



The correlation between selenium levels and autoimmune thyroid disease: a systematic review and meta-analysis

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Background: This investigation systematically evaluated the selenium levels and the effects of selenium supplementation in patients with autoimmune thyroid disease (AITD).

Methods: Randomized controlled trials (RCTs) related to selenium supplementation in patients with AITD were selected from the PubMed, Medline, Web of Sciences, Embase, Cochrane Library, and Spring databases. All related literature published between January 2000 and November 2020 were included. The RCT bias risk assessment was conducted according to the Cochrane Handbook 5.0.2. The Review Manager 5.3 software was applied for meta-analysis of the included literature.

Results: A total of 17 articles meeting the requirements were selected, including a total of 1,911 subjects. Meta-analysis results showed that the serum free triiodothyronine (FT3) levels in patients was greatly reduced after selenium supplementation compared to placebo treatment (MD = -0.40; 95% confidential interval (CI): -0.70--0.10; Z=2.61; P=0.009). Serum free thyroxine (FT4) levels and anti-thyroid peroxidase antibody (TPOAb) levels were also significantly reduced (MD = -0.76; 95% CI: -1.58--0.07; Z=1.79; P=0.07), and anti-thyroid peroxidase antibody (TPOAb) level was decreased observably (MD = -150.25; 95% CI: -04.06--96.43; Z=5.47; P<0.00001). The thyroid stimulating hormone (TSH) levels (MD =0.06; 95% CI: -0.53--0.66; Z=0.21; P=0.83) and anti-thyroglobulin antibody (TGAb) levels (MD =17.19; 95% CI: -254.86--289.25; Z=0.12; P=0.90) were not significantly different between the experimental group and the control group.

Conclusions: Selenium-containing drugs were effective in treating AITD patients, and greatly reduced the levels of FT3, FT4, and TPOAb in AITD patients. These results suggested that selenium level had a great effect on AITD and selenium supplementation showed a very important effect on AITD.

Keywords: Selenium levels; selenium supplementation; autoimmune thyroid disease (AITD); meta-analysis

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Introduction

Autoimmune thyroid disease (AITD) is a typical organ-specific autoimmune condition caused by multiple factors such as genetics, environment, and lifestyle (1). AITD has a high incidence rate and is more common in female patients, usually manifesting as Graves' disease (GD),

hyperthyroidism, Hashimoto's thyroiditis (HT), and subclinical thyroid dysfunction (2). The main clinical manifestations of AITD are goiter, pharyngeal discomfort, neck compression, and dysphagia. Clinical examination shows abnormal thyroid function, elevated anti-thyroglobulin antibody (TGAb) and anti-thyroid peroxidase antibody (TPOAb) (3,4).

Selenium is a trace element necessary for the human body. Studies have shown that, except for the liver and kidney, the content of selenium in the thyroid is higher than in any other organ (5). Selenoproteins play an important role in maintaining the thyroid immune system, antioxidant system, hormone synthesis, and live metabolism (6). Selenium can regulate the levels of thyroid antibodies in patients with AITD and participates in the biosynthesis of thyroid hormones in the body (7). In recent years, many studies have shown that selenium supplementation is beneficial for regulating the serum levels of thyroid stimulating hormone (TSH), triiodothyronine (FT3), thyroxine (FT4), TGAb, and TPOAb, and these in turn have an immunomodulatory effect.

To date, numerous national and international studies have examined the efficacy of selenium supplementation in the treatment of AITD. However, due to the small number of samples in each study, the clinical benefits are still controversial. Therefore, a systematic review and meta-analysis was conducted to examine the clinical effects of selenium supplementation in AITD patients, especially with relation to serum levels of TSH, FT3, FT4, TPOAb, TGAb, and other indicators. These results were intended to provide a more solid basis for the clinical application of selenium supplementation in patients with AITD. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-449>).

Methods

Inclusion and exclusion criteria for the literature search

Published randomized controlled trials (RCTs) involving patients diagnosed with AITD (including GD, HT, hyperthyroidism, autoimmune thyroiditis (AIT), and abnormal thyroid function) where the intervention involved compounds containing selenium were included in this meta-analysis.

Unpublished studies such as degree theses, non-English literature, reports with missing original data or unreferenced results, non-RCTs, studies in which the participants had other diseases, and clinical trials evaluating the combined effects of selenium and other drugs were excluded.

