Original Article

The level and efficacy of lutein in patients with age-related macular degeneration: a comprehensive systematic review and meta-analysis

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Background: Lutein has been linked with various visual performance disorders, including age-related macular degeneration (AMD). However, previous studies evaluating the association between serum lutein and the risk of AMD showed results, and the efficacy of lutein intake in AMD patients remains unclear.

Methods: To comprehensively estimate the relationship between lutein and AMD, a systematic review and meta-analysis was conducted by searching eligible randomized clinical trials (RCT) and case-control studies to study the association between lutein and AMD on the Cochrane Library, MEDLINE, Elsevier, PubMed, Web of Knowledge, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical Database (CBM) databases until April 2020. The weighted mean difference (WMD) with 95% confidence interval (95% CI) was adopted as the primary effect estimate. Meta-analysis was conducted using STATA 12.0.

Results: Nine studies with 855 participants were included in this meta-analysis. The NOS scoring of five case-control studies ranged 5–9. For RCTs, two studies were rated with a low risk of bias, one study with a moderate risk of bias and one with a high risk of bias. The results increased significantly in macular pigment optical density (MPOD) (WMD =0.069; 95% CI: 0.040–0.098, P=0.000) among AMD patients taking lutein supplementation, while there was no difference in circulating lutein levels between AMD patients and controls (WMD =0.00; 95% CI: −0.01 to 0.00, P=0.310). Subgroup analysis suggested that the dose and duration of supplementation could significantly influence the MPOD level in AMD patients. In particular, we observed a larger increase in MPOD of AMD patients using a higher dose (20 mg/d) and longer treatment (>6 months).

Conclusions: Although current evidence does not support circulating lutein as a biomarker for early screening of the high-risk AMD population, this study is the first meta-analysis to explore the relationship between lutein in blood and AMD patients. Given that lutein has a high safety profile as indicated by many studies, it is reasonable to give the current analysis result that high dose (20 mg/d) and long duration (>6 months) of lutein intake could be beneficial to AMD patients.

Keywords: Lutein supplements; macular pigment optical density (MPOD); age-related macular degeneration (AMD)

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Introduction

Age-related macular degeneration (AMD), a progressive disorder primarily affecting the central retina and causing irreversible visual impairment (1), is now one of the dominant causes of blindness in elderly people (2). The number of AMD patients worldwide is estimated to be 288 million by 2050 (2). AMD can be further subdivided into neovascular AMD and atrophic AMD according to its pathophysiology. Although intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs has been used as the standard treatment for neovascular AMD (3,4), the need for regular injection, patients' poor responses to anti-VEGF agents, and the high cost make the use of such treatment schemes relatively limited (5) and there currently are no efficient treatments for atrophic AMD. At present, the main strategies are to use antioxidants, multivitamins, and minerals for treatment, as well as to identify and control risk factors that may increase the incidence and progression of AMD (6).

As the most abundant carotenoid present in the human retina (7), lutein possesses various properties, including oxidation resistance (8), filtering blue light (9), and anti-inflammatory (10). Numerous cellular and animal studies have showed that lutein plays a therapeutic role in alleviating oxidative and inflammatory damages (11-16), which are two major pathological processes in AMD (6). Since lutein must be obtained from the diet (17), some clinical trials exploring the association between dietary supplementation with lutein and AMD have been performed, but the results are inconsistent. Lutein Antioxidant Supplementation Trial (LAST) (18), Lutein Antioxidant Supplementation Trial II (LASTII) (19), Combination of Lutein Effects in the Aging Retina (CLEAR) study (20) and Lutein Intervention Study Austria (LISA) (21) indicated protective effects of lutein for AMD. But Beaver Dam Study (22) and Nurses' Health Study, Health Professionals Follow-up Study (23,24) failed to show a positive association between lutein intake and AMD. Plasma level of lutein may be another predictive factor shown of AMD risks. Several studies support the possibility that higher levels of antioxidants in the blood, especially carotenoids such as lutein, may be related to the reduced risk of AMD (25,26). Meanwhile, one study showed that there is no difference in blood lutein between AMD patients and controls (27). The inconsistent findings of these studies on the level of lutein in patients with AMD in comparison to healthy controls and the efficacy of lutein intake in AMD patients may be attributable to two main reasons. Firstly, the absorption and metabolism of lutein may be different among people with different age, race and gender. Secondly, the AMD patients in some studies may be included by self-reporting or other different criteria, it may lead to differences in classification of cases and conclusions even with the same interventions. For these questions, meta-analysis maybe a good way to explore the relationship between lutein and AMD by giving the unified inclusion and exclusion criteria and then drawing reliable conclusions.

