INPLASY

Effect of selenium supplementation on thyroid peroxidase antibody and thyroid stimulating hormone levels in patients with Hashimoto's thyroiditis: a protocol for a systematic review and meta-analysis

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Yang, Z.

Corresponding author:
Zhuoer Yang

jiaozhu5555@qq.com

Author Affiliation:
Department of Immunology, Xi'an Medical University, Xi'an, Shaanxi, China.

ADMINISTRATIVE INFORMATION

Support - This research received no specific grant from any funding agency.

Review Stage at time of this submission - This protocol was registered retrospectively. Literature searching, study selection, data extraction, and risk of bias assessment were commenced in June 2025 and substantially completed before INPLASY registration, because the authors were initially unaware of the requirement for prospective registration. Data analysis is currently being finalized, and the manuscript has not yet been submitted.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670058

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 July 2026 and was last updated on 17 July 2026.

INTRODUCTION

Review question / Objective The aim of this systematic review is to evaluate the efficacy of selenium supplementation compared with placebo or no selenium supplementation on:
(a) thyroid peroxidase antibody (TPOAb) titers, and
(b) thyroid stimulating hormone (TSH) levels,
in adult patients with Hashimoto's thyroiditis. To this end, only randomized controlled trials will be included to ensure the highest level of evidence for the intervention effect.

Rationale Selenium supplementation has been proposed as a therapeutic approach for Hashimoto's thyroiditis (HT) due to the antioxidant properties of selenoproteins and their role in thyroid hormone metabolism. Several randomized controlled trials (RCTs) have investigated selenium's effect on thyroid autoantibodies, but results have been inconsistent. A recent systematic review by Huwiler et al. (Thyroid, 2024) included 35 studies but incorporated observational and quasi-randomized designs alongside RCTs, potentially diluting the quality of evidence. Our review will focus exclusively on RCTs to provide a higher-quality synthesis. Additionally, we will conduct subgroup analyses by geographical region (Chinese vs non-Chinese studies), which was not performed in the previous review, to explore the substantial heterogeneity observed in the field (I^2 > 90%). An updated meta-analysis restricted to RCTs with explicit geographical stratification is warranted.

Condition being studied Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis, is the most common cause of hypothyroidism in iodine-sufficient regions. It is characterized by elevated thyroid

peroxidase antibodies (TPOAb) and/or thyroglobulin antibodies (TgAb), lymphocytic infiltration of the thyroid gland, and progressive thyroid follicular destruction.

METHODS

Search strategy The following electronic databases will be searched from inception to June 2025:

1. PubMed / MEDLINE (via NCBI)
2. Embase (via Elsevier)
3. Cochrane Central Register of Controlled Trials (CENTRAL)
4. Cochrane Database of Systematic Reviews (CDSR)
5. Web of Science Core Collection
6. China National Knowledge Infrastructure (CNKI)
7. Wanfang Database
8. VIP Database (China Science and Technology Journal Database)
9. ClinicalTrials.gov (clinicaltrials.gov)

Supplementary searches: reference lists of included studies and relevant systematic reviews will be manually screened; trial registers will be checked; authors of eligible studies will be contacted for additional data.

The search strategy for PubMed is as follows: (("Hashimoto's thyroiditis"[MeSH] OR "autoimmune thyroiditis"[MeSH]) AND ("selenium"[MeSH] OR "selenium compounds"[MeSH])) AND ("randomized controlled trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab])

Similar strategies will be adapted for other databases using appropriate controlled vocabulary terms (Emtree for Embase, subject headings for CNKI/Wanfang/VIP).

Participant or population Adult patients (≥18 years) with a confirmed diagnosis of Hashimoto's thyroiditis (HT), defined by the presence of elevated thyroid peroxidase antibodies (TPOAb) and/or thyroglobulin antibodies (TgAb), with or without hypothyroidism, regardless of concurrent levothyroxine (LT4) use.

Excluded populations: pregnant women; children and adolescents (<18 years); patients with Graves' disease or other non-HT thyroid conditions; studies where HT patients constitute a minority (<50%) of the sample and HT-specific data cannot be extracted separately.

Intervention Oral selenium supplementation of any form (selenomethionine, sodium selenite, selenium-enriched yeast), any dose (typically 100–200 μg/day), any duration, as monotherapy or adjunctive therapy with levothyroxine (LT4).

Excluded: selenium administered via non-oral routes (intravenous, topical); combination supplements where selenium's independent effect cannot be isolated (e.g., selenium + myo-inositol without a selenium-only arm).

Comparator Placebo (identical appearance to selenium preparation), or no selenium supplementation (usual care with LT4 alone if applicable).

Excluded: active comparators other than placebo/no selenium (e.g., other antioxidants alone without a selenium arm).

Study designs to be included Only randomized controlled trials (RCTs) with parallel-group design will be included. Crossover trials, cluster-randomized trials, quasi-randomized studies (e.g., allocation by alternation, date of birth, or hospital record number), and observational study designs (cohort, case-control, cross-sectional) will be excluded.

Eligibility criteria Additional exclusion criteria:
- Studies not reporting TPOAb or TSH as outcome measures
- Studies reporting only geometric means without enabling conversion to arithmetic means
- Studies with fewer than 10 participants per group
- Duplicate publications of the same trial data (the most complete version will be included)
- Non-English or non-Chinese full-text publications (abstracts in these languages will be assessed; authors will be contacted for data).