Literature retrieval

A total of 6 English databases (PubMed, Medline, Web

of Science, Embase, Cochrane Library, and Spring) were searched. The retrieved literature was published from January 2000 to November 2020 using the keywords “Graves”, “AIT”, “hyperthyroidism”, “TGAb”, “TPOAb”, “TSH”, “FT3”, “FT4”, “anti-thyroglobulin antibody”, “anti-thyroid peroxidase antibody”, “thyroid stimulating hormone”, “serum free triiodothyronine”, “serum free thyroxine”, “Hashimoto’s thyroiditis”, “chronic lymphocytic thyroiditis”, “selenium”, “selenite”, and “selenium yeast”.

Literature selection

Two senior experts were invited to independently screen the topic and abstracts to eliminating the studies which did not meet the requirements of this study. This was followed by a review of the full text article to further determine whether the studies could be included. If there were inconsistencies between the two experts, a consensus would be obtained through discussion, or a third expert would be invited to arbitrate.

Data extraction

Two evaluators were invited to independently extract data from the included publications using a self-developed data extraction table. Results were cross-examined following independent extraction. The collated data included: (I) the title of the literature, the first author, the year of publication, and the publication journal; (II) the age, gender, sample size, and baseline comparability of the research subjects; (III) preoperative evaluation methods, intraoperative detection indicators, and postoperative observation indicators; (IV) outcome indicators including TSH, FT3, FT4, TGAb, TPOAb, and thyroid function. In the case of inconsistencies between the two experts, a consensus was reached through discussion, or opinion from a third expert was sought.

Document quality evaluation

The overall quality of each study was evaluated according to the RCT bias risk assessment standard provided by the Cochrane Handbook 5.0.2. The evaluation items included the following: whether the research group used a random method sequence; whether there was allocation hiding; whether the researcher and subjects were blinded; whether the research outcome was blinded; whether there were incomplete data; whether there was selective reporting; and whether there were other biases. All the included literature

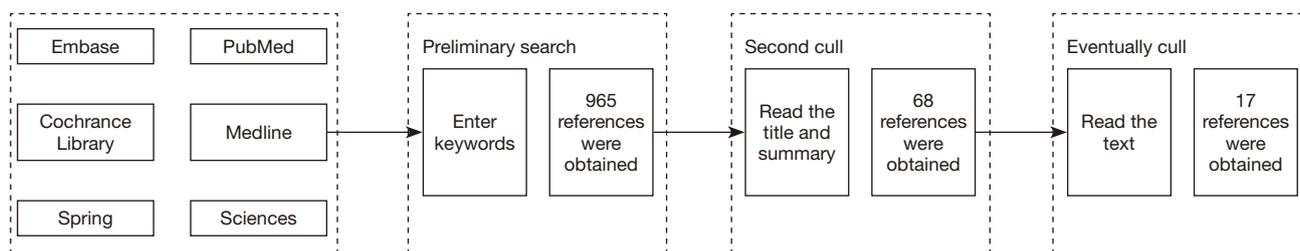


Figure 1 Flow chart of the literature retrieval process.

was evaluated based on the above-mentioned evaluation items to assess the low-risk, unclear-risk, and high-risk bias of each article.

Statistical methods

The data was analyzed according to the Cochrane Handbook 5.0.2 system evaluation manual. The STATA 12.0 software and Review Manager 5.3 software was adopted to organize and realize meta-analysis of the data included in the literature, respectively. The data sorted were all continuous variables, and each effect size was expressed by the mean \pm standard deviation (SD) and the 95% confidence interval (CI). If the measurement unit was not uniform among different samples, the standardized mean difference (SMD) was used. Binary variables were expressed by frequency, and the effect size was calculated by using the changes before and after treatment in the experimental group and the control group, or by using a specific equation (Handbook Chapter 16) using the data before and after treatment directly given in the author's article. When the results of each study could be combined, a meta-analysis was performed. The chi-square test was to detect the heterogeneity of different studies. The effect size deviation caused by heterogeneity rather than sampling error among included studies was represented by I^2 . When $P > 0.05$ or $I^2 < 50\%$, the heterogeneity among the included studies was not statistically significant. When $P < 0.05$ or $I^2 > 50\%$, the heterogeneity among the included studies was considered to be statistically significant, and the source of the heterogeneity was analyzed to eliminate the heterogeneity among the studies as much as possible. If the possible source of heterogeneity could be identified, the fixed-effects model (FEM) was used for meta-analysis. If the source of heterogeneity could not be identified, the random-effects model (REM) was used for meta-analysis. If meta-analysis was not possible (research data less than two),

then descriptive analysis was applied, and the final analysis result was defined with statistical difference at $P < 0.05$.