Although the relationship between lutein and AMD has been explored in some meta-analyses (28-30), which usually involved the combined effect of lutein with other antioxidants, including zeaxanthin, zinc, docosahexaenoic acid and so on. And to the best of our knowledge, there is no meta-analysis to clarify the relationship between lutein in blood and AMD patients.

To clarify these inconsistent findings in the literature and the potential role of lutein in the prevention and progression of AMD, a meta-analysis was performed to evaluate available research on lutein blood levels between AMD patients and controls, and research on lutein supplementation in patients with AMD. We present the following article in accordance with the MOOSE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-173/rc).

Methods

Search strategy

The Cochrane, MEDLINE, Elsevier, PubMed, Web of Knowledge, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical (CBM) databases were electronically searched for publications through April 2020 without language restrictions. The keywords for this search included lutein combined with each of the following words: age-related maculopathy, age-related macular degeneration, and AMD. Additional studies were obtained by manual search of references cited by the screened papers and systematic reviews. The protocol was registered with the INPLASY Register (registration No. INPLASY2021110091).

Selection criteria

The inclusion criteria were as follows: (I) randomized clinical trials (RCT) (studies investigating the effect of lutein supplement on AMD [macular pigment optical density (MPOD) as the outcome] by giving quantitative dietary lutein supplement (test group) and placebo (control

group) to AMD patients) and case-control studies (studying the blood lutein level of AMD patients and control subjects) in which the association between lutein and AMD was investigated; (II) studies involving subjects that were >40 years old; (III) AMD was diagnosed by professionals according to specific criteria; (IV) mean, standard deviation, or sufficient data to calculate these were reported; and (V) lutein was supplemented alone and quantified in randomized clinical trials.

Studies with any of the following conditions were excluded: (I) studies involving subjects that were reported to have other eye diseases other than AMD, or received retinal surgery within 3 months, photosensitive drugs, or corticosteroid therapy; (II) repeated reports, poor quality research (not providing enough information for subjects, interventions and research design), and articles where information was not available; (III) abstracts and reviews which could not provide original research data for analysis; and (IV) animal experimental studies.

Literature searches and articles were screened independently by two investigators (W.R. & Y.Z.). An initial screening was performed by examining the titles and abstracts of all the retrieved articles, and the remaining articles were read in full and checked. Discrepancies were resolved by discussion between the two investigators.

Data extraction

After screening the articles, two investigators (L.Y. & N.M.) independently extracted detailed information from the eligible studies. The following data were extracted: the first author's name, publication date, country where the study was performed, study design, sample size, study population, intervention, AMD diagnostic method, follow-up duration, mean and standard deviation in each subgroup, and outcome measures.

Literature quality assessment

The quality of case-control studies was evaluated independently by two reviewers using the Newcastle Ottawa Scale (NOS), which consists of the following three broad aspects: (I) selection of study groups (four criteria); (II) comparability of study groups (one criterion); (III) assessment of the outcome/exposure (three criteria). Studies that fulfilled all of the criteria were scored 9 stars, and a score ≥6 stars was considered to indicate good quality research. Studies that met four or fewer of these criteria were considered to be either fair or poor quality.

Risk of bias in the RCTs was evaluated using the Cochrane Collaboration tool (31), which is comprised of six aspects: (I) random sequence generation; (II) allocation concealment; (III) blinding of participants and personnel; (IV) blinding of outcome assessment; (V) incomplete outcome data; and (VI) selective reporting. Discrepancies were settled by discussion and consensus.

Statistical analysis

The extracted data were continuous variables, and therefore, mean differences (MDs) with 95% confidence intervals (CIs) were used to summarize and compare between groups. The effects of different doses and treatment durations were compared through subgroup analyses. Between-study heterogeneity was explored by Q tests, with the I^2 value quantifying the degree of heterogeneity. If I^2>50%, it was considered that the heterogeneity was high, and the random model was applied; otherwise, the fixed effect model was used. Publication bias was assessed by Begg's test and funnel plots when sufficient studies (n>10) were available. All statistical analyses were conducted by using Stata, version 12.0 (Stata Corporation, College Station, TX, USA). All P values were two-sided, with statistical significance set at a level of 0.05. Sensitivity analysis was performed by excluding one study at a time and assessing whether the pooled results of the remaining studies were different from those of all studies.

Results

In total, 1,520 citations were initially screened, and duplicates, abstracts, case reports, and obviously irrelevant research was excluded. The remaining 28 articles were read in full, and nine studies were finally included in the meta-analysis (*Figure 1*). Of these studies, five investigated the difference in lutein blood levels between AMD patients and controls, and four explored the relationship between dietary intake of lutein supplement and the risk of AMD.

Study characteristics

Table 1 shows the characteristics of the nine included studies (involving a total of 855 subjects), four of which used a case-control design, one was a dose-ranging study, and four were RCTs.

