>3</td>
<td>10 mg lutein, 1 mg zeaxanthin combined with other antioxidants daily; 20 mg lutein, 2 mg zeaxanthin combined with other antioxidants daily; Placebo</td>
<td>VA, MPOD</td>
<td>84.5</td>
<td>3</td>
</tr>
<tr>
<td>Murray et al.27</td>
<td>72 patients aged (70.5 ± 8.7) y in UK</td>
<td>12 mo</td>
<td>2</td>
<td>10 mg lutein daily; Placebo</td>
<td>VA, MPOD</td>
<td>86.9</td>
<td>5</td>
</tr>
<tr>
<td>Beatty et al.28</td>
<td>433 patients aged (73.9 ± 8.1) y in UK and Republic of Ireland</td>
<td>36 mo</td>
<td>2</td>
<td>12 mg lutein, 0.6 mg zeaxanthin combined with other antioxidants daily; Placebo</td>
<td>VA</td>
<td>75.3</td>
<td>4</td>
</tr>
</tbody>
</table>

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**Figure 1.** Forest plot showing the efficacy of lutein and zeaxanthin supplements on VA for patients with AMD. Error bars indicate 95% CIs of the WMDs. The sizes of the squares correspond to the study weight in the random-effects meta-analysis. Diamonds represent the meta-analysis summary effect estimate.

**Figure 2.** Scatterplot showing the relationship between the dosage of lutein and zeaxanthin supplements and change in VA.
increase was found at all four spatial frequencies (WMD ranging from 0.08–0.18; all \( P < 0.05 \)). The result of dose-response analysis showed that CS improved 0.010, 0.007, and 0.006 at 3, 6, and 12 cycles/degree respectively, due to a 1-mg/day increase in L and Z supplement. In addition, studies which measured this variable by Pelli-Robson chart showed a trend of increase was found at all four spatial frequencies (WMD, 0.43; 95% CI, 0.36–0.59 to 1.45), but this change was not statistically significant (Table 3).

### The Effect of L or/and Z Supplementation on GRT

The effect on GRT in two studies included was consistently in the protective direction after these carotenoids supplementation. However, there was an evidence of statistical heterogeneity across the studies (\( I^2 = 92.0\%; \ P < 0.001 \)). Slightly shorter GRT with the postintervention increase in MPOD (WMD, 0.59 to 1.45), but our study, patients supplemented with these xanthophyll carotenoids had significantly increased CS at all spatial frequencies. Therefore, other tests of visual function are important to detect subtle alteration of the macula; and measurements of CS can provide the fundamental description of spatial vision and prediction of poor quality vision, particularly for patients with macular disease. In concordance with previous studies, which reported the protective effects of these carotenoids on visual performance of AMD patients, our result revealed a significant improvement of VA with the supplementation for AMD patients. Meanwhile, in late AMD, the dysfunction or loss of macular photoreceptors could not undergo processes of biological renewal. Our finding, that a greater improvement in VA was found for early AMD patients receiving xanthophyll carotenoids supplements, provided strong support for this hypothesis. Besides, VA is only related to an ability to resolve details of maximum contrast. Therefore, other tests of visual function are important to detect subtle alteration of the macula; and measurements of CS can provide the fundamental description of spatial vision and prediction of poor quality vision, particularly for patients with macular disease. 

### The Effect of L or/and Z Supplementation on VFQ Scores

The changes of the VFQ scores were assessed in two studies. Likewise, during intervention there was no significant difference in scores improvement found between groups (WMD, 6.51; 95% CI, −6.16 to 19.17; Table 3).

### The Relationship Between the Change in MPOD and Visual Outcomes

Correlation analysis showed that VA was markedly improved with the postintervention increase in MPOD (\( r = −0.58, \ P = 0.02 \)). Additionally, CS at 12 cycles/degree was positively associated with MPOD augmentation (\( r = 0.94, \ P < 0.001 \)), while there was no significant relationship between postintervention change in other frequencies of CS and MPOD increase. Furthermore, the increment in MPOD was not related to the postintervention decrease in GRT (\( P > 0.05 \)).

### Discussion

The results of present meta-analysis suggested that xanthophyll carotenoids supplementation was associated with significant improvements in VA and CS in a dose-response relationship. In addition, a linear association was indicated between MPOD increase and the improvement of VA and CS at middle frequency.