Results

Results of the literature retrieval

The keywords were entered in 6 English databases for the preliminary search. A total of 1,246 related articles were retrieved, including 277 in PubMed, 198 in Medline, 171 in Web of Sciences, 244 in Embase, 332 in the Cochrane Library, and 301 in the Spring database. A total of 965 articles remained after using Endnote X8 software to eliminate duplicate articles. Following a review of the titles and abstracts, 897 literatures that were obviously not related to the inclusion criteria were excluded. The remaining articles were carefully read and cross-checked, and finally a total of 17 publications were included in this study. There were a total of 1,911 subjects in the 17 articles, of which 1,095 cases were in the experimental group and 816 were in the control group (Figure 1, Table 1).

Basic bias risk assessment of the included literature

The included research literature was assessed for risk of bias according to the standards in the Cochrane 5.0.2 version of the systematic review manual. The 17 selected articles all reported random grouping. Of these, 5 studies only mentioned that patients were randomly grouped but failed to provide details on which random method was used, and therefore, they were judged as "unclear risk". A total of 2 articles were determined to have risk of allocation concealment, and 4 articles had undetermined risk of allocation concealment. It was difficult to assess the risk for 8 articles as no blind test information was provided. A total of 2 articles were "high risk" due to the terms of the blind assessment and 3 articles were assessed as "unclear risk" due to a lack of blind test information. A total of 7 publications

Table 1 Basic information of the included randomized controlled trials involving autoimmune thyroid disease

The first author	Published year	Group	Sample size	Gender	Counter measure	Case type
Liu (8)	2005	Experimental	130	♂28; ♀102	Blood test	GD/HT
		Control	20	♂10; ♀10		
Wang (9)	2013	Experimental	80	♂22; ♀58	Blood test	GD/HT
		Control	40	♂12; ♀28		
Zhu (10)	2012	Experimental	77	–	Selenious yeast	AIT
		Control	57		Placebo	
Zhou (11)	2016	Experimental	80	♂25; ♀55	Selenious yeast + thiamazole	hyperthyroidism
		Control	70	♂25; ♀45	Placebo + thiamazole	
Li (12)	2016	Experimental	50	♂10; ♀40	Conventional treatment + selenious yeast	AIT
		Control	50	♂9; ♀41	Conventional treatment	
Liu (13)	2019	Experimental	51	♂11; ♀40	Selenious yeast + thiamazole	hyperthyroidism
		Control	51	♂12; ♀39	Thiamazole	
Wang (14)	2020	Experimental	53	♂23; ♀30	Conventional treatment + selenious yeast	AITD
		Control	52	♂22; ♀30	Conventional treatment	
Pirola (15)	2016	Experimental	96	♂36; ♀60	SE-MET	AIT
		Control	96	♂33; ♀63	–	
Gärtner (16)	2002	Experimental	37	♀37	Sodium selenite placebo	AIT
		Control	34	♀34		
Pilli (17)	2015	Experimental	47	♂7; ♀40	SE-MET	AIT
		Control	28	♂8; ♀20	Placebo	
Rostami (18)	2020	Experimental	49	–	Blood test	HT
		Control	50			
Winther (19)	2014	Experimental	42	–	Selenious yeast	AIT
		Control	20		Placebo	
Pace (20)	2020	Experimental1	29	♂3; ♀26	Se-meth + Myo-I	HT
		Experimental2	43	♂7; ♀36	Se-meth	
		Control	29	♂5; ♀24	–	
Nordio (21)	2017	Experimental	84	♂9; ♀75	Se	AIT
		Control	84	♂10; ♀74	Placebo	
Turker (22)	2006	Experimental	48	♀48	L-SE-MET	HT
		Control	40	♀40	Placebo	
Claudio (23)	2011	Experimental	54	♂6; ♀48	Sodium selenite	Graves
		Control	50	♂9; ♀41	Placebo	
Huang (24)	2014	Experimental	45	♂14; ♀31	Selenious yeast	Graves
		Control	45	♂15; ♀30	–	

GD, Graves' disease; HT, hyperthyroidism; AIT, autoimmune thyroid; ♂, male; ♀, female.