The four case-control studies and one dose-ranging study

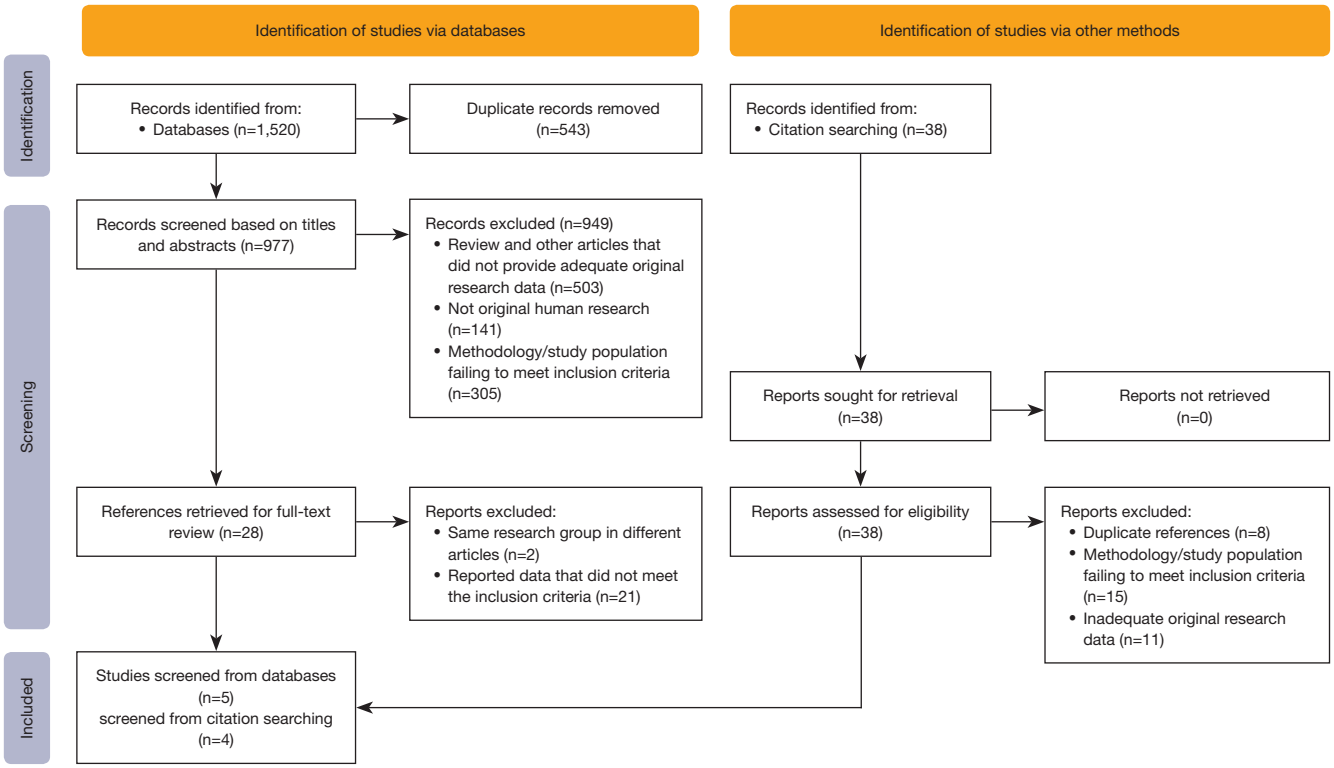

Figure 1 Flow diagram of study selection process.

assessed blood levels of lutein between AMD patients and controls, comprising a total of 291 patients and 277 controls. Blood levels of lutein were analyzed by high performance liquid chromatography (HPLC) in all of these studies.

The four RCTs investigated the effect of lutein supplementation on MPOD of patients with AMD, which included 429 subjects. Patients in the test group were given quantified dietary lutein supplementation for a period ranging from 3 months to 2 years. Patients in the control group received a placebo. All studies included MPOD as an outcome. The NOS scoring of the case-control studies is displayed in *Table 2*. The score of all included case-control studies ≥5 stars, which indicates good quality research. For RCTs, two studies (20,36) were rated with a low risk of bias, one study (37) with a moderate risk of bias and one (38) with a high risk of bias according to the Cochrane Collaboration's tool (31). *Figure 2* shows the result of risk of bias assessment.

Blood lutein levels and AMD

Among the selected five studies, two reported that the blood lutein levels of the cases were higher than those of the controls (32,33), two reported the opposite result (34,35), and one reported no difference in the blood lutein levels between AMD patients and controls (27). There was no significant difference in all results. The fixed-effects meta-analysis of all five studies showed that there was no difference in the total blood lutein between AMD patients and control subjects (WMD =0.00; 95% CI: −0.01 to 0.00; *Figure 3*).