With the long-term bright light exposure and oxidative damage, the presence of oxidized metabolites in the photoreceptor outer segment of retinal pigment epithelium (RPE) might lead to the formation of drusen and pigment disturbances in the macula, which eventually results in AMD development and vision loss. Thus, antioxidants are hypothesized to be beneficial for improving visual function and delaying the progression of AMD. As the majority ingredients of MP, L, and Z are uniquely concentrated at the macula, which might have a possible specific function in the maintenance human eye health. In concordance with previous studies, which reported the protective effects of these carotenoids on visual performance of AMD patients, our result revealed a significant improvement of VA with the supplementation for AMD patients. Meanwhile, in late AMD, the dysfunction or loss of macular photoreceptors could not undergo processes of biological renewal. Our finding, that a greater improvement in VA was found for early AMD patients receiving xanthophyll carotenoids supplements, provided strong support for this hypothesis. Besides, VA is only related to an ability to resolve details of maximum contrast. Therefore, other tests of visual function are important to detect subtle alteration of the macula; and measurements of CS can provide the fundamental description of spatial vision and prediction of poor quality vision, particularly for patients with macular disease. In our study, patients supplemented with these xanthophyll carotenoids had significantly increased CS at all spatial frequencies as comparing with those who received placebo. Furthermore, our dose-response analysis indicated that participants treated with higher doses supplement had more
improvements in VA and CS at low and middle frequency when comparing with those who received lower doses. L and Z could offer protection to reduce the lipofuscin accumulation and enhance lysosomal stability and viability, which preserves macular health and leads to improve functional abnormalities of the central retina in animal studies.\textsuperscript{44} Moreover, all studies found that significant morphologic changes of MP had occurred at the central retina within 24 weeks, while visual function did not improve until 48 weeks.\textsuperscript{24} Similarly, the results were in agreement with the findings of our previous study, which indicated that incubation of the N-retinylidene-N-retinylethanolamine (A2E)-containing RPE with L or Z could significantly attenuate the photooxidation-induced inactivation of the proteasome. Results from animal experiments showed that 6-month supplementation with xanthophyll carotenoids in quails could markedly decrease the level of photoreceptor apoptosis in response to light injury.\textsuperscript{39} The potential mechanism of action of these carotenoids was also thought to involve in the reduction of chromatic aberration by absorbing the blue light.\textsuperscript{39} As refraction of different wavelengths are focused on different extents, multiple overlapping images arise, which potentially degrades a retinal image.\textsuperscript{40} Absorption of poor-focused short wavelengths by the MP would not only decrease the effects of chromatic aberration, but also improve visual resolution.\textsuperscript{41} Because CS could be served as a more accurate and reliable indicator to assess visual capacity comprehensively, the positive effects of xanthophyll carotenoids supplementation on CS improvement might lead to a clinically important benefit for the preservation of visual function for AMD patients. Although xanthophyll carotenoids had been generally recognized as safe (GRAS), their intake was far below recommended level, which was associated with the prevention of age-related eye diseases and tended to decrease in Western countries.\textsuperscript{42} Therefore, increasing intake of xanthophyll carotenoids from food sources or supplement should be guaranteed, especially for the AMD patients.

It should be noted that during the supplementation, MPOD level was significantly positively related to the improvement of VA and CS at middle frequency, which suggested that morphologic restoration of the macula might be responsible for the observed effects on functional promotion. These results were in agreement with the findings of our previous study, which found that significant morphologic changes of MP had occurred at the central retina within 24 weeks, while visual function did not improve until 48 weeks.\textsuperscript{24} Similarly, the results of the TOZAL study also indicated that AMD patients were likely to require for at least 6-months supplementations to effect positive changes in VA outcomes.\textsuperscript{43} This hypothesis was also supported by our stratified analysis that there was a trend toward a greater WMD of VA in the intervention studies over the 1-year period. Therefore, it was conceivable that the individuals receiving long-term xanthophyll carotenoids supplement might derive more benefits from such intervention.

The present study has several potential limitations. First, there were relatively few studies included in this meta-analysis, which might have limited power to detect statistical differences in the individual end points with L or/and Z supplementation compared with observational studies.\textsuperscript{44} Moreover, all studies included were considered as high quality, which might
enhance the reliability of our finding. Second, due to the relatively shorter intervention duration in most studies and the lack of follow-up after intervention cessation, a question remained unanswered whether these carotenoids had long-term beneficial effects on visual function or not. Nevertheless, a significant effect on VA improvement after these carotenoids supplementation was found in the present study. So it is promising that visual function will be improved markedly by L and Z supplementation for AMD patients. Third, majority of the studies were predominately performed in Western participants, and the generalizability of the meta-analyses might be limited to a wider population. Fourth, our results might be affected by some potential confounding factors, although the variables in all the studies incorporated had been adjusted, and identified confounding in each study was also effectively eliminated by randomly allocating patients. Finally, publication bias could not be ruled out completely even though it was not detectable in the current analysis.

In conclusion, this meta-analysis demonstrated significant benefits of L and Z supplementation to VA and CS for AMD patients, which was positively associated with MPOD elevation. However, as the relatively smaller number of RCTs included may limit the power of this study, further large longer-term RCTs are required to confirm the findings of this review, and to determine the mechanism of association between supplementation status and outcomes.

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