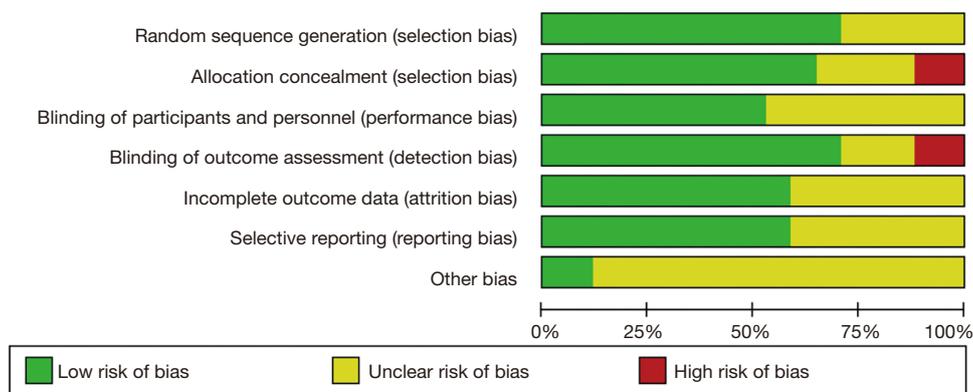


Figure 2 A bar chart showing bias analysis of the included literature.

were judged as “unclear risk” due to unavailable selective report or incomplete data, 15 articles were determined as “unclear risk” as it was difficult to assess if there was any other bias affecting the results. The detailed results of this bias analysis are shown in *Figures 2* and *3*.

Serum levels of TSH

A total of 14 out of the 17 included articles reported changes in TSH levels (9,11-23), and 8 articles could be meta-analyzed (11,13-17,20,21). A total of 851 subjects were included, with 437 in the experimental group and 414 in the control group. The combined effect of Meta-analysis was given in *Figure 4* (MD =0.06; 95% CI: - 0.53-0.66; Z=0.21; P=0.83), which indicated that the selenium combined antithyroid drug treatment group showed no statistical difference in the changes in patients’ TSH levels in contrast to the control group. This suggested that the TSH levels in patients in the selenium combined antithyroid drug experimental group were not statistically different from that in the control group.

Serum levels of FT3

A total of 13 out of the 17 included articles reported changes in FT3 levels (8,9,11-14,17-23). Meta-analysis could be performed on 8 of the articles (11-14,17,18,20,22). There were 659 subjects, including 338 in the experimental group and 321 in the control group. Statistical data showed heterogeneity between the groups ($I^2=92%$, $P<0.00001$), and the REM was used for analysis. The FT3 levels in the experimental group were significantly lower compared

to that observed in the control group (MD =-0.40; 95% CI: -0.70--0.10; Z=2.61; P=0.009), as shown in *Figure 5*. Such results suggested that the combination of selenium and antithyroid drugs in the treatment of AITD greatly improved the levels of FT3 in patients.

Serum levels of FT4

From the 17 included articles, 14 mentioned changes in FT4 levels (8,9,11-15,17-23). Meta-analysis could be performed on 8 articles (11-15,17,20,22). There were 845 subjects, including 427 cases in the experimental group and 418 cases in the placebo group. Heterogeneity was observed between the experimental group and the control group ($I^2=89%$, $P<0.00001$), therefore the REM was applied. A statistical difference was detected in FT4 levels between the two groups (MD =-0.76; 95% CI: -1.58--0.07; Z=1.79; P=0.07), as shown in *Figure 6*. Such results suggested that selenium combined with antithyroid drugs significantly reduced the serum FT4 levels in AITD patients.