Effects of lutein supplementation in AMD patients

Four studies reported 12 research results according to different doses and durations. Six results identified an association between the lutein intake and a higher content of MPOD, and two studies reported a negative correlation, without statistical significance. There was significant heterogeneity across the studies (I^2=52.2%; P for heterogeneity 0.018). The random-effects meta-analysis of all 12 results found a significant increase in MPOD (WMD =0.07; 95% CI: 0.04–0.10) among AMD patients taking lutein supplementation (*Figure 4*).

A subgroup analysis (*Table 3*) according to the dose of lutein supplementation found a significant increase in

Table 1 Characteristics of included trials

Study	Country	Study design	Trial duration	Participant characteristics	Intervention	Age (years)	Diagnosis criteria of AMD	Determination method of serum lutein/MPOD
Studies regarding AMD and blood lutein levels								
Sanders *et al.* [1993] (27)	UK	Case-control study	–	65 patients with AMD and 65 control subjects matched for age and sex	–	66–87	Defined as having degenerative changes that were clearly visible in both maculas	HPLC
Mares-Perlman *et al.* [1995] (32)	US	Nested case-control study	–	167 patients with AMD and 167 controls matched with cases for age, sex, and current smoking status.	–	43–75+	Wisconsin Age-Related Maculopathy Grading System	HPLC
Koh *et al.* [2004] (33)	Singapore	Case-control study	–	Seven patients with early AMD and six volunteers with no retinal pathology	–	58–81	–	HPLC
Cardinault *et al.* [2005] (34)	France	Case-control study	–	37 AMD patients and 24 control subjects	–	Control: 71.0±1.5; patients: 74.7±1.2	Clinical examination by the physician	HPLC
Rosenthal *et al.** [2006] (35)	USA	Dose-ranging study	–	45 participants with no AMD (n=15), large drusen (n=15), or advanced AMD (n=15)	–	60–91	–	HPLC
Studies regarding AMD and MPOD								
Murray *et al.* [2013] (20)	Netherlands	Randomized, double-blind, placebo-controlled, two-center investigation	12 months	73 patients with early AMD	Lutein capsules (10 mg ester) (n=36) or a placebo (n=37) were taken daily	50–80	According to the Rotterdam study (36,37)	Flicker-based technique (MPS9000)
Huang *et al.* [2015] (38)	China	Randomized, double-blind, placebo-controlled trial	2 years	108 patients with early AMD	10 mg lutein (n=26); 20 mg lutein (n=27); 10 mg lutein + 10 mg zeaxanthin (n=27); placebo (n=28) daily	>50	Age-Related Eye Disease Study System	Fundus autofluorescence images
Ma *et al.* [2017] (39)	China	Randomized, double-blind, placebo-controlled trial	48 weeks	200 patients with early AMD	20 mg lutein (n=100); placebo (n=100)	50–79	Fundus photographic severity scale (40)	Not given
Gao *et al.* [2018] (41)	China	Randomized, controlled trial	3 months	48 AMD patients; 52 eyes	20 mg lutein; blank	61.9±11.24	Fluorescence fundus angiography and optical coherence tomography	The non-mydriatic fundus camera ZEISS Visucam 500

*, this study meets all the inclusion criteria. AMD, age-related macular degeneration; HPLC, high performance liquid chromatography; MPOD, macular pigment optical density.

Table 2 Quality assessment of case-control studies included in this meta-analysis[1]

Study	Adequate definition of cases	Representativeness of cases	Selection of control	Definition of control	Control for important factor or additional facto[2]	Exposure assessment	Same method of ascertainment for cases and controls	Non-response rate[3]	Total quality scores
Sanders *et al.* [1993] (27)	★	★	★	★	★	★	★	★	8
Mares-Perlman *et al.* [1995] (32)	★	★	★	★	★★	★	★	★	9
Koh *et al.* [2004] (33)	★	–	–	★	★	★	★	★	6
Cardinault *et al.* [2005] (34)	–	–	★	★	★★	–	–	★	5
Rosenthal *et al.* [2006] (35)	★	★	★	★	★★	★	★	★	9

[1], a study could be awarded a maximum of one star for each numbered item, except for the item Control for the most important factor or second important factor; [2], a maximum of two stars could be awarded for Control for the most important factor or second important factor. Studies that controlled for other mental and physical illnesses and genetic history received one star, while studies that controlled for age, sex, and living environment received one additional star; [3], one star was awarded if there was no significant difference in the response rate between control subjects and cases in the chi-square test (P>0.05).

