Effects of vitamin D on thyroid autoimmunity markers in Hashimoto's thyroiditis: systematic review and meta-analysis

Jingwen Zhang[1], Yuting Chen[2], Hongyan Li[1]
and Hong Li[1] 🔵

Abstract

Objective: To perform a meta-analysis of randomized controlled trials to evaluate the efficacy of vitamin D supplementation on thyroid autoimmunity markers in Hashimoto's thyroiditis (HT).

Methods: This meta-analysis included randomized controlled clinical trials identified by a systematic search of electronic databases (PubMed®, MEDLINE®, EMBASE, The Cochrane Library, China National Knowledge Infrastructure) from inception to August 2020. All studies included patients with HT that received vitamin D supplementation irrespective of the doses administered or the duration of treatment. The primary and secondary outcome measures were thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TGAb) titres.

Results: Eight studies ($n = 652$) were included. There was significant heterogeneity between the studies. Using a random-effect model, vitamin D supplementation reduced TPOAb titre (standardized mean difference [SMD]: −1.11; 95% confidence interval [CI]: 1−1.92, −0.29) and TGAb titre (SMD: −1.12; 95% CI: −1.96, −0.28). A subgroup analysis demonstrated that vitamin D supplementation for >3 months resulted in a decrease in TPOAb titre (SMD: −1.66, 95% CI: −2.91, −0.41) but treatment ≤3 months was ineffective. Treatment with vitamin D_3 decreased TPOAb titre (SMD: −1.48; 95% CI: −2.53, −0.42) whereas vitamin D did not.

Conclusion: These data suggest that vitamin D reduces autoantibody titre in patients with HT.

[1]Department of Endocrinology, Long Hua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China
[2]Department of Endocrinology, Zhejiang Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang Province, China

Corresponding author:
Hong Li, Department of Endocrinology, Long Hua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 725 South Wanping Road Xuhui Area, Shanghai, 200032, China.
Email: shanhong_li@126.com

Introduction

Hashimoto's thyroiditis (HT), also known as autoimmune thyroiditis and first described in 1912 by Hakaru Hashimoto, is the leading cause of primary hypothyroidism.[1,2] Its incidence is estimated to be 0.3–1.5 per 1000 people per year and it is 5–10 times more common in women than men.[3] The disease is characterized by the presence of thyroid autoantibodies against thyroid peroxidase or thyroglobulin.[4] The antibody titre levels are positively correlated with hypothyroidism,[5] but there is no specific drug to reduce the antibody titre.

Vitamin D plays an important role in immune and endocrine processes. For example, a recent meta-analysis involving 26 observational studies found that the 25-hydroxyvitamin D (25(OH)D) level was significantly lower in patients with HT than in healthy controls.[6] The effect of vitamin D on immunity in patients with HT patients remains obscure. Some studies found that after supplementation with $25(OH)D_3$ in patients with HT with vitamin D deficiency, the titre of thyroid autoantibodies decreased significantly, suggesting that vitamin D treatment could delay the development of hypothyroidism.[7–11] Other studies, however, reached the opposite conclusion that there was no significant effect on thyroid autoantibodies after supplementation with vitamin D in patients with HT.[12–14] This current study aimed to systematically evaluate the effect of vitamin D on thyroid autoimmunity markers in patients with HT.

Materials and methods

Study methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] It was registered into PROSPERO (CRD42020206000). This current study strictly followed a pre-set protocol.

Data source and search strategy

A systematic search of publications listed in electronic databases (PubMed®, MEDLINE®, EMBASE, The Cochrane Library, China National Knowledge Infrastructure [CNKI]) from inception to August 2020 was undertaken using a set of key words. The full search strategy for PubMed® was: ("hashimoto disease" [MeSH Terms] OR "hashimoto struma" [Title/Abstract] OR "hashimotos syndrome"[Title/Abstract] OR "chronic lymphocytic thyroiditis" [Title/Abstract] OR "hashimotos disease" [Title/Abstract]) AND ("vitamin D" [MeSH Terms] OR "Ergocalciferols" [MeSH Terms] OR "Cholecalciferol" [Title/Abstract] OR "Hydroxycholecalciferols" [Title/Abstract] OR "Ergocalciferols" [Title/Abstract] OR "25-hydroxyvitamin D3"[Title/Abstract] OR "Dihydrotachysterol" [Title/Abstract]) AND ("randomized controlled trials as topic"[MeSH Terms] OR "clinical study" [Publication Type] OR "clinical trial" [Publication Type] OR "controlled clinical trial"[Publication Type]). The search

strategies for the other databases are presented in the appendix file (see supplementary materials). The work was conducted by two researchers (J.Z. & Y.C.) independently to ensure a comprehensive screening. No language restrictions or limitations were applied. A manual review of the reference lists from primary or review articles was undertaken to identify any additional relevant studies.