Serum levels of TPOAb

Among the 17 included studies, 14 mentioned changes in the TPOAb levels (9-24). Meta-analysis could be performed on 8 articles (11,13-16,21,22,24), involving a total of 896 cases, of which 454 were in the experimental group and 442 were in the control group. The statistics analysis showed heterogeneity between the groups ($I^2=99%$, $P<0.00001$), and the REM was applied. As illustrated in *Figure 7*, the changes in TPOAb levels were significantly different

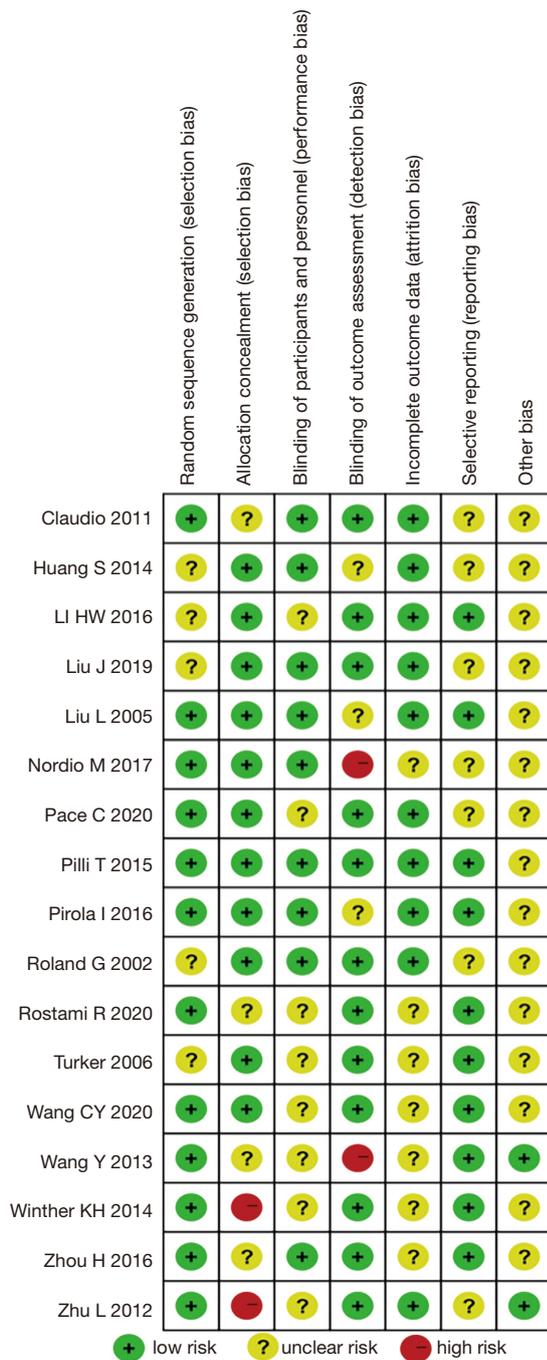


Figure 3 A bias risk evaluation of the included literature.

between patients in the experimental group and patients in the control group (MD = -150.25; 95% CI: -204.06–-96.43; Z=5.47; P<0.00001). This suggested that selenium combined with antithyroid drugs significantly reduced serum TPOAb levels in AITD patients.

Serum levels of TGAb

Among the 17 included publications, 9 mentioned the changes in TPOAb levels (9,13,16-18,20-23). Meta-analysis was performed on 4 articles (13,16,21,22) involving a total of 429 cases, including 220 and 209 cases in the experimental group and the control group, respectively. There was no statistical difference in the serum levels of TGAb in patients in the two groups (MD = -17.19; 95% CI: -254.86–289.25; Z=0.12; P=0.90) (Figure 8).

Analysis of publication bias

Review Manager 5.3 software was used to study the analysis index based on the effect of selenium combined with antithyroid drugs in the treatment of AITD. The data regarding TSH, FT3, TPOAb, and TGAb levels were relatively scattered, and some literature data fell outside the funnel chart (Figure 9). In contrast, data regarding FT4 levels were relatively concentrated with fewer data outside the funnel chart (Figure 9), indicating that the publication bias of the included literature was low.