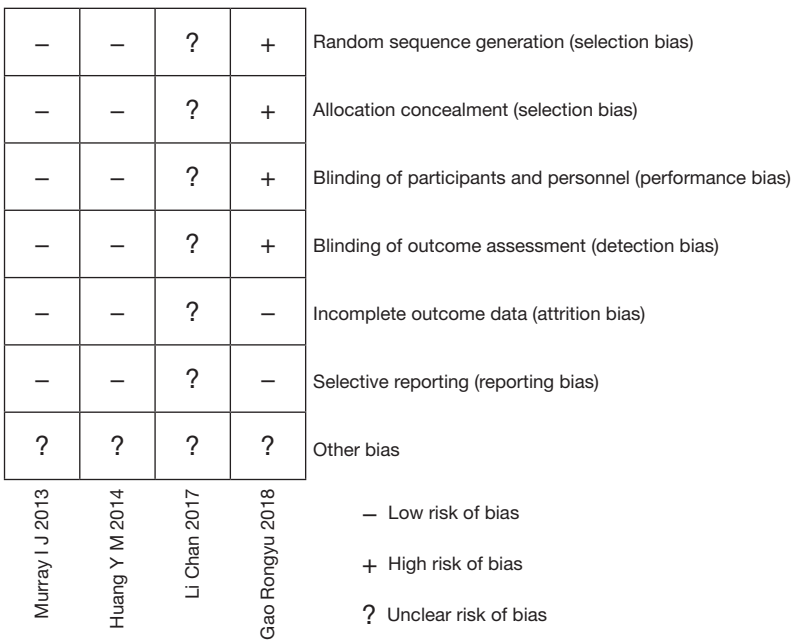

Figure 2 Risk of various biases determined by the Cochrane Collaboration tool.

MPOD only in the treatment subgroup with 20 mg/d (WMD =0.098; 95% CI: 0.074–0.122), but not the treatment group with 10 mg/d lutein (WMD =0.032; 95% CI: –0.018–0.081). Similarly, a subgroup analysis according to the duration of lutein supplementation showed that a significant increase in MPOD only existed in the >6 months group (WMD =0.087; 95% CI: 0.052–0.122), but not in the <6 months group (WMD =0.048; 95% CI: 0.001–0.094).

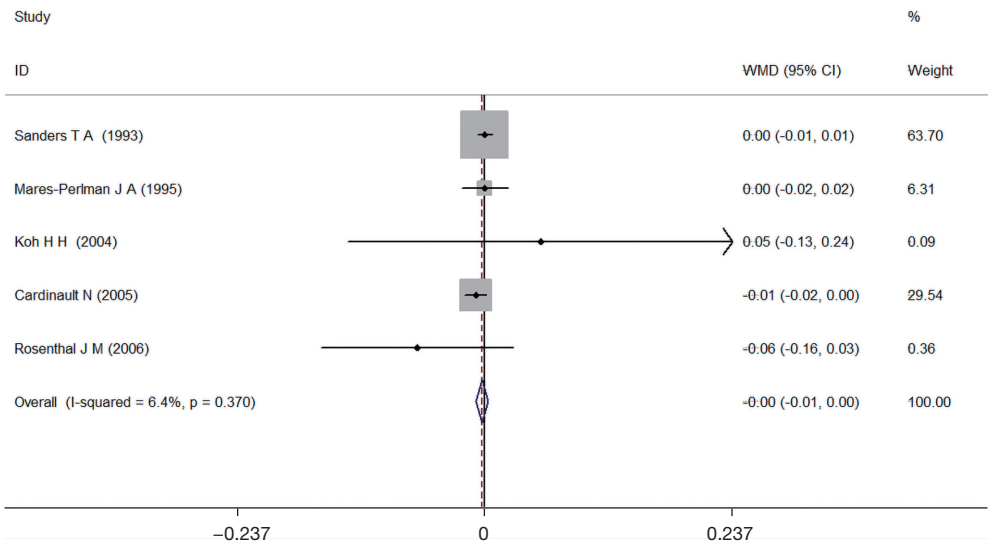

Figure 3 Forest plot of studies of blood lutein levels for AMD patients versus controls. The combined WMD and 95 % CI were calculated using the fixed-effects model. WMD, weighted mean difference; AMD, age-related macular degeneration; CI, confidence interval.