Study selection

Studies were considered eligible for inclusion if they met the following criteria: (i) study design: randomized controlled clinical trials; (ii) population: patients with HT; (iii) intervention: vitamin D to treat HT, regardless of its doses and courses; (iv) outcome variables: at least one of either thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TGAb) titres. Studies were excluded based on the following criteria: (i) duplicate studies; (ii) case reports, conference abstracts or reviews; (iii) trials tested in animals; (iv) TPOAb or TGAb titres were not included in the results.

Data extraction and quality evaluation

Important information from each study was extracted as follows: authors, publication year, country, sample size, mean age, sex ratio, intervention time and measures, levothyroxine (LT4) intake and main outcomes. Two independent researchers (J.Z. & Y.C.) extracted the relevant data from the articles using the same standard. Any disagreement was resolved by discussing with a third researcher (H.L.).

Two researchers (J.Z. & Y.C.) independently evaluated the methodological quality of the eligible trials using the Cochrane Collaboration Risk of Bias tool Statistical analysis. The study quality assessment covered: (i) random generation; (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective reporting; (vii) other factors that could impact the bias of studies such as the equality of baseline data between groups in the studies.

Statistical analyses

All analyses were undertaken using Stata® software (version 14.0; Stata Corporation, College Station, TX, USA). Continuous variables were evaluated using standardized mean difference (SMD) and 95% confidence interval (CI). In two-tailed tests, a P-value <0.05 was considered statistically significant. The χ^2-test and I^2 statistics were used to test for heterogeneity. If there was heterogeneity ($P < 0.05$, $I^2 > 50\%$) in the results, a random-effect model was used. Otherwise, a fixed-effect model was used. If there was significant heterogeneity, a subgroup analysis was conducted using two factors (treatment duration, form of vitamin D administration) to find the source of the heterogeneity. Sensitivity analysis was made to test the stability of the primary outcomes. Begg's test was also used to evaluate publication bias. $P < 0.10$ indicated the presence of publication bias.

Results

A flowchart showing the selection process for eligible studies is shown in Figure 1. Initially, 345 relevant articles were retrieved from five databases (PubMed®: 105; EMBASE: 11; The Cochrane Library: 21; MEDLINE®: 40; CNKI: 168). Of these, 153 duplicate studies were removed. Of the remaining 192 articles, 168 were excluded after reading the titles and abstracts. After reviewing the full text of 24 articles, eight eligible randomized controlled trials were included in the meta-analysis.[7–14]
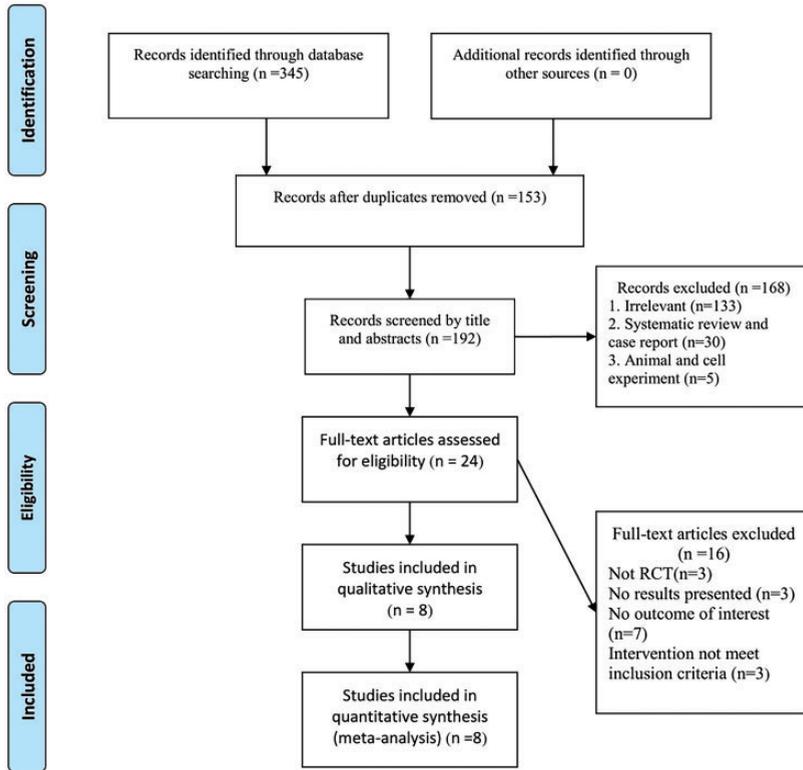
Figure 1. Literature search and study selection flowchart.

