

ORIGINAL ARTICLE

Effects of vitamin D treatment on thyroid function and autoimmunity markers in patients with Hashimoto's thyroiditis—A meta-analysis of randomized controlled trials

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Abstract

Introduction: Recent evidence suggested that vitamin D deficiency was associated with Hashimoto's thyroiditis (HT) pathogenesis and thyroid hypofunction. This study aimed to investigate whether vitamin D supplementation would be effective in the prevention and progression of hypothyroidism in patients with HT.

Methods: PubMed, Embase and the Cochrane library were searched for randomized controlled trials (RCTs) and prospective cohort studies published from inception to August 2021.

Results: A total of 7 cohorts of patients from six clinical trials with 258 patients with HT were included. Significant difference was found (WMD = 19.00, 95% CI: 12.43, 25.58, $p < 0.001$; $I^2 = 90.0\%$, $p_{\text{heterogeneity}} < 0.001$) between the vitamin D group and control group in serum 25-hydroxyvitamin D level. And the combined results indicated vitamin D supplementation significantly reduced the level of thyroid peroxidase antibodies (TPO-Ab) compared to the control group (WMD = -158.18, 95% CI: -301.92, -14.45, $p = 0.031$; $I^2 = 68.8\%$, $p_{\text{heterogeneity}} = 0.007$). Whereas no significant differences were found on the levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) compared to the control group ($p > 0.05$).

What is New and Conclusion: Our study demonstrated that vitamin D treatment might significantly increase the serum 25(OH)D levels and produce changes in TPO-Ab titres.

No significant association was found between serum vitamin D treatment and the levels of TG-Ab, TSH, FT3 and FT4, suggesting that vitamin D is not associated with the function of the thyroid in patients with HT.

KEYWORDS

hashimoto's thyroiditis, meta-analysis, thyroid, vitamin D

1 | WHAT IS KNOWN

Hashimoto's thyroiditis (HT), also called chronic lymphocytic thyroiditis, is the most prevalent organ-specific autoimmune disorder as well as the most common cause of thyroid hypofunction, with an incidence of 0.3–1.5 cases per 1000 people in developed countries.^{1,2} This autoimmune event is believed to be initiated by the activation of thyroid antigen-specific auxiliary T lymphocytes and patients may present with various thyroid function states but most of them eventually evolve into hypothyroidism.³ The main purpose of HT treatment is the control of hypothyroidism, including oral administration of a synthetic hormone to achieve normal circulating thyrotropin levels. But the effectiveness of the current treatments such as glucocorticoids, levothyroxine and specific diet for the management of HT has been questioned in recent years.^{4–7}

Vitamin D is a steroid molecule whose primary function is to control bone metabolism and calcium and phosphorus homeostasis. Recent evidence suggested that vitamin D is also associated with non-skeletal roles including in autoimmune diseases, infectious diseases, metabolic syndrome, cardiovascular diseases and cancers.^{8–10} A recent published meta-analysis analysed the effects of vitamin D¹¹ on autoantibodies in patients with autoimmune thyroiditis (AIT). Based on the combined results of six randomized controlled trials, they concluded that vitamin D treatment might be a good choice for AIT based on vitamin D, especially for those with vitamin D deficiency, which is common worldwide.¹² Low levels of vitamin D were found to be associated with HT, and the association between vitamin D deficiency, HT pathogenesis and thyroid hypofunction has been demonstrated in several studies.^{13–15} Given the low cost and the minimal side effects of oral vitamin D supplementation, the treatment of vitamin D supplementation in patients with HT may be recommended.

1.1 | Objective

In light of the current information, vitamin D might be effective in the treatment of hypothyroidism in patients with HT. Therefore, this study aimed to review the association between vitamin D treatment in patients with HT by assessing patients' serum circulating 25-hydroxyvitamin D level to evaluate whether a change occurs in the course of disease.

2 | METHODS

2.1 | Ethical statement

We developed the framework of the current systematic review and meta-analysis according to the recommendations issued by the Cochrane Collaboration for the purpose of ensuring the methodological quality because we did not register formal protocol.¹⁶ We did not impose ethical approval and patients' informed consent because all essential data in the current systematic review and meta-analysis were extracted from published studies.

