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Review Article

Effects of Antioxidant Supplementation on Graves' Disease: A Meta-Analysis

Qi Song, Xiaoxue Ji, and Ying Xie

Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China

Correspondence should be addressed to Ying Xie; 13013883877@126.com

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Objective. The main objective of this study is to evaluate the clinical efficacy of antithyroid drugs combined with antioxidant supplementation represented by selenium in the treatment of Graves' disease. *Methods*. Relevant randomized controlled trials (RCTs) were searched in PubMed, MEDLINE, Embase, the Cochrane Library databases, and the Chinese Medical Association. The search was conducted from the time of library construction to December 20, 2022. Three writers gradually examined, evaluated, and graded the literature and then used RevMan 5.3 to analyze the data and develop conclusions. *Results*. A total of seven papers were screened according to the search requirements. The results showed that free triiodothyronine (FT3) (WMD = −2.29, 95% CI: −3.55 to −1.02, $P = 0.0004$), free thyroxine (FT4) (WMD = −0.62, 95% CI: −1.05 to −0.18, $P = 0.0005$), thyrotropin receptor antibody (TRAb) (WMD = −1.31, 95% CI: −1.63 to −0.99, $P < 0.00001$), and thyroid peroxidase antibody (TPOAb) (WMD = −9.8, 95% CI: −16.57 to −3.03, $P = 0.005$) in the observation group (selenium supplementation combined with antithyroid drugs) were significantly lower than those in the control group (antithyroid drugs combined with or without placebo). In addition, selenium supplementation can increase serum selenium (WMD = 33.29, 95% CI: 30.7 to 35.87, $P < 0.00001$), selenoprotein levels (WMD = 1.3, 95% CI: 0.8 to 1.8, $P < 0.00001$), and blood lipid levels (WMD = 32.3, 95% CI: 17.87 to 46.74, $P < 0.0001$). It cannot be excluded that the process of selenium supplementation treatment will affect the patient's lipid levels. *Conclusion*. Selenium is a trace mineral that is crucial for human health. In patients with Graves' disease, the use of antithyroid medications along with selenium supplementation can considerably enhance thyroid function. It has the potential to drastically lower TPOAb and TRAb levels as well as FT3 and FT4 levels, which is crucial for the treatment, recovery, and prognosis of hyperthyroid patients. Further research is required to determine whether the impact of antioxidant supplementation on blood lipids will restrict the use of this medication.

1. Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism. It is an autoimmune disease with complex immunopathogenesis, and thyrotropin receptor antibody (TRAb) is the ultimate cause of hyperthyroidism [1]. Three methods have historically been used to treat hyperthyroidism: medication, ^{131}I, and surgery. Patient adherence to therapy is hampered by the disease's high risk of recurrence and lengthy medication regimen. There is no optimum treatment for the autoimmune response of the thyroid gland, although Graves' illness is receiving more and more attention as its prevalence rises year after year. Glucocorticoids are mainly applied to improve the autoimmune response, but their serious adverse effects limit their clinical use [2].

Additionally, research has shown that selenium plays a significant part in the therapy of hyperthyroidism by acting as an antioxidant. In medicine, the disruption of the balance between oxidants and antioxidants in favor of oxidants is called oxidative stress (OS) [3]. Oxidative stress is thought to play an important role in Graves' hyperthyroidism [4–6]. The inflammatory response due to autoimmunity is mainly reflected in the imbalance between the oxidative and antioxidant systems of the body, with increased production of reactive oxygen radicals and cytokines, which in turn drive the development of Graves' disease [7]. The typical hypermetabolic state of

hyperthyroidism leads to the release of large amounts of reactive oxygen species (ROS) from peripheral tissues. In the thyroid, ROS can cause damage to thyroid epithelial cells and expose autoantigens to the immune system, leading to the worsening of autoimmunity. In peripheral tissues where thyroid hormones act, ROS can cause tissue damage, which leads to the clinical manifestations of hyperthyroidism [8].

Selenium occupies a unique place in the immune system. It efficiently enhances the body's humoral and cellular immune functions. When lacking, both cellular and humoral immune functions may be compromised. In addition, selenium plays an important role in the synthesis, activation, and metabolic processes of thyroid hormones and the immune system [9, 10]. In animals and humans, there is a Se-dependent enzyme called glutathione peroxidase [11, 12], which is an important peroxidolytic enzyme widely present in the organism and can be used as an indicator to assess the body's resistance to peroxidation. Moreover, as a component of selenoprotein, selenium has structural and enzymatic functions. In the context of the latter, it can act as an antioxidant and catalyst for the production of active thyroid hormones [13].

At present, there are different reports on the efficacy of selenium supplementation in the treatment of GD, and its effectiveness needs to be further clarified. At the same time, there is a lot of disagreement regarding selenium's impact on blood lipids. To further assess the impact of selenium supplementation on individuals, this study aimed to compile randomized controlled trials (RCTs) on this research issue for a systematic review and meta-analysis. The pretopic of the article included in this paper was a randomized controlled trial on Graves' disease. The topic was to compare the efficacy of antithyroid drugs alone and antithyroid drugs combined with antioxidants for Graves' disease. Outcome indicators included thyroid function, lipids, serum selenium, and serum selenoprotein. Thyroid function included free triiodothyronine (FT3), free thyroxine (FT4), thyrotropin receptor antibodies (TRAb), and thyroid peroxidase antibodies (TPOAb). Articles that did not meet the inclusion criteria or did not report the outcome indicators for this study were excluded.