The study characteristics are shown in Table 1.[7–14] These eight studies involved 652 patients with HT, including 332 in the intervention groups and 320 in the control groups. All were published between 2015 and 2020, with study periods ranging from 4 to 24 weeks. Among them, one study evaluated only females;[12] and fours studies evaluated the effect of LT4 tablets.[8–11]

The bias assessment of all eight trials is detailed in Figure 2. The Cochrane risk of bias tool was used to assess the risk of bias of each study. Three studies explicitly described the random sequence generated by a random number table or block randomization. The other studies only mentioned the word 'randomization', thus their bias was considered to be 'unclear'. Three articles described the ways of

allocating concealment by sealed drug boxes and packages, thus their bias was assessed as 'low risk' for 'allocation concealment'. The other studies did not mention if there was any allocation concealment. Only three studies used dummy placebos and neither patients nor researchers knew the grouping. Both TPOAb and TGAb were laboratory indicators, so all eight studies had a blinded outcome assessment. No patients were lost to follow-up or dropped out in five studies, thus their bias was assessed as 'low risk' for 'incomplete outcome data'. Three studies reported that patients were lost to follow-up and discontinued intervention, therefore these studies were regarded as having a high risk in this domain. All included studies showed a low bias risk in 'selective reporting' because

Table 1. Characteristics of the eight randomized controlled trials included in a meta-analysis of the effect of vitamin D supplementation on thyroid autoimmunity markers in patients with Hashimoto's thyroiditis (HT).[7–14]

Author/year	Country	Interventions TG/CG	n	Age, years Mean ± SD	Female n (%)	Treatment duration	LT4 treatment	Main outcomes
Han et al.[11]/2015	China	1,25(OH)2D3 25 µg QD + LT4	32	34.8 ± 8.2	27 (84.4%)	24 weeks	Yes	25(OH)D2, 25(OH)D3, TPOAb, TGAb, FT3, FT4, TSH
		LT4	30	35.2 ± 7.1	26 (86.7%)			
Simsek et al.[7]/2016	Turkey	Vitamin D 1000 IU QD	46	35.8 ± 12.0	37 (80.4%)	1 month	No	Vitamin D, TSH, FT4, TPOAb, TGAb
		Sunshine and diet	36	39.7 ± 12.6	31 (86.1%)			
Zhao et al.[8]/2016	China	1,25(OH)2D3 25 µg QD + LT4	18	41.0 ± 5.0	14 (77.8%)	24 weeks	Yes	25(OH)D3, TPOAb, TGAb, FT3, FT4, TSH
		LT4	18	42.0 ± 7.0	13 (72.2%)			
Vahabi Anaraki et al.[13]/2017	Iran	Vitamin D 50000 IU QW	33	43.6 ± 1.6	21 (63.6%)	12 weeks	No	CRP, TPOAb, TSH, 25(OH)D, PTH, Ca
		Placebo	32	44.1 ± 1.6	15 (46.9%)			
Knutsen et al.[14]/2017	Middle East, Africa, or South Asia	Vitamin D3 25 µg QD	83	Female: 35.0 ± 7.5 Male: 40.0 ± 9.1	57 (68.7%)	16 weeks	No	Vitamin D3, TSH, FT4, TPOAb, PTH
		Placebo	82	Female: 38.0 ± 7.6 Male: 39.0 ± 7.8	63 (76.8%)			
Chahardoli et al.[12]/2019	Iran	1,25(OH)2D3 50000 IU QW	19	36.4 ± 5.2	19 (100.0%)	12 weeks	No	25(OH)D, TPOAb, TGAb, T3, T4, TSH, Ca
		Placebo	21	35.9 ± 7.8	21 (100.0%)			
Yin et al.[10]/2019	China	1,25(OH)2D3 25 µg QD + LT4	50	45.6 ± 4.0	42 (84.0%)	20 weeks	Yes	25(OH)D3, TPOAb, TGAb, FT3, FT4, TSH
		LT4	50	45.3 ± 3.8	45 (90.0%)			
Jia et al.[9]/2020	China	1,25(OH)2D3 25 µg QD	51	42.0 ± 9.3	29 (56.9%)	16 weeks	Yes	25(OH)D2, 25(OH)D3, TPOAb, TGAb, FT3, FT4, TSH
		LT4	51	42.20 ± 8.98	31 (60.8%)			