2.2 | Literature search

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁷ The relevant clinical trials were searched based on the PICO process.¹⁸ A systematic search was performed from PubMed, Embase and the Cochrane library for available studies published up to August 2021, using the MeSH term 'Hashimoto Disease' and 'Vitamin D', as well as relevant keywords. For studies that have not been completed and published but had previously published their design and protocol with their registration number in ClinicalTrials.gov, we manually searched them to ensure whether the results were posted or not.

2.3 | Eligibility criteria

The eligibility criteria were as follows: (1) population: patients diagnosed with HT; (2) interventions: treated by vitamin D; (3) control: placebo or matched individualized therapy; (4) study type: any prospective studies or RCTs published in scientific peer-reviewed journals; (5) outcome: serum 25-hydroxyvitamin D level after treatment; and (6) language was limited to English. No ethical consent was required because this study was performed based on previous data.

2.4 | Data extraction

Two investigators (Hui Jiang and Xiao-luo Chen) independently extracted the following items using the pre-designed data extraction sheet: basic characteristics of the study including first author, year of publication, country, and type of study design, patients' characteristics including sample size, mean age and gender, and clinical characteristics of study including vitamin D status at inclusion, serum thyrotropin levels at inclusion, treatment in both groups, dose of treatment, follow-up period. Serum 25-hydroxyvitamin D level after treatment was included as primary outcome. If an included study was designed to have more than two groups, then the methods recommended by the Cochrane Handbook for Systematic Reviews of Interventions were used to divide the individual study into two unique RCTs or combine groups to create a single pair-wise comparison.¹⁹ If essential information was missed from the original study, then the leading author was contacted for additional information. Any inconsistencies in data extraction were solved based on the consensus principle.

2.5 | Outcomes

The primary outcome was the serum 25-hydroxyvitamin D level after treatments. The secondary outcomes were the levels of thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (TG-Ab), thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) after treatments.

2.6 | Quality of the evidence

The level of evidence of all included studies was assessed independently by two authors (Hui Jiang and Xiao-luo Chen) using the RoB-2 criteria or MINORS (Methodological Index for Non-Randomized Studies) scoring system.^{20,21} Discrepancies in the assessment were resolved through discussion until a consensus was reached.

2.7 | Statistical analysis

All analyses were performed using STATA SE 14.0 (StataCorp). The outcomes were presented as weighted mean differences (WMD). The effects and corresponding 95% confidence intervals (CIs) were used to compare the outcomes. For studies that did not present their results as means \pm standard deviations, the results were estimated based on the reported parameters (median, standard error, IQR or 95% CI).²² Statistical heterogeneity among studies was calculated using Cochran's Q test and the I^2 index. An $I^2 > 50\%$ and a Q test $p < 0.10$ indicated high heterogeneity, and the random effects model was used; otherwise, the fixed-effects model was applied. p -values < 0.05 were considered statistically different. Sensitivity analysis was performed using the leave-one-out method.²⁰ We did not assess the potential publication bias by funnel plots and Egger's test, because the number of studies included in every meta-analysis was fewer than ten, in which case the funnel plots and Egger's test could yield misleading results and are not recommended.

3 | RESULTS

3.1 | Study inclusion

Figure 1 presents the study inclusion process. A total of 416 studies were first retrieved, and 61 trials were left after removing the duplicates. Then, 182 were excluded because of the type of article or the language. From the 173 trials left, after reviewing the full texts, 56 case-report studies, 36 retrospective designed studies, 11 in vivo studies, 29 studies with unsuitable population, 34 with inappropriate interventions and 1 with unwanted outcome were excluded. Therefore, a total of seven cohorts of patients from six studies (3 prospective cohort study and 3 RCTs) entered our analysis (Table 1).^{23–28} At the end of our research, 258 patients with HT were included in our analyses.

3.2 | Quality of all included studies

Among the three randomized controlled trials,^{23,27,28} all three studies were graded as low risk of bias in the assessment for bias arising from the randomization process, bias due to missing outcome data and bias in selection of the reported result. Some concerns were raised in the assessment for bias due to deviations from intended interventions in one study.²⁷ All three studies were concerned in

the assessment for bias in measurement of the outcome. Among the four prospective studies,^{24–26} the total quality score of individual study was all more than 6. We summarized the results of appraising quality of all included studies in Online appendix A1.