Discussion

Selenium is an essential trace element for the human body and is widely distributed in thyroid tissue. It is present as a protein in the form of L-selenocysteine. Selenocysteine is encoded by the stop codon UGA and is synthesized into the polypeptide chain to form the secretion-centric protein called selenoprotein (25). Selenoproteins play an important role in the human body and are of great significance in thyroid hormone synthesis, the thyroid antioxidant system, and the immune system. So far, scholars have discovered 25 kinds of selenoproteins, the majority of which are involved in regulating thyroid diseases including iodothyronine deiodinase (ID), glutathione peroxidase (GSH-Px), and thioredoxin reductase (TR). These participate in the synthesis of thyroid hormone, limit its synthesis rate, regulate the proliferation or differentiation of certain cells, promote the synthesis of immunoglobulins, and inhibit the occurrence of immune responses (26,27). AITD is a common endocrine disease with a higher prevalence in females compared to males. It is caused by immune dysfunction in the body whereby T lymphocytes are activated and B lymphocytes are induced to produce a large number of antibodies against the thyroid's own antigens, and this in turn causes thyroid hormone metabolism

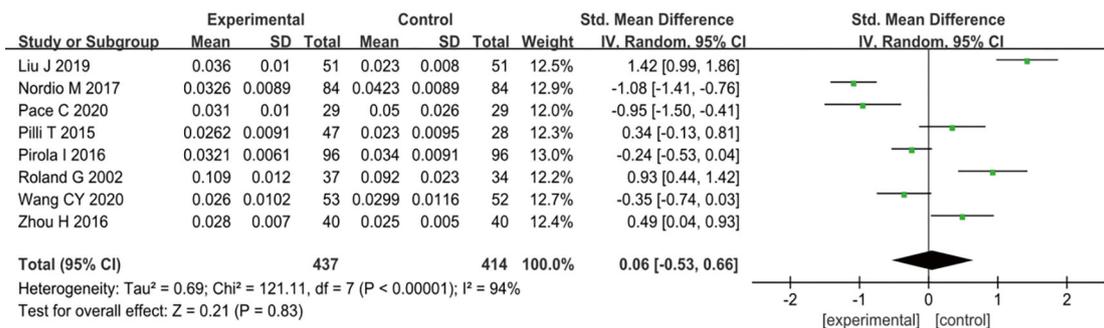


Figure 4 A forest plot comparing the levels of thyroid stimulating hormone in patients treated with selenium and control patients. SD, standard deviation; Std, standard; IV, inverse variance; CI, confidence interval.

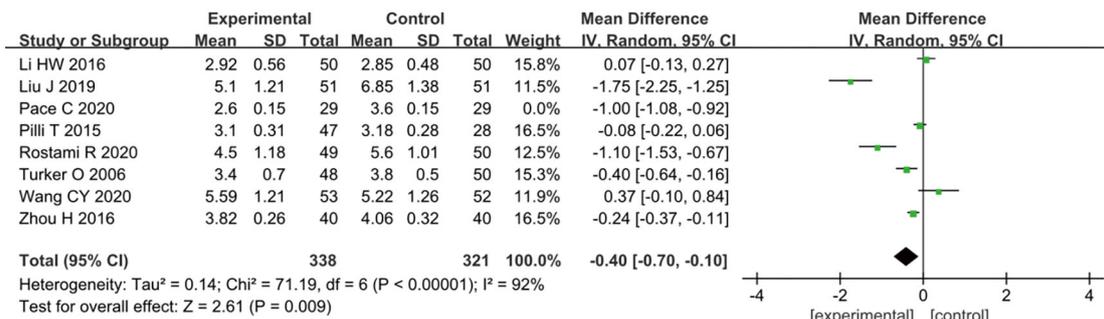


Figure 5 A forest plot showing triiodothyronine levels after treatment of patients with selenium or placebo. SD, standard deviation; IV, inverse variance; CI, confidence interval.

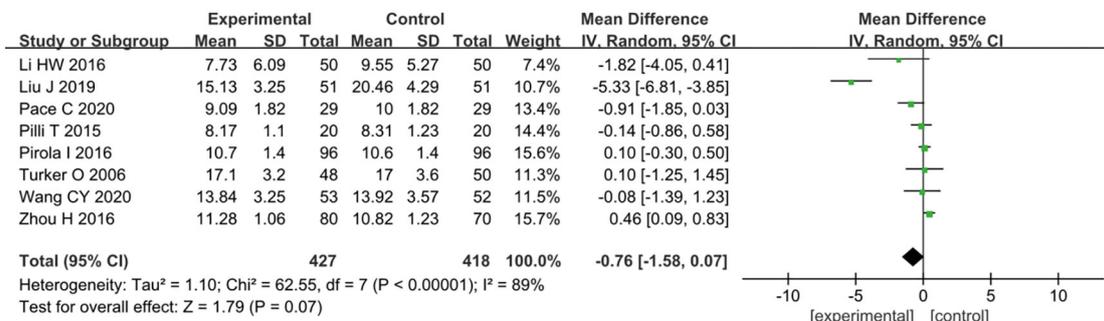


Figure 6 A Forest plot showing thyroxine levels after treatment with selenium or placebo. SD, standard deviation; IV, inverse variance; CI, confidence interval.