TG, treatment group; CG, control group; LT4, levothyroxine; QD, once a day; TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; QW, once a week; CRP, C-reactive protein; PTH, parathormone; T3, total triiodothyronine; T4, thyroxine; Ca, calcium.

Figure 2. Risk of bias graph and summary of bias assessment of the eight randomized controlled trials included in a meta-analysis of the effect of vitamin D supplementation on thyroid autoimmunity markers in patients with Hashimoto's thyroiditis (HT).[7–14] The colour version of this figure is available at: http://imr.sagepub.com.

their statistical outcomes were prespecified in the protocol.

All eight studies reported data on TPOAb, but there was significant heterogeneity ($\chi^2 = 150.02$; $I^2 = 95.3\%$, $P < 0.001$) (Figure 3) so a random-effect model was used.[7–14] The pooled evidence showed that vitamin D supplementation was effective in reducing the TPOAb titre (SMD: –1.11; 95% CI: –1.92, –0.29; $P = 0.008$).

A subgroup analysis was performed based on treatment duration. The results showed that vitamin D supplementation could decrease TPOAb titre in the subgroups in whom the treatment duration >3 months (SMD: –1.66, 95% CI: –2.91, –0.41; $P = 0.009$), but not in the subgroups in whom the treatment duration was ≤3 months (SMD: –0.16; 95% CI: –0.51, 0.20; $P = 0.392$) (Figure 4A).

A subgroup analysis was performed based on the form of vitamin D administration. The results showed that vitamin D supplementation could decrease TPOAb titre in the subgroups that were treated with vitamin D_3 (SMD: –1.48; 95% CI: –2.53, –0.42; $P = 0.006$), but not in the subgroups that were treated with vitamin D (SMD: –0.01; 95% CI: –0.35, 0.32; $P = 0.945$) (Figure 4B).

Six studies provided data on TGAb, but there was significant heterogeneity ($\chi^2 = 75.12$; $I^2 = 93.3\%$, $P < 0.001$) (Figure 5) so a random-effect model was used.[7–12] The pooled evidence showed that vitamin D supplementation was effective in reducing the TGAb titre (SMD: –1.12; 95% CI: –1.96, –0.28; $P = 0.009$). Due to limited data, no subgroup analysis and meta-regression analysis were performed.

Sensitivity analyses were performed to examine the influence of each individual study on the overall effect size. The effect sizes after one-by-one elimination were all within the 95% CI of the total effect size, indicating that the results of this meta-analysis were stable and reliable (Figure 6).