3.3 | Effect of vitamin D on the serum 25-hydroxyvitamin D

All 7 cohorts of patients from six studies reported the serum 25-hydroxyvitamin D level after treatment in both treatment and control group. Significant difference was found (WMD = 19.00, 95% CI: 12.43, 25.58, $p < 0.001$; $I^2 = 90.0\%$, $p_{\text{heterogeneity}} < 0.001$, Figure 2A) between the vitamin D group and control group in serum 25-hydroxyvitamin D level. The sensitivity analyses showed that no specific study contributed to heterogeneity (Online appendix A2a).

3.4 | Secondary outcomes

Six cohorts of patients from five studies reported the level of TPO-Ab after treatment from vitamin D or control.^{23–26,28} Combined results indicated vitamin D significantly reduced the level of TPO-Ab compared to the control group (WMD = -158.18, 95% CI: -301.92, -14.45, $p = 0.031$; $I^2 = 68.8\%$, $p_{\text{heterogeneity}} = 0.007$, Figure 2B). The sensitivity analysis showed that no specific study contributed to heterogeneity (Online appendix A2b).

Five cohorts of patients from four studies reported the level of TG-Ab after treatment from vitamin D or control.^{23–26} Combined results indicated vitamin D did not significantly reduce the level of TG-Ab compared to the control group (WMD = -68.21, 95% CI: -143.04, 6.62, $p = 0.074$; $I^2 = 35.8\%$, $p_{\text{heterogeneity}} = 0.183$, Figure 2C). The sensitivity analysis showed that no specific study contributed to heterogeneity (Online appendix A2c).

Combined results showed vitamin D did not significantly change the levels of TSH, FT3 and FT4 compared to the control group (Figure 2D–F).

3.5 | Subgroup analyses

All subgroup analyses were presented in Table 2. The level of serum 25-hydroxyvitamin D was increased from the treatment of vitamin D regardless of the length of follow-up, the vitamin status at initiation and the gender of patients compared to the controls group in patients with HT. The sensitivity analyses showed that no specific study contributed to heterogeneity Online appendix A2d&e&f).

4 | DISCUSSION

The present meta-analysis suggested that despite a significant increase in serum 25-hydroxyvitamin D level and decrease in TPO-Ab

among patients who received vitamin D were observed, we did not find any significant effect of vitamin D treatment on TG-Ab, TSH, FT4 and FT3.

It has been well acknowledged that vitamin D plays a significant role in modulation of the immune system. It can enhance the innate immune response while exert an inhibitory action on the adaptive

immune system.^{29,30} Our results showed that after patients with HT were treated by vitamin D supplementation, their serum 25(OH)D levels significantly increased by 19.00 (95% CI: 12.43–25.58) ng/ml compared to the patients who were treated by placebo or other thyroid replacement medication. Till now, some studies have reported an association between serum 25(OH)D levels and autoimmune thyroid