2. Methods

2.1. Search Strategy. A number of database resources, including MEDLIN, Embase, the Cochrane Library databases, Pubmed, and the Chinese Medical Association were searched from the inception of each resource to December 2022, using the strategy of subject term joint free word search (Supplementary Description) (available here*). Two review authors (Song and Ji) independently reviewed the titles and abstracts of the search records to identify articles that met the inclusion criteria. When there is disagreement, it will be determined through communication and consultation with the third author.*

2.2. Selection Criteria. The included studies must meet the following criteria: (1) study type: the type of included articles must be RCT studies; (2) study population: patients with Graves' disease who meet the diagnostic criteria of the 2016 American Thyroid Association (ATA) guidelines; (3) interventions: the experimental group is antithyroid medication combined with selenium supplementation; the control group is antithyroid medication combined with blank control or placebo use. The duration of treatment was not limited. (4) Outcome indicators: must include thyroid function indicators, such as FT3, FT4, TPOAb, and TRAb. Exclusion criteria were defined as follows: (1) nonrandomized controlled trials, reviews, etc.; (2) animal experiments, non-Graves' patients (mainly including Graves' ophthalmopathy, autoimmune thyroiditis patients, or patients with other autoimmune diseases); (3) the treatment plan does not conform to the article in this study, such as patients treated with ^{131}I or surgery; (4) studies that do not include the outcome indicators that must be included in this paper; (5) studies in which the form of outcome data is not available or the full text is not available; and (6) repeated published research or secondary analysis.

2.3. Data Extraction. Two researchers independently screened, extracted, and cross-checked the literature according to the inclusion and exclusion criteria. The articles that met the requirements were pooled after completing the screening. If there is any disagreement, it will be resolved through discussion with the third researcher. The data we extracted included the first author, the year of publication, the number of subjects in the two groups in the article, the sex ratio, the age range, the outcome measures, the duration of follow-up, the dose used, and the observed results.

2.4. Quality Assessment. Two authors independently assessed the quality of the included articles according to the Cochrane Handbook for Systematic Reviews of Interventions. Divergence will be communicated with the third author, and the final results will be plotted as a graph. The details of quality evaluation include (1) random sequence generation; (2) allocation concealment; (3) the blinding of participants and personnel; (4) the blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias.

2.5. Statistical Analysis. Each included outcome was estimated by calculating the change from baseline to outcome by means ± standard deviation (M ± SD) as provided in the article. If not explicitly provided, it was calculated using other available data. For time points where data on multiple outcome indicators existed, we took the data from the last time point for statistical analysis. A meta-analysis was performed using Review 5.3, and heterogeneity between studies was assessed using the χ^2 test and I^2. The fixed-effect model was used if $I^2 < 50\%$ and the random-effect model was used if $I^2 \geq 50\%$. The fixed-effect model was used when the number of studies included in the meta-analysis was less than 5 [14]. Also, when significant clinical heterogeneity was observed, subgroup analysis was performed to find possible causes. Publication bias was detected by the funnel plot.

3. Results

3.1. Study Selection. Based on the search strategy, we searched the database for 232 records and found no additional records through other sources. After removing 45 duplicate records, we initially screened 187 articles. Subsequently, 134 articles were excluded by reading the titles and abstracts. We read the full text of the remaining 53 studies and excluded 46 studies due to article type and data availability. Finally, 7 articles met the criteria and were included in our meta-analysis. The flow chart of the research screening process is shown in Figure 1.

3.2. Study Characteristics. A total of 209 patients were included in seven studies [15–21]. The basic characteristics of the included studies are summarized in Table 1. Of all seven studies, seven included FT3 and FT4, five focused on TRAb indicators, and four included TPOAb antibody indicators; three articles included serum selenium levels; two articles compared serum selenoprotein levels; and two included lipid levels.

3.3. Quality Assessment. Based on the limited information provided in the articles, we evaluated the quality bias of the articles as follows (Figure 2). Among the seven included articles, three explicitly specified the randomization method and two explicitly assigned the hidden method; for blinding, four articles explicitly used blinding; all seven outcomes data reporting was complete; five articles did not selectively report risk; one did not introduce bias from other sources; and the risk profile of the remaining articles could not be judged.

4. Results Analysis

4.1. Improvement in the FT3 Level (Figure 3(a)). FT3 levels were significantly lower in the observation group compared with the control group, and the difference was statistically significant (WMD = −2.29, 95% CI: −3.55 to −1.02, $P = 0.0004$; P for heterogeneity = 0.01, $I^2 = 64\%$). Further subgroup analysis by the duration of treatment revealed differences in subgroup heterogeneity. The heterogeneity was significantly lower for treatment duration ≤3 months ($I^2 = 0\%$, $P = 0.96$), and the difference in FT3 levels within the group was statistically significant (WMD = −2.41, 95% CI: −3.34 to −1.48, $P < 0.00001$); the heterogeneity was higher for treatment duration >3 months ($I^2 = 82\%$, $P = 0.0010$), and the difference in FT3 levels within the group was statistically significant (WMD = −2.64, 95% CI: −3.16 to −2.11, $P < 0.00001$). The results of the subgroup analysis suggest that the degree of control of the disease with increasing duration of treatment may be responsible for the heterogeneity. The results of the overall analysis showed that selenium combined with antithyroid drug treatment improved FT3 levels better than the control group in patients with Graves' disease.