Begg's test was used to measure publication bias. The TPOAb results showed Z = 1.61.pr > |Z| = 0.108, suggesting no obvious publication bias in the references included in this meta-analysis (Figure 7). The TGAb results showed Z = 0.00.pr > |Z| = 1.000, suggesting no significance and no obvious bias.
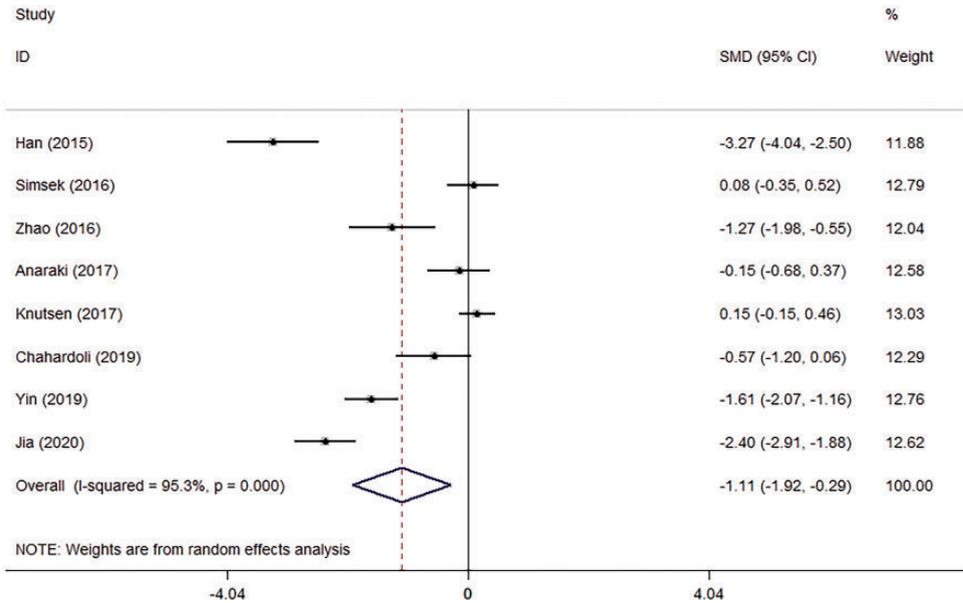
Figure 3. Forest plot showing the effects of vitamin D supplementation on thyroid peroxidase antibody titre in patients with Hashimoto's thyroiditis using a random-effect model.[7–14]
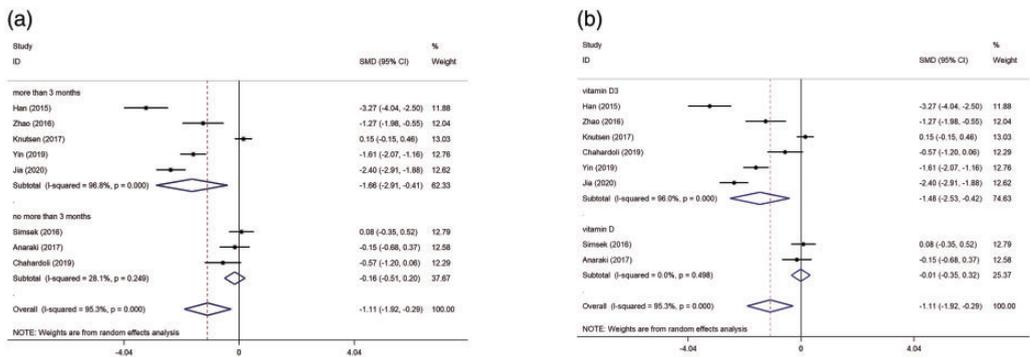
Figure 4. Forest plots showing subgroup analyses of the effects of vitamin D supplementation on thyroid peroxidase antibody titre in patients with Hashimoto's thyroiditis: (a) subgroup analysis based on treatment duration; (b) subgroup analysis based on the form of vitamin D administration.[7–14]

