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Efficacy of Lutein and Carotenoid Supplementation in Treating Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - Non financial support.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 October 2024 and was last updated on 24 October 2024.

INTRODUCTION

Review question / Objective The population (P), intervention (I), comparison (C), and outcome (O) for this study were as follows: P, human participants with AMD; I, either taking pure lutein alone or consuming a compound that contains lutein, epilutein, and zeaxanthin; C, patients taking a placebo; and O, changes in MPOD, VA, and CS after completing treatment.

Rationale This systematic review and meta-analysis aimed to evaluate the efficacy of lutein and carotenoid supplementation in patients with age-related macular degeneration (AMD), mainly focusing on its effects on macular pigment optical density (MPOD), visual acuity (VA), and contrast sensitivity (CS).

Condition being studied Age-related macular degeneration (AMD) is a main cause of vision loss in older adults, with its prevalence increasing particularly in those over 65 years old [1]. AMD primarily damages the central macular region of the retina, resulting in vision impairment. AMD can be categorized into early, intermediate, and late phases by pathological characteristics, and the late stage includes wet and dry types [2]. Early and intermediate AMD are characterized by pigment abnormalities in the macular region and the occurrence of drusen. Clinically, it is usually recommended to limit disease development through lifestyle and dietary changes, especially by increasing the consumption of foods high in antioxidants and carotenoids. In late AMD, wet AMD can be managed through anti-vascular endothelial growth factor therapy, while dry AMD lacks effective treatment choices. Therefore, seeking for nutritional supplements that can decrease disease progression has become a current trend.

Lutein and carotenoids, present naturally in foods such as leafy greens, fruits, and egg yolks, have been widely researched as preventive and treatment agents for AMD [4]. The macula in humans contains lutein and zeaxanthin, which filter

blue light and minimize oxidative stress on retinal cells to protect the retina [5, 6]. One study indicates that high concentrations of lutein and carotenoids in the macula may sustain visual function and slow the progression of AMD [7]. Some of the Age-Related Eye Disease Study (AREDS) and AREDS2 studies found that lutein and zeaxanthin supplementation significantly lowers the chance of developing late-stage AMD [8, 9]. However, the efficacy of lutein and carotenoid supplementation in AMD patients still remains controversial, especially regarding macular pigment optical density (MPOD) and visual acuity (VA).

METHODS

Search strategy Two authors independently conducted data searches using electronic databases. Databases used include PubMed, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov, and the following keywords were used: [("carotenoid" OR "lutein" OR "zeaxanthin") AND ("age-related maculopathy" OR "age-related macular degeneration" OR "AMD") AND ("randomized" OR "placebo" OR "randomized controlled trial")].

Participant or population P, human participants with AMD.

Intervention I, either taking pure lutein alone or consuming a compound that contains lutein, epilutein, and zeaxanthin.

Comparator C, patients taking a placebo.

Study designs to be included Only RCTs.

Eligibility criteria The inclusion criteria were as follows: 1) RCTs with human participants; 2) placebo-controlled RCTs (without any age or treatment duration restrictions); 3) RCTs providing data on MPOD and VA before and after treatment; 4) Studies that specify the composition of the administered medication, including the dosage of lutein; and 5) AMD diagnosed by ophthalmologists. The exclusion criteria were as follows: 1) non-RCTs; 2) RCTs not involving lutein supplementation; and 3) non-placebo-controlled RCTs.

Information sources Databases used include PubMed, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov.

Main outcome(s) Primary Outcome : Macular Pigment Optical Density, Visual Acuity

All comparative data for AMD outcomes are detailed in Table 1. In 9 studies, various methods were used to assess MPOD and VA, and we applied Hedges' g to reduce bias. Among these 9 RCTs, lutein supplementation resulted in a statistically significant improvement in MPOD (Hedges' g −0.589 [95% CI −0.340 to −0.839]; $p<0.001$; $I^2 = 70.6\%$) (Figure 3a). However, high heterogeneity was observed. Consequently, a sensitivity analyses using the "one-study removal method" was performed. The results showed that the efficacy of lutein supplementation in improving MPOD remained statistically significant across all analyses, in spite of the exclusion of any single study (Figure 3b).In 7 of the 9 trials, the lutein group showed a statistically significant improvement in VA compared to the placebo group (Hedges' g −0.827 [95% CI −0.323 to −1.331]; p=0.001) (Figure 4).