4.2. Improvement in the FT4 Level (Figure 3(b)). The results showed that FT4 levels were significantly lower in the observation group compared with the control group, with statistically significant differences (WMD = −0.62, 95% CI: −1.05 to −0.18, $P = 0.0005$; P for heterogeneity <0.00001, $I^2 = 89\%$). Similarly, subgroup analysis by treatment duration showed differences in within-group heterogeneity: heterogeneity was significantly lower for treatment duration ≤3 months ($I^2 = 24\%$, $P = 0.27$), and the difference in FT4 levels within this group was statistically significant (SMD = −1.18, 95% CI: −1.54 to −0.82, $P < 0.00001$); heterogeneity was higher for treatment duration >3 months ($I^2 = 93\%$, $P < 0.00001$) and a statistically significant difference in FT4 levels (SMD = −0.59, 95% CI: −0.62 to −0.57, $P < 0.00001$). The results of the subgroup analysis were similar to the appeal, and the duration of treatment may be the main reason for the heterogeneity; the overall analysis showed that selenium combined with antithyroid drug treatment could better reduce FT4 levels in patients with Graves' disease.

4.3. Improvement in TPOAb (Figures 3(c)) and TRAb (Figure 3(d)) Levels. Further analysis is needed for selenium effects on TPOAb and TRAb levels. The results showed that TPOAb (WMD = −9.8, 95% CI: −16.57 to −3.03, $P = 0.005$; P for heterogeneity = 0.21; $I^2 = 34\%$) and TRAb levels (WMD = −1.31, 95% CI: −1.63 ~ −0.99, $P < 0.00001$; P for heterogeneity = 0.12; $I^2 = 45\%$) were significantly lower than the control group. The difference was statistically significant. The results indicated that the use of selenium in the experimental group could significantly reduce TPOAb and TRAb levels and improve the clinical prognosis of patients with Graves' disease.

Further analysis of the effects on serum selenium (Figure 4(a)). The result showed that the serum selenium levels in the combined selenium treatment group were significantly higher than those in the control group, with statistically significant differences (WMD = 33.29, 95% CI: 30.7 to 35.87, $P < 0.00001$; P for heterogeneity <0.00001, $I^2 = 96\%$) similar to the serum selenoprotein (Figure 4(b)) levels (WMD = 1.3, 95% CI: 0.8 to 1.8, $P < 0.00001$; P for heterogeneity = 0.17; $I^2 = 48\%$). The results showed that the treatment of selenium combined with an antithyroid drug significantly increased serum selenium and selenoprotein levels in patients with Graves' disease. Regarding the effect of selenium supplements on lipid levels in patients, the results (Figure 4(c)) showed that selenium supplementation affected lipid levels and led to further elevated lipid levels (WMD = 32.3 95% CI 17.87 to 46.74, $P < 0.0001$; P for heterogeneity = 0.05, $I^2 = 73\%$), the outcome was statistically significant. However, this conclusion has certain limitations due to the limited number of included articles.

5. Publication Bias

The results of FT3 were used to make funnel plots for evaluation (Figure 5). Two studies were outside the 95% CI, and many studies were concentrated at the top of the funnel plots, which were approximately symmetric.

6. Discussion

The pathophysiology of Graves' disease is still not completely understood. According to the currently prevalent idea, the condition is defined by hereditary predisposition and causes