Discussion

Hashimoto's thyroiditis is characterized by specific immune responses against the thyroid gland, which usually manifests as increased levels of serum TPOAb and TGAb.[4] In general, the antibody titre is positively correlated with the extent of hypothyroidism.[5] The present meta-analysis demonstrated that vitamin D supplementation could reduce TPOAb and TGAb titres in patients with HT. A meta-analysis of six randomized controlled trials published in 2018 showed that vitamin D supplementation could decrease serum antibody titres in patients with HT in the
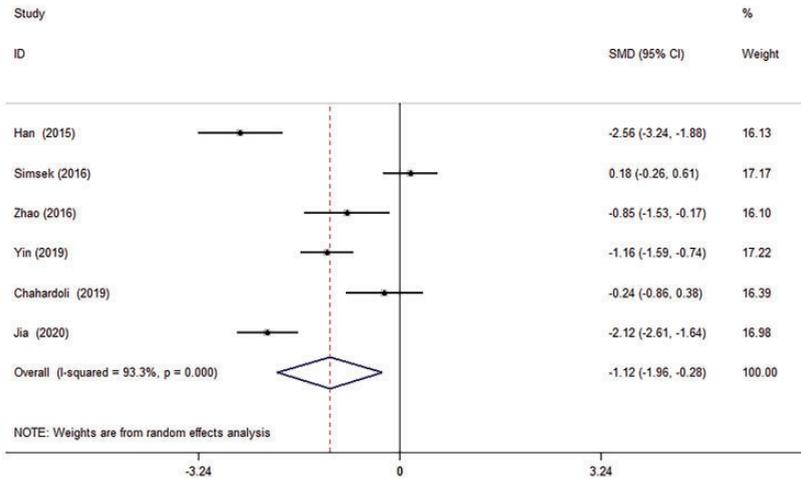
Figure 5. Forest plot showing the effects of vitamin D supplementation on thyroglobulin antibody titre in patients with Hashimoto's thyroiditis using a random-effect model.[7–12]
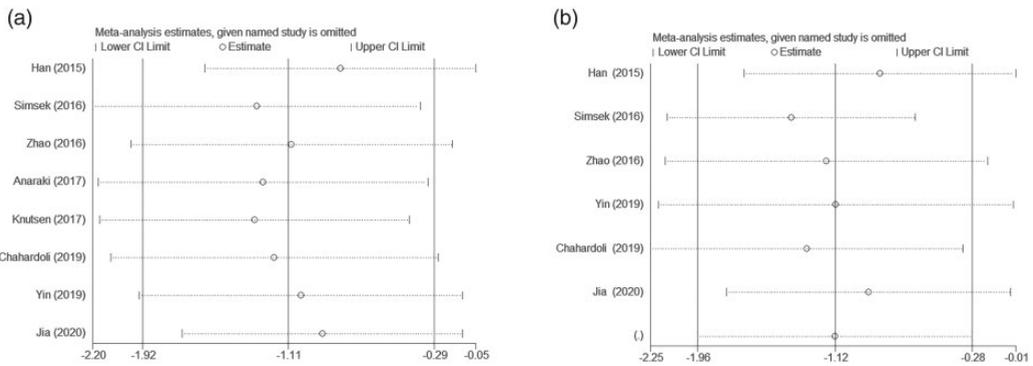
Figure 6. Sensitivity analyses of the included studies: (a) sensitivity analysis for the studies about the effect of vitamin D supplementation on thyroid peroxidase antibody titre; (b) sensitivity analysis for the studies about the effect of vitamin D supplementation on thyroglobulin antibody titre.[7–14]

short-term (approximately 6 months).[16] This current meta-analysis evaluated additional recent randomized controlled trials and reached a similar conclusion.[16] This current meta-analysis showed that taking vitamin D_3 was more effective than taking vitamin D, but this finding needs to be demonstrated by more randomized controlled trials.

Hashimoto's thyroiditis is characterized by the homing of leukocytes, such as cluster of differentiation (CD) 4^+ T cells, cytotoxic T lymphocytes, B cells and natural killer cells, to the thyroid gland.[17] These leukocytes proceed to destroy thyroid follicular cells via antibody-dependent cytotoxicity and/or apoptosis.[18] Once the type 1 helper T (Th$_1$) cell/type 2 helper T (Th$_2$) cell immune balance is disrupted, Th$_1$ cell-dominated cellular immunity is initiated, which is the main mechanism of the pathogenesis of HT.[19] Moreover, complement is
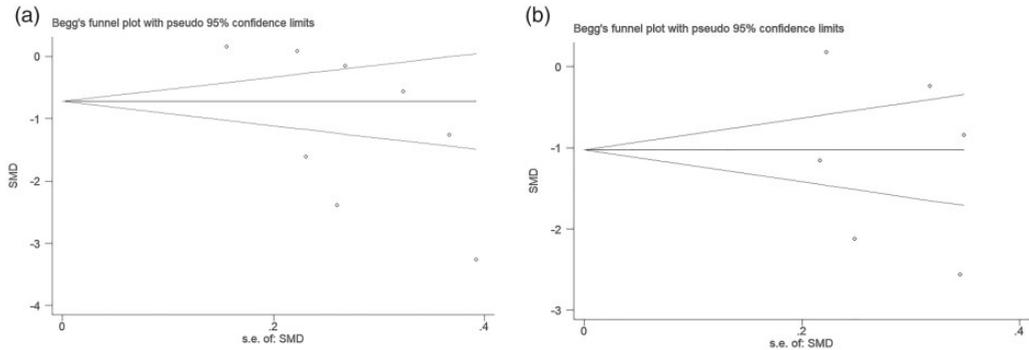
Figure 7. Begg's method for investigating publication bias: (a) Begg's funnel plot of the publication bias for studies about the effect of vitamin D supplementation on thyroid peroxidase antibody titre; (b) Begg's funnel plot of the publication bias for studies about the effect of vitamin D supplementation on thyroglobulin antibody titre. SMD, standardized mean difference; s.e., standard error.[7–14]