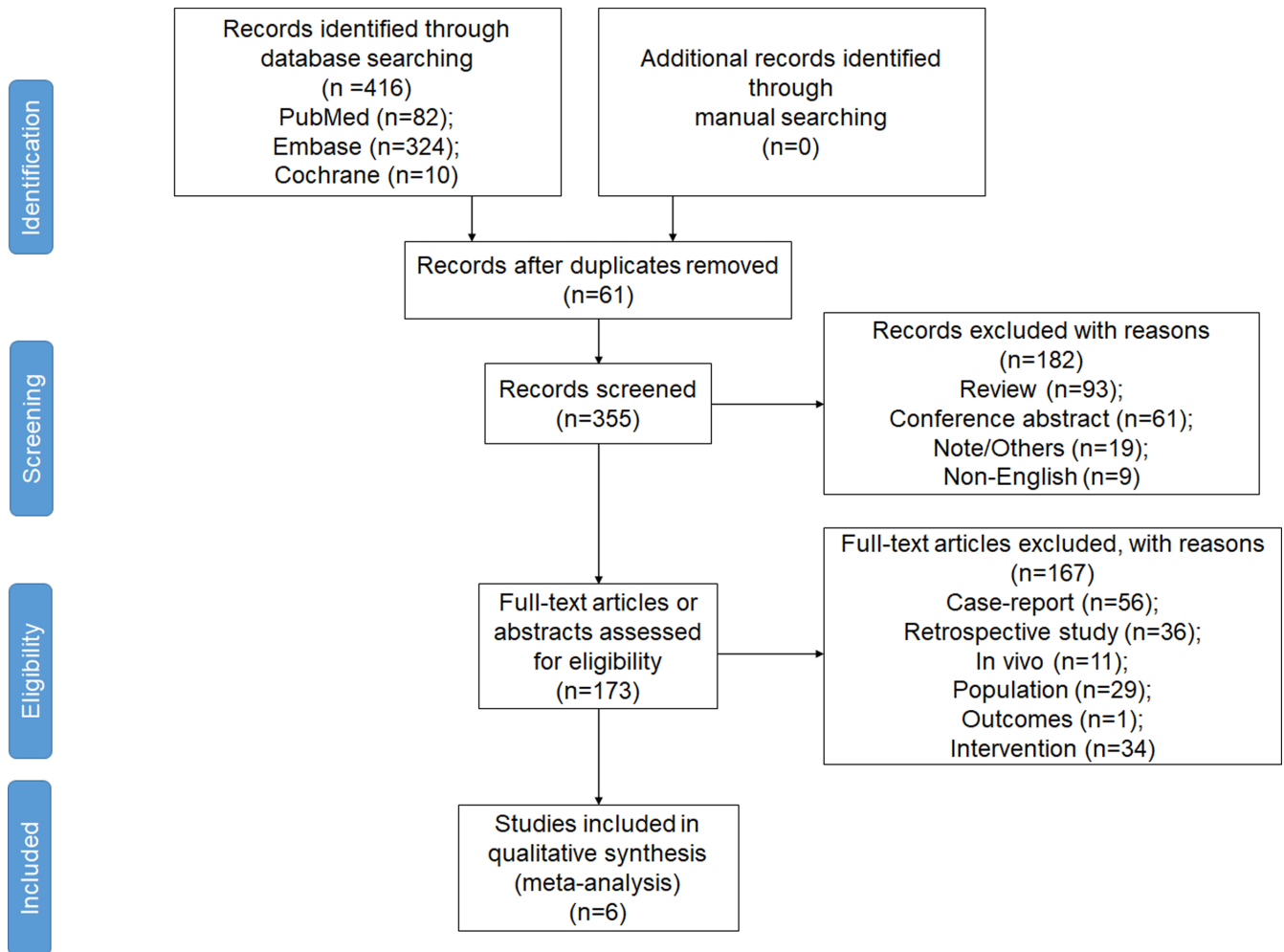


FIGURE 1 PRISMA 2009 flow diagram

TABLE 1 Characteristics of the literatures

Author, year	Country	Study design	VD status	Serum thyrotropin levels, mU/l	Intervention	Control
Chahardoli, 2019	Iran	RCT	Not limited	NA	VD	Placebo
Nodehi, 2019	Iran	RCT	Not limited	NA	VD	Placebo
Vahabi, 2017	Iran	RCT	Insufficiency	NA	VD	Placebo
Krysiak, 2016	Poland	Prospective	Normal	0.4 to 8	VD + Levothyroxine	Levothyroxine
Krysiak, 2017a	Poland	Prospective	Insufficiency	0.45 to 4.5	VD + Simvastatin	Simvastatin
Krysiak, 2017b	Poland	Prospective	Insufficiency	0.45 to 4.5	VD	Simvastatin
Krysiak, 2018	Poland	Prospective	Not limited	0.4 to 4	VD	Selenomethionine

Abbreviations: NA, not applicable; RCT, randomized control trial; VD, vitamin D.

disorder (AITD) or HT.³¹⁻³⁵ Kivity et al.³⁶ pointed out that vitamin D deficiency was linked to the presence of anti-thyroid antibodies and abnormal thyroid functions. Their results showed a significant correlation between vitamin D deficiency and the presence of anti-thyroid antibodies ($p = 0.010$), suggesting the involvement of vitamin D in the pathogenesis of AITD. Several studies demonstrated that the prevalence of vitamin D insufficiency was significantly higher in patients with HT compared to healthy controls, and the serum 25(OH)D levels in patients with HT were significantly lower than the controls.³⁷ Additionally, the severity of vitamin D deficiency was also correlated with the duration of HT, thyroid volume and antibody levels, suggesting a potential role of vitamin D in the development of HT and its progression to hypothyroidism.³⁸ Mansournia et al.³⁹ showed that by 5 ng/ml increases in the level of vitamin D, the risk of occurrence of HT would be decreased by 19%. The inverse association between vitamin D level and HT strongly implies that vitamin D supplementation could be effective in patients with HT.