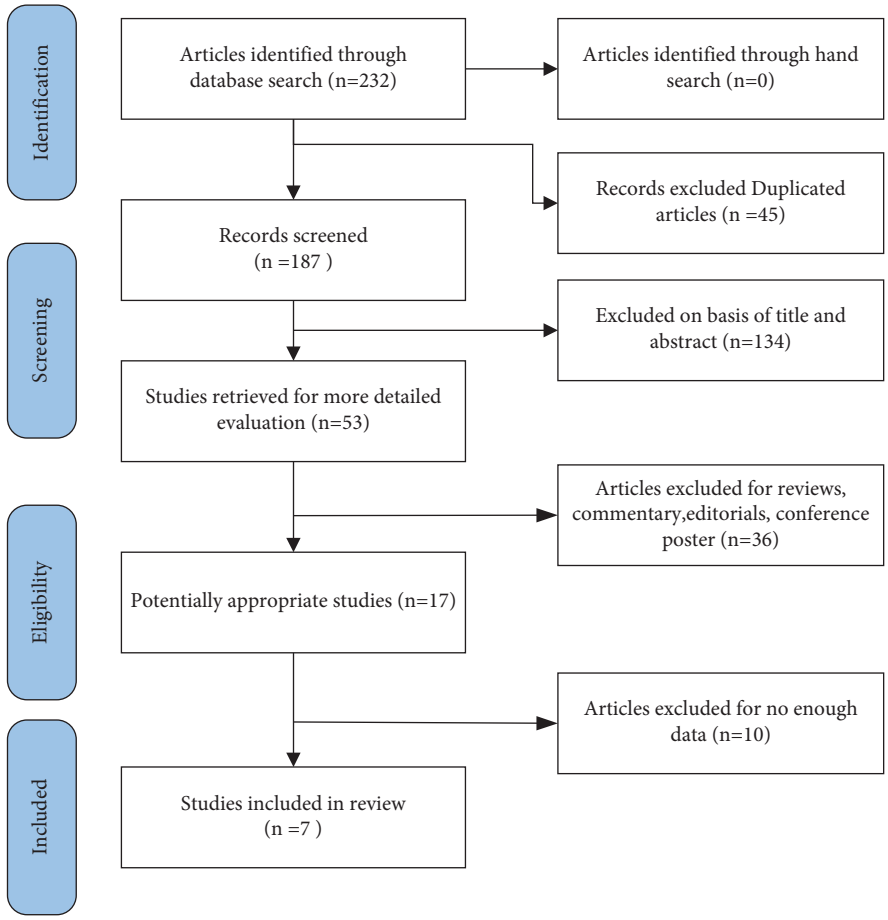

Figure 1: Flow diagram of search and selection processes.

an immunological malfunction in vivo when infection, mental trauma, and other variables interact. To keep the thyroid gland functioning normally, it has an associated antioxidant system and oxidative metabolism. Selenium is an essential trace mineral and nutrient for the synthesis of selenocysteine, which is synthesized into many selenoproteins. So far, 25 human genes encoding selenoproteins are known, most of which are enzymes [22]. The human thyroid contains a large amount of selenium because it produces H_2O_2 for the oxidation of thyroid hormone synthesis and protects itself from oxidative damage through the expression of selenium peroxidase [23]. In the thyroid hormone synthesis step, iodine oxidation is carried out by a special enzyme, thyroid peroxidase, which utilizes superoxide of hydrogen produced physiologically by thyroid tissue. On the one hand, the synthesis of thyroid hormones requires the formation of hydrogen peroxide, which is a highly reactive oxidant. Hydrogen peroxide and iodine oxide are used in the peroxidation reaction, which is catalyzed by thyroid peroxidase. The thyroid gland has an efficient antioxidant mechanism that shields thyroid cells from reactive oxygen species. Peroxiredoxin, glutathione peroxidase, thioredoxin, and catalase are all involved in this antioxidant system. Selenium is located in the catalytic site of GPX and is important for the antioxidant effect of the enzyme, which protects the body from oxidative stress by reducing H_2O_2 to H_2O [24]. Graves' disease is characterized by increased oxidative stress. The effect of H_2 O_2 on normal thyroid follicular epithelial cells is to promote the synthesis of thyroid hormone. However, the pathological process occurs when the concentration of thyroglobulin is greater than required by the iodination process. The continuous accumulation of H_2O_2, a free radical generator, in thyroid follicular cells leads to additional cell membrane destruction and a cascade of harm. Thyroid tissue should contain a relatively high concentration of selenium as the basic component of glutathione peroxidase [25, 26]. This enzyme is involved in cell defense because it reduces the concentration of toxic free radicals and hydroperoxides in tissues.

It is critical to track changes in pathogenic antibodies as well as thyroid hormone levels while treating hyperthyroidism. The return of thyroid function is typically quicker with medication than the serum TRAb. At the end of the course of drug treatment, if the TRAb value exceeds the normal value, it indicates the recurrence of hyperthyroidism [27]. Therefore, the measurement of serum TRAb levels and positivity in patients with Graves' disease is clinically important in determining efficacy [28]. TRAb is the pathogenic antibody of this disease. In patients with hyperthyroidism, paying attention to the change in TRAb titer is very important. In this paper, it was found that selenium combined with antithyroid drugs had a significant effect on the

Table 1: Characteristics of randomized controlled trials included in this meta-analysis.

Studies	Experimental group			Placebo group			Main outcome measures	Duration (m)	Dose of MMI (mg)	Dose of Se (μg)
	M : WM	Age	Plan A	M : WM	Age	Plan B				
Vrca V. B. [20]	23 : 04	44 ± 12	MMI + Se	23 : 01	41 ± 14	MMI	FT3. FT4. TSH. SOD. TC. TG. LDL. Selenium	2	40–12	60
Xu B. et al. [15]	14 : 30	38.89 ± 11.59	MMI + Se	19 : 31	40.2 ± 12.63	MMI	FT3. FT4. TSH A-TG. A-TPO. TRAb	6	30	300
Kahaly G. J. et al. [16]	7 : 28	44.5 ± 13.8	MMI + Se	9 : 26	44.5 ± 13.4	Placebo + MMI	FT3. FT4. TSH. TPO-Ab. TgAb. TRAb. SePP. Selenium	9	10	300
Leo M. et al. [19]	2 : 13	43 ± 11	MMI + Se	1 : 14	38 ± 11	MMI	Serum selenium. FT3. FT4. TC	3	5–20	200
Wang L. et al. [18]	5 : 16	37.4 ± 15.0	MMI + Se	2 : 18	38.9 ± 14.3	MMI	FT4. FT3. TSH. TRAb	12–26	17.5–18.5	200
Calissendorff J. et al. [17]	4 : 13	*N*	MMI + Se	3 : 16	*N*	Placebo + MMI	FT3. FT4. TSH. TPO-Ab TRAb. SePP	9	30	200
Li S. et al. [21]	43 : 22	45.16 ± 10.43	MMI + Se	41 : 24	45.69 ± 10.28	MMI	FT3. FT4. TSH. TPOAb. TGAb TRAb	3	20–30	100