Additional outcome(s) Secondary Outcome: Contrast Sensitivity, Serum Lutein Level
In 3 of the 9 trials, the lutein group showed statistically significant improvement in CS at 3, 6, 12, and 18 cycles per degree (c/d) compared to the placebo group, with particularly notable differences in low-frequency CS (Hedges' g −1.847; −1.730; −1.025; −0.702) (Figure 6). Additionally, in 3 of the 9 trials, the lutein group demonstrated a significant increase in serum lutein levels (Hedges' g −4.325 [95% CI −3.011 to −5.639]), indicating that lutein supplementation effectively raises lutein levels in patients' serum (Figure 7).

Data management The primary outcomes of this study were the changes in MPOD and VA following treatment. The secondary outcome was the change in CS and serum lutein level after treatment. In these continuous variable data, some studies present the mean along with the standard deviation (SD) and the number of patients (N). If a study provides the standard error (SE), we convert it to the SD by the appropriate formula ($SE = SD/\sqrt{N}$). Other studies present the mean along with the p-value from paired T-tests.

Quality assessment / Risk of bias analysis The analysis of overall RoB reported that 66.6% of the studies presented low risk, 33.3% presented some risk, and none (0%) presented high risk (Figure 2). Further examination found that three studies were categorized as having "some RoB" owing to inadequate disclosure regarding allocation details in their randomization process. One study was assessed as having "some RoB" due to missing outcome data in a small sample size. Additionally, one study was assessed as having "some RoB" in

outcome measurement, since it did not describe the method used for evaluating outcomes. A detailed summary of the RoB is available in Supplementary Table S2.

Strategy of data synthesis Two authors independently collected data from the screened studies, including demographic information, study design, intervention methods for both the lutein supplement and control groups, as well as the results of each study. In case of data from different time points after the treatment, we used the final experimental results for our analysis. Data extraction and the merging of results from the different study arms were performed following the instructions in the related chapter of the Cochrane Handbook for Systematic Reviews of Interventions [12].

Subgroup analysis We conducted two separate subgroup analysis for MPOD and VA. One analysis categorized patients based on their AMD stage into early, late, and early-to-late groups. The other analysis divided the regimen groups into those receiving lutein only and those receiving a compound (lutein + zeaxanthin/epilutein). In the subgroup analysis of AMD, patients in the early stage group showed significant improvements in both MPOD and VA following lutein supplementation (Hedges' g −0.725, p<0.001; Hedges' g −0.880, p=0.01) (Figure 5a, b). However, for the late-stage group, there were no significant differences in MPOD and VA following lutein supplementation (Hedges' g −0.260, p=0.425; VA data pending). Similarly, the early-to-late stage group also showed no significant differences (Hedges' g −0.414, p=0.209; Hedges' g −0.931, p=0.109).
In the subgroup analysis of the lutein regimen, the lutein-only group showed significant improvements in both MPOD (Hedges' g −0.606, p<0.001) and VA (Hedges' g −0.985, p=0.002) (Supplementary Figure S1). In contrast, the compound group demonstrated significant improvement in MPOD (Hedges' g −0.551, p=0.029) but no significant difference in VA (Hedges' g −0.484, p=0.291) (Supplementary Figure S1).

Sensitivity analysis The sensitivity analyses showed that the efficacy of lutein supplementation in improving MPOD remained consistently statistically significant across all analyses.

Language restriction No language restriction.

Country(ies) involved Taiwan.

Other relevant information Not applicable.

Keywords Lutein, carotenoid, age-related macular disease, meta-analysis, systematic review.

Dissemination plans The findings of this systematic review and meta-analysis will be disseminated through peer-reviewed journal publications and presentations at national and international conferences.

Contributions of each author
Author 1 - Wei-Xiang Wang - The first author was responsible for data analysis, manuscript writing, and revisions.
Email: wales0315@gmail.com
Author 2 - Chen-Chi Wang - The second author contributed to data collection and the writing of the method section.
Author 3 - Wei-Cherng Hsu - The third author was responsible for proofreading and refining the wording.
Author 4 - Yi-Jie Peng - The fourth author was responsible for correspondence and proofreading.