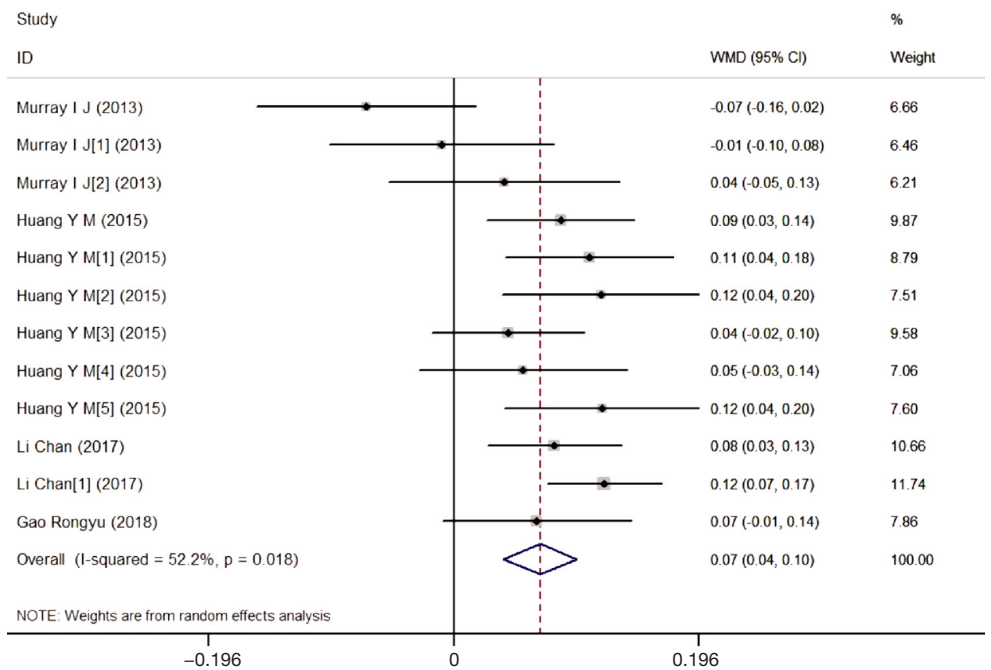

Figure 4 Forest plot displaying the effect of lutein supplementation on MPOD in patients with AMD. The combined WMD and 95% CI were calculated using the random-effects model. Murray IJ: dose of supplements: 10 mg; duration of supplements: 4 months. Murray IJ [1]: dose of supplements: 10 mg; duration of supplements: 8 months. Murray IJ [2]: dose of supplements: 10 mg; duration of supplements: 12 months. Huang YM: dose of supplements: 20 mg; duration of supplements: 24 weeks. Huang YM [1]: dose of supplements: 20 mg; duration of supplements: 48 weeks. Huang YM [2]: dose of supplements: 20 mg; duration of supplements: 24 months. Huang YM [3]: dose of supplements: 10 mg; duration of supplements:24 weeks. Huang YM [4]: dose of supplements: 10 mg; duration of supplements: 48 weeks. Huang YM [5]: dose of supplements: 10 mg; duration of supplements: 24 months. Li Chan: dose of supplements: 20 mg; duration of supplements: 24 weeks. Li Chan [1]: dose of supplements: 20 mg; duration of supplements: 48 weeks. Gao Rongyu: dose of supplements: 20 mg; duration of supplements: 3 months. WMD, weighted mean difference; MPOD, macular pigment optical density; AMD, age-related macular degeneration; CI, confidence interval.

Table 3 Subgroup analysis of studies on MPOD

Subgroup	No. of studies	WMD (95% CI)	P value	Test of heterogeneity	
				P value	I^2
Overall	12	0.07 (0.04–0.10)	0.000	0.018	52.20%
Supplement dose					
10 mg	6	0.032 (–0.018–0.081)	0.047	0.206	55.50%
20 mg	6	0.098 (0.074–0.122)	0.133	0.000	0.00%
Supplement duration					
<6 months	5	0.048 (0.001–0.094)	0.044	0.041	59.80%
>6 months	7	0.087 (0.052–0.122)	0.000	0.150	36.40%

MPOD, macular pigment optical density; CI, confidence interval; WMD, weighted mean difference.