Lymphocytic infiltration of the thyroid gland correlates well with the thyroid antibodies, which are considered the most

reliable prognostic factors to predict HT and the development of hypothyroidism.^{40,41} Thyroid function tests include FT3, FT4, TSH, TPO-Ab and TG-Ab concentrations. In our analyses, we found a significantly lower TPO-Ab level in patients who were treated by vitamin D compared to those who were treated by placebo or other thyroid replacement medication (WMD: -158.18 , 95% CI: -301.92 , -14.45 , $p = 0.031$). Considering the significantly higher level of serum 25(OH)D in vitamin D group compared to other treatments, it is reasonable to speculate that there was a negative association between serum 25(OH)D level and TPO-Ab in patients with HT. Comparing to the meta-analysis¹¹ investigating the effect of vitamin D on AIT, they found a significant decrease of TPO-Ab levels (three studies, random effects SMD: -0.57 , 95% CI: -1.08 to -0.07 , $I^2 = 79.7\%$) in the vitamin D-treated group as well. In addition, they also observed a significantly lower Tg-Ab titres (four studies, random effects SMD: -0.55 , 95% CI: -1.05 to -0.04 , $p = 0.033$) in vitamin D group compared to the controls. The possible explanations for the differences are that only three studies in their analysis investigated specifically patients with HT, and only

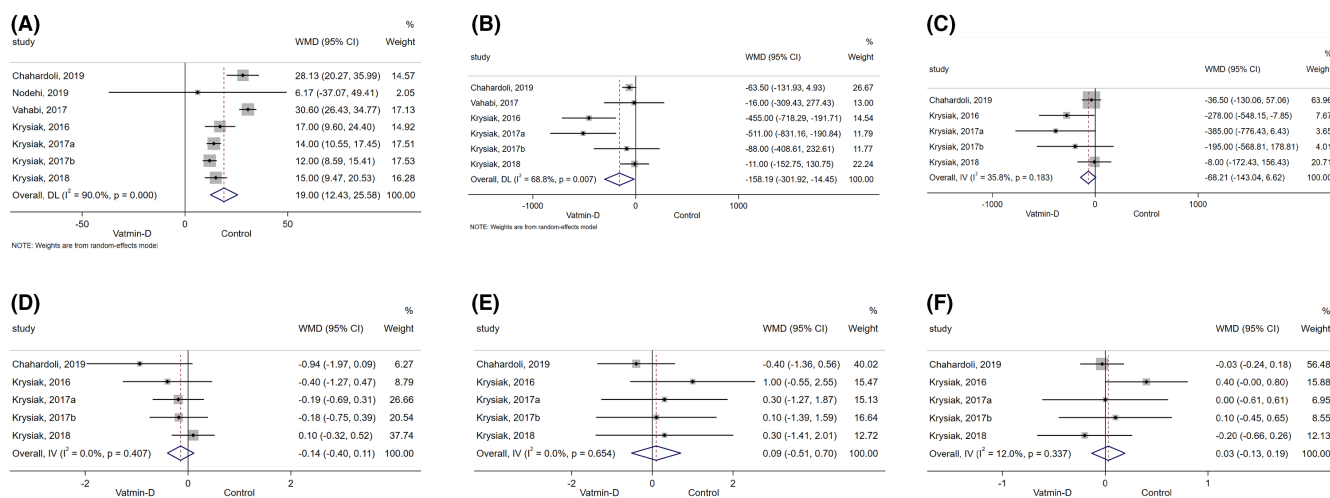


FIGURE 2 Forest plot comparing the autoimmunity markers between vitamin D group with the control group. (A) 25-Hydroxyvitamin D Level; (B) thyroid peroxidase antibodies; (C) thyroglobulin antibodies; (D) thyroid-stimulating hormone; (E) free thyroxine; (F) free triiodothyronine

Sample size		Dose		Gender	Age (intervention/control), y	Follow-up
Intervention	Control	Intervention	Control			
19	21	50000 IU/week	/	Female	$36.4 \pm 5.2/35.9 \pm 7.8$	3 months
17	17	50000 IU/week	/	Female	$36.4 \pm 5.2/35.9 \pm 7.8$	3 months
30	26	50000 IU/week	/	Both	$43.6 \pm 1.6/44.1 \pm 1.6$	3 months
16	18	2000 IU/d Levothyroxine: NA	NA	Female	$34 \pm 7/36 \pm 6$	6 months
19	9	VD: 2000 IU/d Simvastatin: 40 mg/day	40 mg/day	Female	$38 \pm 7/37 \pm 6$	6 months
20	9	2000 IU/day	40 mg/day	Female	$39 \pm 5/37 \pm 6$	6 months
20	17	4000 IU/day	200 µg/day	Male	$35 \pm 8/34 \pm 7$	6 months