disorders and autoimmune thyroid damage. The thyroid is the main organ containing selenium in the human body and selenium plays a vital role in AITD. Selenium participates in the synthesis of thyroid hormones, maintains the integrity of the thyroid under strong oxidative stress, and protects the thyroid tissue (28). To date, a large number of reports have

shown that selenium supplementation may have an effect on thyroid antibodies and affect serum levels of TSH, FT3, FT4, TPOAb, and TGAb in patients with autoimmune thyroid.

In recent years, there have also been some related research on selenium supplementation in the treatment of

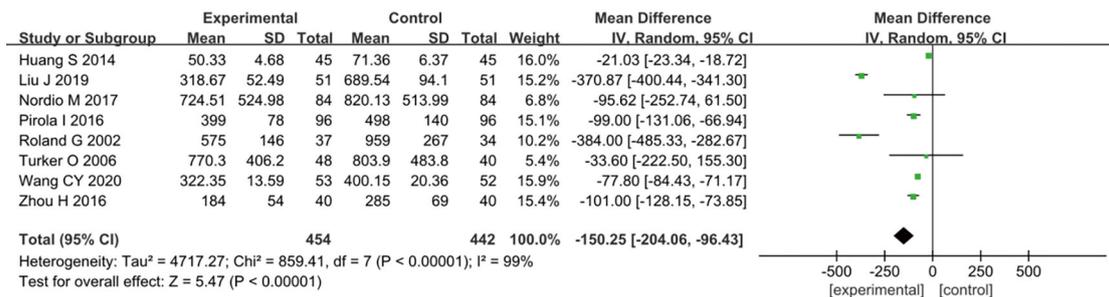


Figure 7 A forest plot showing the serum levels of TPOAb after treatment with selenium or placebo. SD, standard deviation; IV, inverse variance; CI, confidence interval.

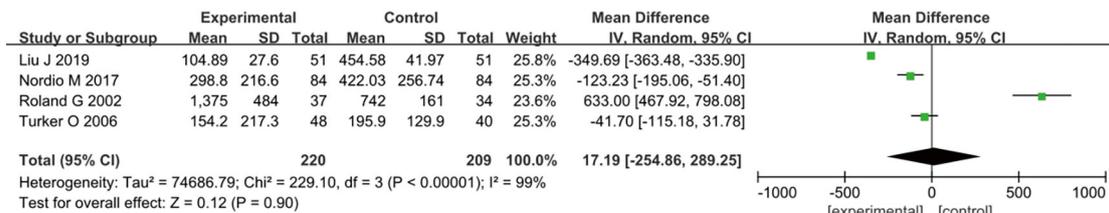


Figure 8 A forest plot showing the levels of anti-thyroglobulin antibody after treatment with selenium or placebo. SD, standard deviation; IV, inverse variance; CI, confidence interval.

thyroid diseases, including a meta-analysis on the clinical effects of selenium supplementation in the treatment of GD (29). The results showed that selenium supplementation could greatly reduce the serum levels of TSH, FT3, FT4, TPOA, and TGAb in patients. Another meta-analysis by Fang *et al.* (30) demonstrated that selenium treatment had no significant effect on serum TSH levels in patients with AITD, but had significant effects on serum levels of FT3, FT4, TPOA, and TGAb. Considering the controversial data in the field, these present investigations aimed to comprehensively analyze the therapeutic effects of selenium supplementation on AITD patients through a meta-analysis of the available literature.

Conclusions

A meta-analysis was conducted to examine the correlation between selenium levels and AITD. The results demonstrated that selenium could visibly reduce the

serum levels of FT3, FT4, and TPOAb in patients with AITD, but no observable effects were detected on the levels of TSH and TGAb. There were some limitations in this study. First, some included publications did not explicitly mention whether the REM applied in the study used allocation concealment and blind testing, and some analysis data were ambiguous. This may have affected the strength of the evidence in this study. Second, many different types of AITD were included in this study, with no specific AITD selected for analysis, and this may have caused the meta-analysis to be insufficiently accurate. There was limited literature examining TGAb levels and only 4 cases were screened. This may explain the differences in the TGAb results observed between this current meta-analysis and previous publications. Therefore, further high-quality and large-sample RCTs should be selected for future meta-analysis to determine the benefits of selenium supplementation in patients with AITD.