MMI, methimazole; Se, selenium; M (Men); WM, (women); FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody; TGAb, antithyroglobulin antibodies; TRAb, thyrotropin receptor antibody; TC, total cholesterol; TG, Triglycerides; LDL, low-density lipoprotein; SePP, selenoprotein; SOD, superoxide dismutase.

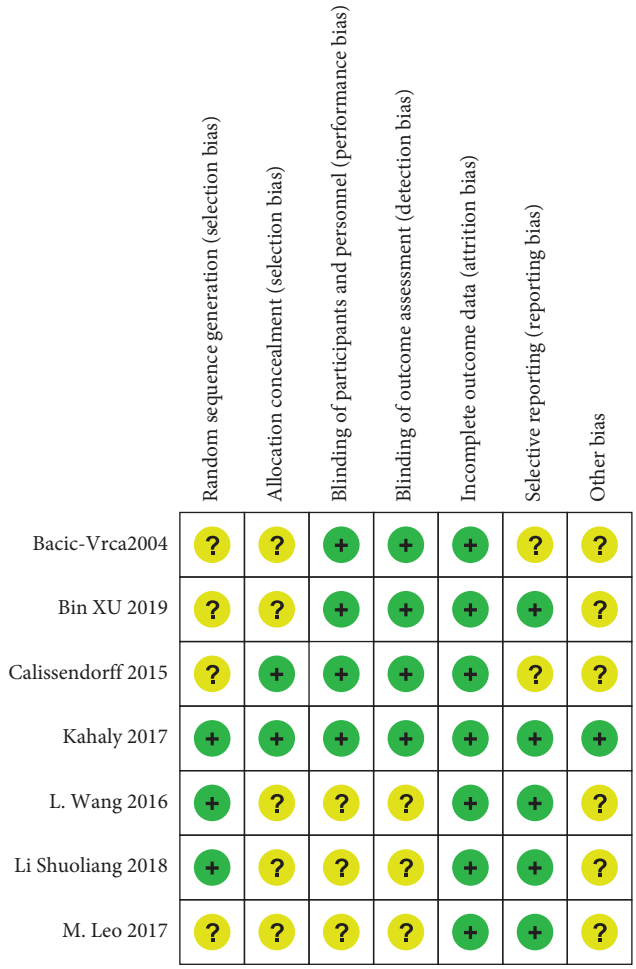

Figure 2: Risk of bias summary.

decrease of antibody titer compared with antithyroid drugs alone.

TPO is very common in autoimmune thyroid and plays an important role in the occurrence and development of many diseases [29]. It destroys thyroid cells through complement-mediated cytotoxicity, which is a sign of autoimmune damage. The increase in antibody levels can be used as one of the indicators of the severity and prognosis of hyperthyroidism. Abnormally increased serum levels of antibodies not only trigger the development of autoimmune inflammation but also give a chronic character to autoimmune thyroid disease (AITD) with hyperthyroidism and correlate with the progression of chronic prolonged inflammatory lesions. When TPO is inactivated, the body is stimulated to produce TPOAb, which can directly damage thyroid cells and cause autoimmune thyroid diseases [30, 31]. TPO is a potential autoantigen. Elevated levels of TPOAb occur in 90% of Hashimoto thyroiditis (HT) cases and 70% of GD [32].

In addition, some studies have shown that antioxidant therapy may improve some clinical manifestations of hyperthyroidism without changing serum thyroid hormone concentration [33]. Regarding the effect on blood lipids, the results of the current study are divergent. Several studies have found that serum selenium is related to the increase of TC (total cholesterol) level [34–37] and TG (triglycerides) level [35–38]. In addition, some studies found that serum selenium was associated with the decrease of TC and TG levels [39], but there was also a report that there was no statistical correlation between selenium and TG [34]. Other studies have shown that the relationship between selenium and blood lipids is dose-dependent, and high normal levels of selenium may increase the risk of diabetes [40]. Of course, these studies include racial differences as well as regional differences. Selenoprotein P (SePP) is the most abundant serum selenoprotein and is produced by the brain and testes via the apolipoprotein E receptor [41]. Some experiments have shown the regulatory role of selenium in lipoprotein biosynthesis [42]. The decreased lipid levels in patients supplemented with selenium maybe possibly explaining this.

