INPLASY PROTOCOL

To cite: Liu et al. Lutein and age-related macular degeneration: a comprehensive systematic review and meta-analysis. Inplasy protocol 2021110091. doi: 10.37766/inplasy2021.11.0091

Received: 24 November 2021

Published: 24 November 2021

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Support: **None.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Lutein and age-related macular degeneration: a comprehensive systematic review and meta-analysis

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Review question / Objective: **To clarify these inconsistent findings in the literature and the potential role of lutein in the prevention and progression of AMD, the 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.**
Condition being studied: **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 AMD risk showed inconsistent results and the relationship between lutein supplements and AMD risk remains unclear. Moreover, the treatment effect of lutein in AMD patients is also unknown.**
Information sources: **Cochrane Library, MEDLINE, Elsevier, PubMed, Web of Knowledge, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Database (CBM).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 November 2021 and was last updated on 24 November 2021 (registration number INPLASY2021110091).

INTRODUCTION

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METHODS

Search strategy: Cochrane, MEDLINE, Elsevier, PubMed, Web of Knowledge, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Database (CBM) were electronically searched for publications through April 2020 without language restrictions. The keywords for this search were 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.

Participant or population: Age-related macular degeneration.

Intervention: Lutein.

Comparator: This study is the first meta-analysis exploring the relationship between lutein in blood and AMD patients in English.

Study designs to be included: (1) Randomized clinical trials (RCT) and case-control studies in which the association between lutein and AMD was investigated; (2) subjects were > 40 years old; (3) AMD was diagnosed by professionals according to specific criteria; (4) Mean, standard deviation or sufficient data to calculate these were reported; (5) lutein was supplemented alone and quantified in randomized clinical trials.

Eligibility criteria: The following requirements would be satisfied:(1) Randomized clinical trials (RCT) and case-control studies in which the association between lutein and AMD was investigated; (2) subjects were > 40 years old; (3) AMD was diagnosed by professionals according to specific criteria; (4) Mean, standard deviation or sufficient data to calculate these were reported; (5) lutein was supplemented alone and quantified in randomized clinical trials.Studies with any of the following conditions will be excluded: (1) Subjects were reported to have other eye diseases other than AMD, have retinal surgery within three months, take photosensitive drugs or have corticosteroid therapy; (2) Repeated reports, poor quality and too little information were not available; (3) Abstracts and reviews which cannot provide original research data for analysis; (4) Animal experimental study.Literature searches and articles were screened independently by two investigators (W. R. & Y. Z.). An initial screen was performed by examined 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.

Information sources: Cochrane Library, MEDLINE, Elsevier, PubMed, Web of Knowledge, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Database (CBM).

Main outcome(s): Of 1520 citations screened for duplicates and titles and abstracts, case reports, obviously irrelevant, the remaining 28 articles were read in full and 9 studies were finally in the meta-analysis (Fig. 1.). Of the 9 studies, 5 investigated the difference of lutein blood levels between AMD patients and controls, 4 explored the relationship between dietary intake of lutein supplement and the risk of AMD.

Quality assessment / Risk of bias analysis: 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: (a) selection of study groups (four

criteria); (b) comparability of study groups (one criterion); (c) assessment of the outcome/explosure (three criteria). Studies that fulfilled all the criteria were 9 stars and a score ≥ 6 stars is considered to be categorized as good quality. Studies that met four or fewer of these criteria were considered fair quality or poor quality. Risk of bias in RCT was evaluated using the Cochrane Collaboration tool (Higgins J. et al., 2011) which is comprised of six aspects: (a) random sequence generation; (b) allocation concealment; (c) blinding of participants and personnel; (d) blinding of outcome assessment; (e) incomplete outcome data; and (f) selective reporting. Discrepancies were settled by discussion and consensus.

Strategy of data synthesis: 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 I2 value quantifying the degree of heterogeneity. If I2>50%, it was considered that the heterogeneity was high, 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.

Subgroup analysis: Subgroup analysis suggested that dose and duration of supplement could significantly influence the MPOD level in AMD patients.

Sensitivity analysis: Sensitivity analysis was performed by excluding one study at a time and assessing whether the pooled results of the remaining studies were differed from those of all studies.

Language: English, Chinese.

Country(ies) involved: China.

Keywords: Lutein supplements; macular pigment optical density; age-related macular degeneration.

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