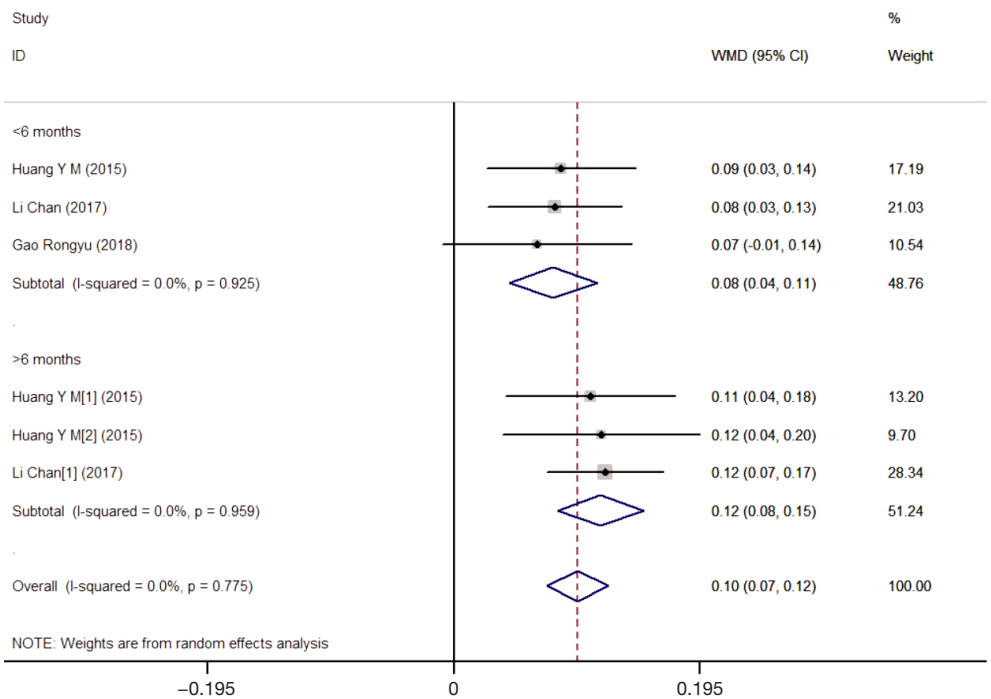

Figure 5 Forest plot displaying the effect of 20 mg/d lutein supplementation on MPOD in patients with AMD when supplementation lasted <6 or >6 months. Huang YM: dose of supplements: 20 mg; duration of supplements: 24 weeks. Huang YM [1]: dose of supplements: 20 mg; duration of supplements: 48 weeks. Huang YM [2]: dose of supplements: 20 mg; duration of supplements: 24 months. Li Chan: dose of supplements: 20 mg; duration of supplements: 24 weeks. Li Chan [1]: dose of supplements: 20 mg; duration of supplements: 48 weeks. Gao Rongyu: dose of supplements: 20 mg; duration of supplements: 3 months. WMD, weighted mean difference; CI, confidence interval; MPOD, macular pigment optical density; AMD, age-related macular degeneration.

Stratified analyses based on the lutein supplementation dose demonstrated that the levels of MPOD were significantly higher in the treatment group with 20 mg/d lutein compared to the placebo group (WMD =0.10; 95% CI: 0.07–0.12), regardless of whether the duration is more than 6 months (WMD =0.12; 95% CI: 0.08–0.15) or fewer than 6 months (WMD =0.08; 95% CI: 0.04–0.11) (*Figure 5*). Meanwhile, no difference was observed in the treatment

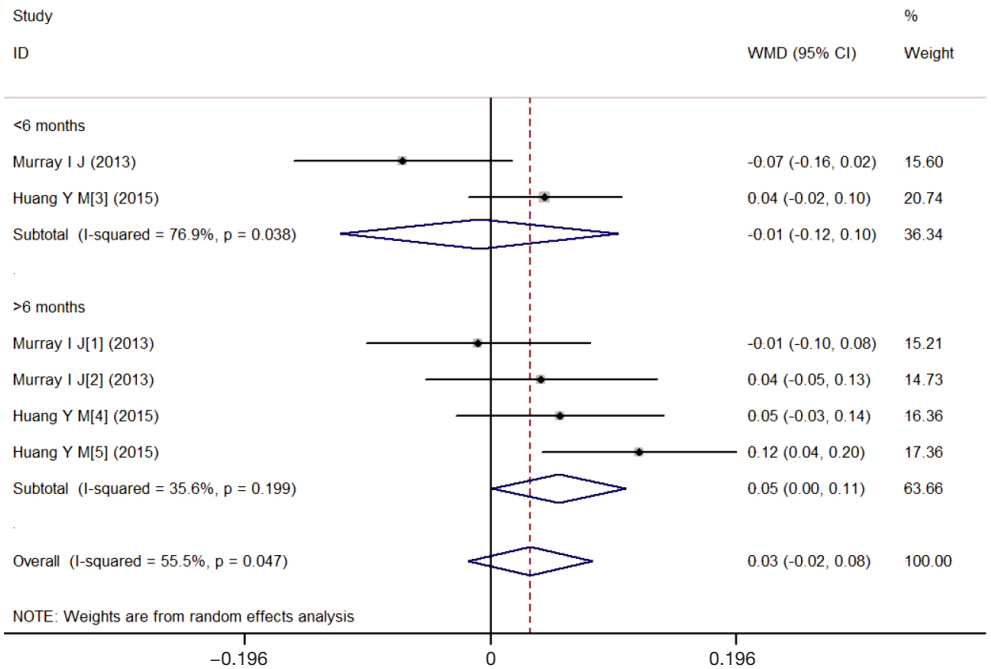

Figure 6 Forest plot displaying the effect of 10 mg/d lutein supplementation on MPOD in patients with AMD when supplementation lasted <6 or >6 months. Murray IJ: dose of supplements: 10 mg; duration of supplements: 4 months. Murray IJ [1]: dose of supplements: 10 mg; duration of supplements: 8 months. Murray IJ [2]: dose of supplements: 10 mg; duration of supplements: 12 months. Huang YM [3]: dose of supplements: 10 mg; duration of supplements: 24 weeks. Huang YM [4]: dose of supplements: 10 mg; duration of supplements: 48 weeks. Huang YM [5]: dose of supplements: 10 mg; duration of supplements: 24 months. WMD, weighted mean difference; CI, confidence interval; MPOD, macular pigment optical density; AMD, age-related macular degeneration.