TABLE 2 Combined results of the subgroup analyses

	N	WMD (95% CI)	p (Heterogeneity)	I ² , %	p
25-hydroxyvitamin D	7	19.00 (12.43, 25.58)	<0.001	90	<0.001
Follow-up					
3 months	3	29.89 (26.22, 33.55)	0.482	0	<0.001
6 months	4	13.62 (11.49, 15.74)	0.582	0	<0.001
Vitamin D status					
Insufficient	3	18.80 (8.05, 29.56)	<0.001	96.1	0.001
Normal	1	17.00 (9.60, 24.40)	.	.	<0.001
Both	3	20.25 (8.58, 31.92)	0.023	73.4	0.001
Gender					
Women	5	16.60 (11.43, 21.77)	0.006	72	<0.001
Men	1	15.00 (9.47, 20.53)	.	.	<0.001
Both	1	30.60 (26.43, 34.77)	.	.	<0.001
Thyroid peroxidase antibodies	6	-158.18 (-301.92, -14.45)	0.007	68.8	0.031
Follow-up					
3 months	2	-61.05 (-127.69, 5.59)	0.727	0	0.073
6 months	4	-251.51 (-520.68, 17.66)	0.003	78.4	0.067
Vitamin D status					
Insufficient	3	-201.15 (-501.79, 99.49)	0.061	64.3	0.190
Normal	1	-455.00 (-718.29, -191.71)			0.001
Both	2	-53.58 (-115.20, 8.05)	0.513	0	0.088
Gender					
Women	4	-260.38 (-509.17, -11.60)	0.002	79.2	0.040
Men	1	-11.00 (-152.75, 130.75)	.	.	0.879
Both	1	-16.00 (-309.42, 277.42)	.	.	0.915
Thyroglobulin antibodies	5	-68.21 (-143.04, 6.62)	0.183	35.8	0.074
Follow-up					
3 months	1	-36.50 (-130.06, 57.06)	.	.	0.445
6 months	4	-124.48 (-249.12, 0.16)	0.171	40.1	0.050
Vitamin D status					
Insufficient	2	-285.63 (-555.97, -15.29)	0.491	0	0.038
Normal	1	-278.00 (-548.15, -7.85)	.	.	0.044
Both	2	-29.53 (-110.85, 51.79)	0.768	0	0.477
Gender					
Women	4	-83.94 (-167.97, 0.09)	0.134	46.2	0.050
Men	1	-8.00 (-172.43, 156.43)			0.924
Thyrotropin	6	-0.00 (-0.66, 0.66)	<0.001	88.9	0.998
Follow-up					
3 months	2	0.20 (-1.92, 2.31)	<0.001	93.5	0.855
6 months	4	-0.09 (-0.36, 0.18)	0.675	0	0.503
Vitamin D status					
Insufficient	3	0.30 (-0.73, 1.34)	<0.001	93.5	0.569
Normal	1	-0.40 (-1.27, 0.47)	.	.	0.366
Both	2	-0.05 (-0.44, 0.34)	0.066	70.3	0.808
Gender					
Women	4	-0.29 (-0.62, 0.03)	0.594	0	0.079

TABLE 2 (Continued)