There are some limitations in this paper: (1) The duration of hyperthyroidism is not taken into account, and the influence of the length of the course on the therapeutic effect is ignored; (2) Effects of different ATD and Se dosages and treatment times on the outcome; (3) The included articles partly did not describe in detail the specific randomization grouping method, the setting of blinding, selectivity bias, and publication bias, which to some extent limits the

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Bacic-Vrca2004	-18.8	28.89	27	-16.7	17.67	28	1.0	-2.10 [-14.81, 10.61]
Bin XU 2019	-22.64	10.35	44	-15.03	12.78	50	6.0	-7.61 [-12.29, 2.93]
Calissendorff 2015	-21.84	7.78	19	-18.02	8.7	19	5.0	-3.82 [-9.07, 1.43]
Kahaly 2017	-4.2	3.8	35	-5.2	5.11	35	17.4	1.00 [-1.11, 3.11]
L. Wang 2016	-8.2	1.25	21	-5.4	0.25	20	31.8	-2.80 [-3.35, -2.25]
Li Shuoliang 2018	-15.23	2.94	65	-12.78	2.74	65	28.2	-2.45 [-3.43, -1.47]
M. Leo 2017	-6.8	4.67	15	-4.8	4.26	15	10.7	-2.00 [-5.20, 1.20]
Total (95% CI)			*226*			*232*	*100.0*	*-2.29 [-3.55, -1.02]*

Heterogeneity: tau²= 1.23, chi²= 16.54, df = 6 (P = 0.01); I^2 = 64%
Test for overall effect: Z = 3.55 (P = 0.0004)

Mean Difference IV, Random, 95% CI

-20 -10 0 10 20

Favours (experimental) Favours (control)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
9.1.1 ≤ 3M								
Bacic-Vrca2004	-18.8	28.89	27	-16.7	17.67	28	0.1	-2.10 [-14.81, 10.61]
Li Shuoliang 2018	-15.23	2.94	65	-12.78	2.74	65	21.8	-2.45 [-3.43, -1.47]
M. Leo 2017	-6.8	4.67	15	-4.8	4.26	15	2.0	-2.00 [-5.20, 1.20]
Subtotal (95% CI)			107			108	23.9	-2.41 [-3.34, -1.48]
Heterogeneity: chi²= 0.07, df = 2 (P = 0.96); I^2 = 0%								
Test for overall effect: Z = 5.07 (P < 0.00001)								
9.1.2 > 3M								
Bin XU 2019	-22.64	10.35	44	-15.03	12.78	50	0.9	-7.61 [-12.29, -2.93]
Calissendorff 2015	-21.84	7.78	19	-18.02	8.7	19	0.8	-3.82 [-9.07, 1.43]
Kahaly 2017	-4.2	3.8	35	-5.2	5.11	35	4.7	1.00 [-1.11, 3.11]
L. Wang 2016	-8.2	1.25	21	-5.4	0.25	20	69.7	-2.80 [-3.35, -2.25]
Subtotal (95% CI)			119			124	76.1	-2.64 [-3.16, -2.11]
Heterogeneity: chi²= 16.29, df = 3 (P = 0.0010); I^2 = 82%								
Test for overall effect: Z = 9.89 (P < 0.00001)								
Total (95% CI)			*226*			*232*	*100.0*	*-2.58 [-3.04, -2.13]*

Heterogeneity: chi²= 16.54, df = 6 (P = 0.01); I^2 = 64%
Test for overall effect: Z = 11.11 (P < 0.00001)
Test for subgroup differences: chi²= 0.17, df = 1 (P=0.68); I^2 = 0%

Mean Difference IV, Fixed, 95% CI

-10 -5 0 5 10

Favours (experimental) Favours (control)

(a)

Figure 3: Continued.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Bacic-Vrca2004	-3.48	3.42	29	-2.6	2.74	28	5.4	-0.88 [-2.49, 0.73]
Bin XU 2019	-4.79	2.12	50	-3.85	1.94	50	12.2	-0.94 [-1.74, -0.14]
Calissendorff 2015	-2.53	1.1	19	-2.33	1.65	19	11.0	-0.20 [-1.09, 0.69]
Kahaly 2017	-0.7	0.53	35	-0.9	0.53	35	19.5	0.20 [-0.05, 0.45]
L. Wang 2016	-1.23	0.04	20	-0.63	0.04	21	20.8	-0.60 [-0.62, -0.58]
Li Shuoliang 2018	-6.61	1.34	65	-5.21	1.28	65	17.0	-1.40 [-1.85, -0.95]
M. Leo 2017	-2.28	0.92	15	-1.52	0.9	15	14.1	-0.76 [-1.41, -0.11]
Total (95% CI)			*233*			*233*	*100.0*	*-0.62 [-1.05, -0.18]*

Heterogeneity: tau²= 0.23, chi²= 53.64, df = 6 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 2.78$ ($P = 0.005$)