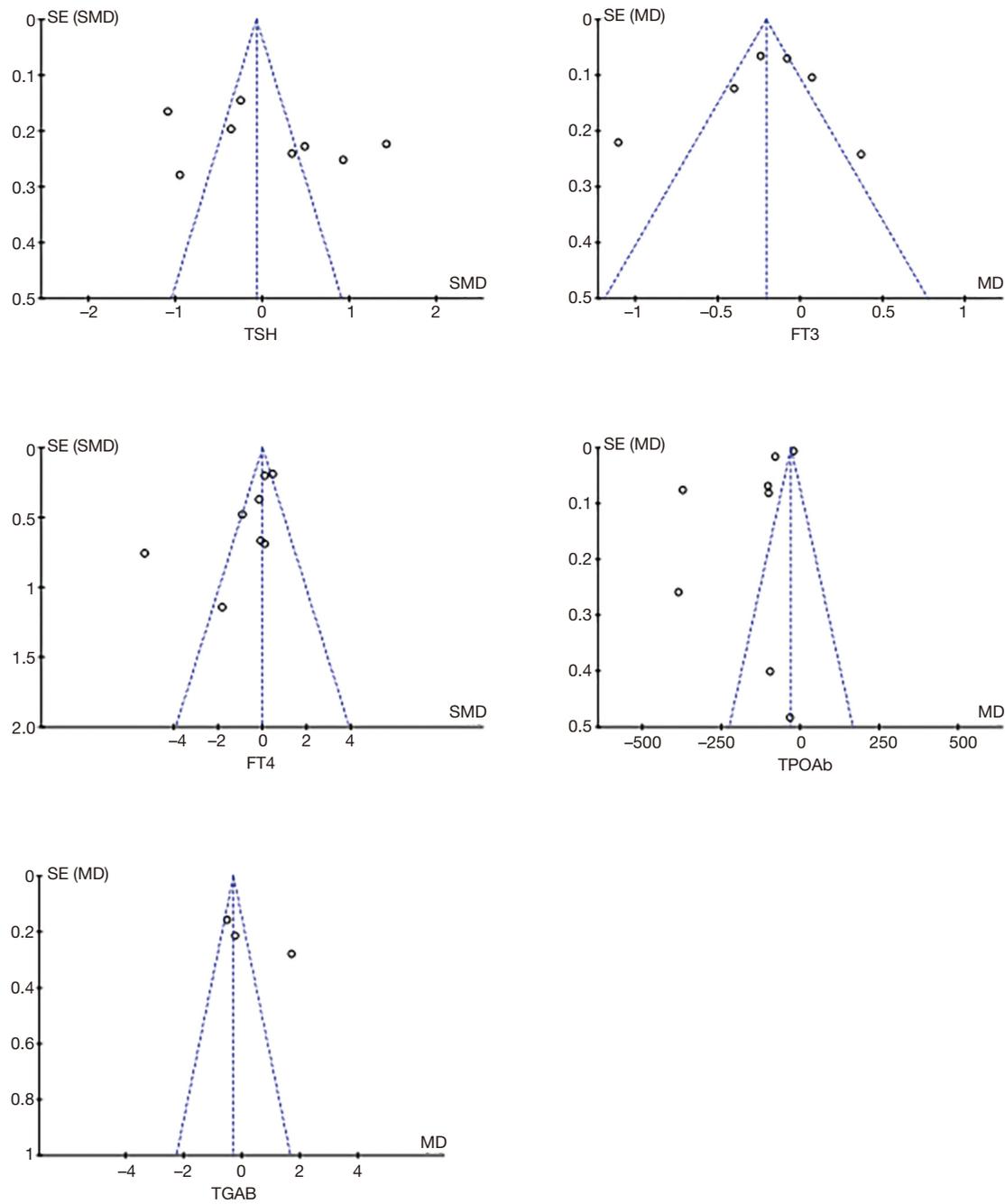


Figure 9 Funnel charts showing the various evaluation indicators.

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-21-449>). 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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