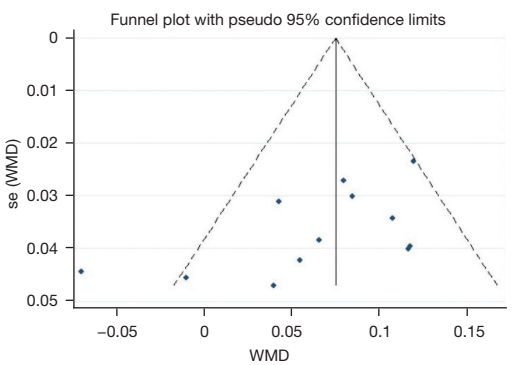

Figure 7 Funnel plot for MPOD across all studies. MPOD, macular pigment optical density. WMD, weighted mean difference.

group with 10 mg/d lutein (WMD =0.03; 95% CI: −0.02–0.08) (*Figure 6*).

The sensitivity analysis showed that the overall results did not change by excluding any one of studies from the analysis. Also, according to the results of Begg's test (P=0.086) and the funnel plot (*Figure 7*), there was no significant publication bias.

Discussion

The results of the present meta-analysis suggested that no difference in blood lutein was observed between the AMD patients and control subjects. However, one meta-analysis (42) showed that the serum lutein level of AMD patients was lower than that of control group, and the difference was statistically significant. The results of that meta-analysis may be doubtful, because among the eight included studies, two determined the levels of total lutein and zeaxanthin, while the remaining six only determined the lutein content, and the original format of the data report in one article did not meet the inclusion requirements.

Data on evaluating the effects of lutein supplementation among AMD patients found that lutein supplement could increase MPOD, which is consistent with the findings of previous meta-analyses (43,44). Stratified analyses by dose

and duration indicated that lutein supplement showed efficacy only at high doses (>20 mg) and for long periods of time (>6 months), and there was no significant effect when the dose was 10 mg or the duration was less than 6 months. Feng *et al.* (43) also reached a consistent result about the duration when evaluating the effects of lutein supplementation on MPOD among AMD patients, but they also showed that dietary intake of lutein at 10 mg/d lasting longer than 6 months can significantly improve MPOD levels in patients with AMD. The divergent result about dose may have come from five studies that involved the combined supplementation of lutein with other antioxidants, including zeaxanthin, docosahexaenoic acid, and eicosapentaenoic acid in Feng *et al.*'s research (43). Such mixtures may be more effective in antioxidation than individual lutein at the same concentration (45,46). Given that AMD is a chronic progressive disease, this stratified analysis confirmed the importance of dose and duration of use for these supplements. Whether lutein is combined with other antioxidants is also an important factor to determine the effective time and dose. In addition, other factors may have a certain impact on AMD. For example, ethnic (47), increased body fat (48,49), extended exposure to sunlight (50-52), genetic factors (53) and smoking (54) have been shown to play a role in MPOD/AMD. However, the impact of these factors on AMD needs to be confirmed by more studies. In addition to efficacy, safety is also an important factor in supplements. Lutein is classified as Generally Regarded as Safe (GRAS) by the US Food and Drug Administration (FDA) (55). Besides, lutein is safe at the dose up to 20 mg/d according to the Council for Responsible Nutrition (CRN) (56). Two clinical research investigated the effects of lutein with the intake at 40 mg/d for 9 weeks, 20 mg/d thereafter up to 26 weeks and 30 mg/d for 120 days, respectively (57,58). No adverse health effects were reported. Thus, it may be reasonable to supplement lutein at 20 mg/d to improve MPOD in AMD patients for both the safety and efficacy.

There are some weaknesses of the present study that should be noted. Firstly, the study assessing the difference in serum lutein levels between AMD patients and controls was based on observational studies with limited a sample size, which might have potential bias and confounding effects. Secondly, the types and stages of AMD were not strictly distinguished due to the limited information given in the included literature and the various classification criteria applied. Despite these limitations, this study strived to clarify the association between serum lutein levels and AMD. In addition, studies involving the combined supplementation of lutein with other antioxidants were excluded to lower the heterogeneity and increase the reliability of results.

In conclusion, the evidence available to date demonstrates that no difference was observed between AMD patients and control subjects in total serum lutein. Nevertheless, dietary intake of lutein (20 mg/day) can significantly improve MPOD in AMD patients.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-173/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-173/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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