Mean Difference IV, Random, 95% CI

-2 -1 0 1 2
Favours (experimental) Favours (control)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
10.1.1 ≤ 3M								
Bacic-Vrca2004	-3.48	3.42	29	-2.6	2.74	28	0.0	-0.88 [-2.49, 0.73]
Li Shuoliang 2018	-6.61	1.34	65	-5.21	1.28	65	0.3	-1.40 [-1.85, -0.95]
M. Leo 2017	-2.28	0.92	15	-1.52	0.9	15	0.1	-0.76 [-1.41, -0.11]
Subtotal (95% CI)			*109*			*108*	*0.5*	*-1.18 [-1.54, -0.82]*
Heterogeneity: chi²= 2.65, df = 2 ($P = 0.27$); $I^2 = 24\%$								
Test for overall effect: $Z = 6.39$ ($P < 0.00001$)								
10.1.2 > 3M								
Bin XU 2019	-4.79	2.12	50	-3.85	1.94	50	0.1	-0.94 [-1.74, -0.14]
Calissendorff 2015	-2.53	1.1	19	-2.33	1.65	19	0.1	-0.20 [-1.09, 0.69]
Kahaly 2017	-0.7	0.53	35	-0.9	0.53	35	1.0	0.20 [-0.05, 0.45]
L. Wang 2016	-1.23	0.04	20	-0.63	0.04	21	98.4	-0.60 [-0.62, -0.58]
Subtotal (95% CI)			*124*			*125*	*99.5*	*-0.59 [-0.62, -0.57]*
Heterogeneity: chi²= 40.96, df = 3 ($P < 0.00001$); $I^2 = 93\%$								
Test for overall effect: $Z = 47.66$ ($P < 0.00001$)								
Total (95% CI)			*233*			*233*	*100.0*	*-0.59 [-0.62, -0.57]*
Heterogeneity: chi²= 53.64, df = 6 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: $Z = 47.99$ ($P < 0.00001$)								
Test for subgroup differences: chi²= 10.03, df = 1 ($P = 0.002$); $I^2 = 90.0\%$								

Mean Difference IV, Fixed, 95% CI

-2 -1 0 1 2
Favours (experimental) Favours (control)

(b)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Bin XU 2019	-226.14	27.41	50	-224.93	36.83	50	28.3	-1.21 [-13.94, 11.52]
Calissendorff 2015	-222.25	298.5	19	-457	811.4	19	0.0	234.75 [-154.00, 623.50]
Kahaly 2017	-123.93	513.27	35	-208.47	568.45	35	0.1	84.54 [-169.19, 338.27]
Li Shuoliang 2018	-36.8	23.67	65	-23.4	22.87	65	71.6	-13.40 [-21.40, -5.40]
Total (95% CI)			*169*			*169*	*100.0*	*-9.80 [-16.57, -3.03]*
Heterogeneity: chi²= 4.58, df = 3 ($P = 0.21$); $I^2 = 34\%$								
Test for overall effect: $Z = 2.84$ ($P = 0.005$)								

Mean Difference IV, Fixed, 95% CI

-500 -250 0 250 500
Favours (experimental) Favours (control)

(c)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Bin XU 2019	-16.76	11.86	50	-15.74	10.4	50	0.5	-1.02 [-5.39, 3.35]
Calissendorff 2015	-8.53	6.47	19	-1.88	9.7	19	0.4	-6.65 [-11.89, -1.41]
Kahaly 2017	-3	9.26	35	-1.88	9.71	35	0.5	-1.12 [-5.57, 3.33]
L. Wang 2016	-8.33	0.7	21	-7.22	0.52	20	70.8	-1.11 [-1.49, -0.73]
Li Shuoliang 2018	-4.46	1.17	38	-2.7	1.27	28	27.9	-1.76 [-2.36, -1.16]
Total (95% CI)			*163*			*152*	*100.0*	*-1.31 [-1.63, -0.99]*
Heterogeneity: chi²= 7.26, df = 4 ($P = 0.12$); $I^2 = 45\%$								
Test for overall effect: $Z = 8.12$ ($P < 0.00001$)								

Mean Difference IV, Fixed, 95% CI

-10 -5 0 5 10
Favours (experimental) Favours (control)

(d)

Figure 3: Forest plot of selenium supplementation's effects on thyroid hormones and antibody level. CI: confidence interval; SMD: standard mean difference. (a) FT3. (b) FT4. (c) TPOAb. (d) TRAb.