	N	WMD (95% CI)	p (Heterogeneity)	I ² , %	p
Both	1	1.22 (0.89, 1.55)			<0.001
Men	1	0.10 (-0.32, 0.52)			0.640
Free thyroxine	5	0.09 (-0.51, 0.70)	0.654	0	0.760
Follow-up					
3 months	1	-0.40 (-1.36, 0.56)	.	.	0.416
6 months	4	0.43 (-0.36, 1.21)	0.860	0	0.290
Vitamin D status					
Insufficient	2	0.20 (-0.89, 1.28)	0.856	0	0.723
Normal	1	1.00 (-0.55, 2.55)	.	.	0.206
Both	2	-0.23 (-1.07, 0.61)	0.484	0	0.589
Gender					
Women	4	0.06 (-0.59, 0.72)	0.497	0	0.845
Men	1	0.30 (-1.41, 2.01)	.	.	0.731
Free triiodothyronine	5	0.03 (-0.13, 0.19)	0.337	12	0.707
Follow-up					
3 months	1	-0.03 (-0.24, 0.18)			0.784
6 months	4	0.11 (-0.13, 0.35)	0.280	21.7	0.378
Vitamin D status					
Insufficient	2	0.06 (-0.35, 0.46)	0.812	0	0.792
Normal	1	0.40 (-0.00, 0.80)			0.052
Both	2	-0.06 (-0.25, 0.13)	0.513	0	0.545
Gender					
Women	4	0.06 (-0.11, 0.23)	0.327	13.1	0.474
Men	1	-0.20 (-0.66, 0.26)			0.397

one of which was included in our analysis (the other two published in Mandarin were excluded from this study). Our result is consistent with the previous research that demonstrated a significant negative correlation between serum 25(OH)D levels and TPO-Ab in patients with AITDs.⁴² Moreover, Ucan et al.⁴³ observed a relatively lower 25(OH)D concentration in the HT group as compared with the control group, and a significant reduction in antibody concentration after vitamin D replacement was given. They demonstrated a statistically significant decrease in TPO-Ab ($p = 0.003$) and TG-Ab ($p = 0.020$) antibody concentrations after vitamin D replacement in patients with euthyroid HT. However, other studies did not find any association between serum TPO-Ab or TG-Ab and 25(OH)D levels in newly diagnosed HT patients.^{30,44,45} As in our study, the association between TG-Ab and 25(OH)D levels was not pronounced ($p = 0.074$). Though it is worth mentioning that a decrease in TPO-Ab titres may better reflect the effect of vitamin D on thyroid autoimmunity than its action on TG-Ab as the general measurements of TPO-Ab often have higher sensitivity and at least equal specificity to TG-Ab measurements in the diagnosis of autoimmune disorders of the thyroid gland.⁴⁶

Our results should be interpreted cautiously as we did not reveal any association between serum 25(OH)D and the levels of TSH, FT3 and FT4, suggesting that vitamin D supplementation is not

associated with the function of the thyroid in HT. One recent retrospective study found TSH is an independent risk factor for HT, but no association was found between HT and FT3 or FT4, suggesting HT patients were more prone to subclinical hypothyroidism.¹⁵ However, this study also revealed a potential role of 25(OH)D supplementation in regulating the thyroid hormone level based on the results of positive correlation between 25(OH)D and the level of FT3 and FT4. Moreover, Krysiak et al. suggested that vitamin D supplementation produced no effect on the post-treatment levels of FT4 and free thyroid hormone.

The results of the present meta-analysis must be considered in light of the study's limitation. Firstly, the estimated means \pm standard deviations might potentially bias the results, but the sensitivity analysis showed a robust outcome even when the individual studies with estimated parameters were left out of the analyses. Second, some of the studies used different regimen and individualized dose of the treatment, which would probably result in heterogeneity. Of note, several studies could not be included because they did not report results specifically for patients with HT. Third, all studies have rather small sample sizes. To our knowledge, there are only a few prospective studies that investigated the effect of vitamin D supplementation on patients with HT, and the thyroid indicators in each study were reported differently. Despite only seven studies being

included in this meta-analysis in total, there were no previous meta-analyses that analysed the effect of vitamin D supplementation in patients with HT for a given outcome. Fourth, only papers in English were included, possibly leaving out valuable results. Although the difference is statistically significant, the clinical significance should be cautiously interpreted since the patients were clustered by gender. Additional studies might be necessary to determine the exact functional impact of vitamin D treatment on HT patients. Finally, the combined estimates of our outcomes were not reported at the same duration after patients had been treated.

5 | WHAT IS NEW AND CONCLUSIONS

Our study demonstrated that vitamin D might significantly increase the serum 25(OH)D levels and produce changes in TPO-Ab titres. But no significant association was found between serum vitamin D supplementation and the levels of TG-Ab, TSH, FT3 and FT4, suggesting that vitamin D is not associated with the function of the thyroid in patients with HT. Well-designed RCTs with sufficient sample sizes investigating the effect of vitamin D on thyroid function are still warranted.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

PATIENT CONSENT STATEMENT

This study did not contain any patients and patient consent is not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article and its supplementary information files.

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