Information sources See Item 11 above. The following databases and supplementary sources will be searched:
- PubMed/MEDLINE, Embase, CENTRAL, CDSR, Web of Science, CNKI, Wanfang, VIP, ClinicalTrials.gov
- Manual screening of reference lists of included studies and relevant systematic reviews
- Trial registers (ClinicalTrials.gov, WHO ICTRP)
- Contacting authors for unpublished or additional data
- Dissertation databases (CNKI dissertation database).

Main outcome(s) Primary outcome 1: Change in serum thyroid peroxidase antibody (TPOAb) titer

from baseline to end of intervention, measured as mean ± standard deviation (IU/mL or equivalent units). Effect measure: Standardized Mean Difference (SMD) with 95% confidence interval, because different studies use different assay methods and units.

Primary outcome 2: Change in serum thyroid stimulating hormone (TSH) level from baseline to end of intervention, measured as mean ± SD (mIU/L). Effect measure: Mean Difference (MD) with 95% confidence interval, because all studies use the same unit (mIU/L).

Additional outcome(s) Secondary outcome 1: Change in serum thyroglobulin antibody (TgAb) titer from baseline to endpoint, measured as mean ± SD. Effect measure: SMD with 95% CI.

Secondary outcome 2: Adverse events related to selenium supplementation (e.g., gastrointestinal symptoms, nail/hair changes, garlic breath odor), reported as number and percentage per group where available.

Data management Two reviewers (ZY and ML) will independently screen titles/abstracts and full texts against the eligibility criteria, using EndNote for duplicate removal and record management. Disagreements will be resolved by discussion or adjudication by a third reviewer.

Data extraction will be performed independently by two reviewers using a standardized data extraction form. Disagreements will be resolved by consensus or consultation with a third reviewer. RevMan 5.4 will be used for statistical analysis.

For studies reporting median [IQR] or median [range], the Wan et al. (2014) method will estimate mean ± SD. For geometric means, log-transformation will be applied. If only SEM is reported, SD = SEM × √n. Authors will be contacted for missing data (up to two email attempts).

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers using the Cochrane Risk of Bias tool version 2 (RoB 2) for randomized trials (Higgins et al., 2019), covering five domains: (D1) randomization process; (D2) deviations from intended interventions; (D3) missing outcome data; (D4) measurement of the outcome; (D5) selection of the reported result. Each domain will be classified as 'Low risk', 'Some concerns', or 'High risk'. Overall bias determined by the RoB 2 algorithm. Disagreements resolved by discussion or third reviewer. Judgments presented in traffic-light plots via RevMan 5.4.

Certainty of evidence will be assessed using the GRADE approach for each primary outcome, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Summary of Findings tables will be created using GRADEpro GDT.

Strategy of data synthesis Statistical analyses will be performed using RevMan 5.4 (Cochrane Collaboration, Oxford, UK). For continuous outcomes: TPOAb will use Standardized Mean Difference (SMD) with 95% CI (different assay units across studies); TSH will use Mean Difference (MD) with 95% CI (all studies use mIU/L). A random-effects model (DerSimonian-Laird) will be the primary analysis, given anticipated clinical and methodological heterogeneity. Heterogeneity will be quantified by I^2 and Cochran's Q test (P 75% substantial). If heterogeneity is substantial, potential causes will be explored through pre-specified subgroup and sensitivity analyses. Publication bias will be assessed by funnel plots and Egger's regression test (if ≥10 studies per outcome). Trim-and-fill analysis may estimate the impact of missing studies.

Subgroup analysis Subgroup analyses are planned for:
1. Geographical region: Chinese studies vs non-Chinese studies
2. Concurrent LT4 use: selenium + LT4 vs selenium alone
3. Selenium dose: ≥100 μg/day vs <100 μg/day
4. Intervention duration: ≥6 months vs <6 months

Subgroup differences will be tested using RevMan's subgroup analysis function with a random-effects model within each subgroup.

Sensitivity analysis Sensitivity analyses will include:
1. Excluding Chinese studies (to assess whether effect estimates are robust without the subgroup driving heterogeneity)
2. Excluding studies rated as high risk of bias (RoB 2 overall = High)
3. Using a fixed-effect model instead of the random-effects model
4. Excluding the largest trial (Larsen 2024, n=412) in an influence analysis

Results of sensitivity analyses will be compared with the primary analysis to assess the robustness of conclusions.

Language restriction No language restrictions will be applied. English and Chinese language publications will be included. Authors of potentially eligible studies published in other languages will be contacted for data extraction.

Country(ies) involved China (review team). Included studies are expected from multiple countries including China, Turkey, Austria, Greece, Germany, Brazil, Iran, Poland, Netherlands, and Denmark, which will be reported as study characteristics.

Keywords Selenium; Hashimoto's thyroiditis; autoimmune thyroiditis; TPOAb; TSH; randomized controlled trial; meta-analysis; systematic review.

Dissemination plans Results will be disseminated through peer-reviewed journal publication and academic presentation at Xi'an Medical University. The INPLASY registration number will be cited in all resulting publications.

Contributions of each author

Author 1 - Zhuoer Yang - Conception, design, data collection, data analysis, writing.
Email: jiaozhu5555@qq.com

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