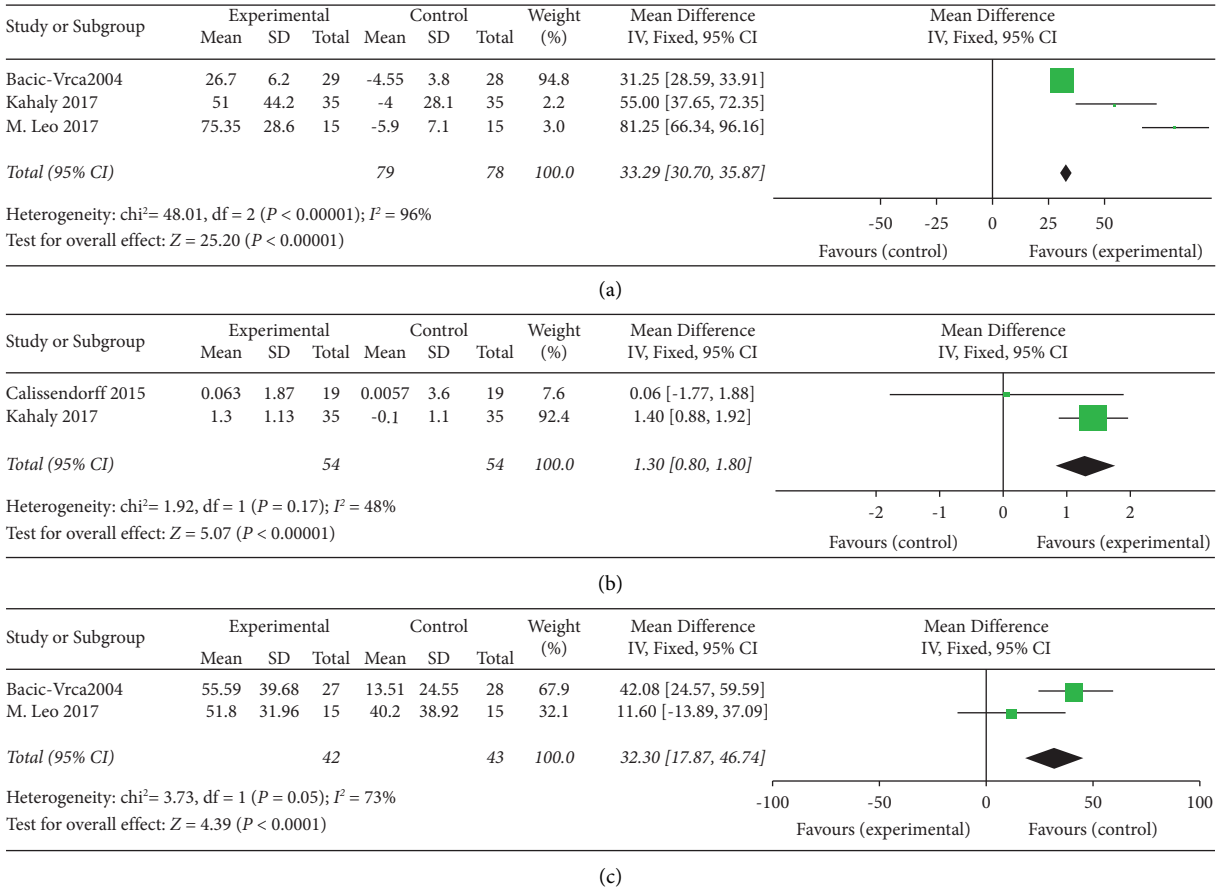

Figure 4: Forest plot of selenium supplementation effects on selenium and selenoprotein levels and blood lipids. (a) Selenium, (b) selenoprotein, and (c) blood lipids.

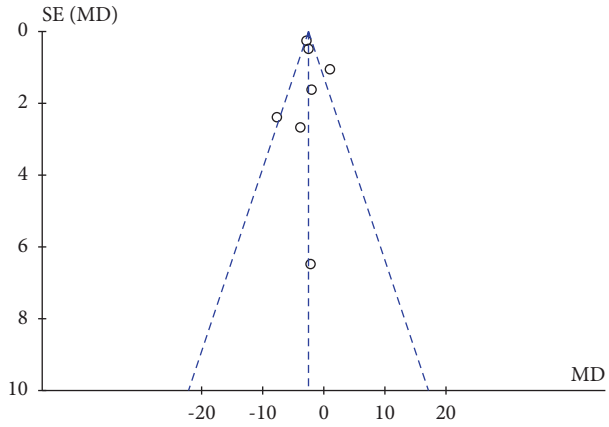

Figure 5: Funnel plot of FT3.

reliability of this article; and (4) The number of articles included is small, and the interpretation of the influence significance has certain limitations. Therefore, more high-quality, large-sample, long-term studies are needed to support the effectiveness of selenium supplements in adjuvant therapy for Graves' disease.

7. Conclusion

This study demonstrated that antithyroid medications combined with selenium supplementation can significantly lower the levels of FT3 and FT4 in Graves' disease and also contribute to the reduction of related antibody levels (TRAb

and TPOAb titers). In addition, it can increase serum selenium and selenoprotein levels. However, whether the effect on lipid levels will limit this drug's use needs to be further explored.

Data Availability

The data used in this study are made available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Qi Song conceived and designed the study. Qi Song and Xiaoxue Ji searched the studies and extracted and analyzed the data. Qi Song wrote the manuscript. Ying Xie directed the writing and revised the manuscript. All authors read and approved the final manuscript.

Supplementary Materials

English database retrieval strategy: (1) exp graves disease/, (2) (Disease, graves or basedow disease or disease, basedow, hyperthyroidism, autoimmune). ti, ab, (3) 1 or 2, (4). exp selenium/, (5) (novamed selen or selenium-80 or selenium 80 or radioactive selenium). ti, ab, (6). 4 or 5, (7) exp randomized controlled trial/, (8) (randomized or controlled trial or randomized or placebo random or randomized). ti, ab, kw, (9). 7 or 8, (10) 3 and 6 and 9.*Chinese database retrieval strategy*: (keywords = hyperthyroidism ∗ graves disease ∗ basedow disease) and (keywords = selenium ∗ Se). (*Supplementary Materials*)

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