activated and thyroid autoantibodies are produced, leading to thyroid follicular cell damage and ultimately hypothyroidism.[20] TGAb and TPOAb are two types of thyroid tissue autoantibodies, the levels of which are positively associated with the severity of thyroid inflammation and hypothyroidism.[21] In particular, TPO, a key enzyme located in thyroid cells, is involved in iodinated tyrosine synthesis, iodinated tyrosine coupling and other processes.[22] TPO is the most important autoantigen involved in the induction of autoimmune thyroid disease.[23–25] TGAb and TPOAb positivity, especially almost 100% positivity for TPOAb, is one of the necessary criteria for the diagnosis of Hashimoto's encephalopathy.[26–29] However, it has not been determined whether antithyroid antibodies play a direct role in the pathogenesis of Hashimoto's encephalopathy or simply serve as a marker of autoimmune reactivity.[26–29]

As an active form of vitamin D, 1,25-dihydroxyvitamin D_3 can cooperate with vitamin D receptors to regulate calcium and phosphorus metabolism, control the proliferation and differentiation of cells and generate immunomodulatory effects.[30] 1,25 $(OH)_2D_3$ down-regulates the expression of the major histocompatibility complex class II and stimulating molecules (CD40, CD80, CD86), increases the production of interleukin (IL)-10 and reduces the secretion of IL-12, thus repressing the Th_1 cell immune response.[31] In contrast, $1,25(OH)_2D_3$ inhibits plasma cell generation, memory cell formation and subsequent secretion of immunoglobulin (Ig)G and IgM by activated B cells.[32] Vitamin D also regulates regulatory B (B_{reg}) cells involved in immunological tolerance by producing IL-10, IL-35 and transforming growth factor-β.[33] Therefore, these current findings suggest that the effect of vitamin D supplementation in reducing thyroid tissue autoantibodies may be related to its regulation of immune function.

This current meta-analysis had several limitations as follows: (i) the power of the analysis may be restricted because of the limited study numbers and population sizes; (ii) there was significant heterogeneity among the included studies; (iii) most of the included studies were conducted in China, which affects the extrapolation of the conclusions to other populations to some extent; (iv) only published data were included, which may lead to a reporting bias by overestimating the effect of vitamin D.

The findings of this current meta-analysis suggest that vitamin D supplementation reduces TGAb and TPOAb titre in patients with HT. The effect was increased if patients received vitamin D_3 and the duration of treatment was >3 months. More randomized, double-blind, placebo-controlled trials with longer follow-up durations are required to confirm these preliminary findings.

Author contributions

Jingwen Zhang and Hong Li designed the study. Jingwen Zhang and Yuting Chen independently carried out the literature search and screening of articles. Hongyan Li analysed the data. Jingwen Zhang and Yuting Chen wrote the manuscript. Hongyan Li helped edit the manuscript; Hong Li revised the manuscript. All authors read and approved the final version of the manuscript.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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ORCID iD

Hong Li https://orcid.org/0000-0002-9614-2964

Supplemental material

Supplemental material for this article is available online.

References

1. Lorini R, Gastaldi R, Traggiai C, et al. Hashimoto's Thyroiditis. *Pediatr Endocrinol Rev* 2003; 1: 205–211.

2. Caturegli P, Kimura H, Rocchi R, et al. Autoimmune thyroid diseases. *Curr Opin Rheumatol* 2007; 19: 44–48. DOI: 10.1097/BOR.0b013e3280113d1a.

3. Hiromatsu Y, Satoh H and Amino N. Hashimoto's thyroiditis: history and future outlook. *Hormones (Athens)* 2013; 12: 12–18. DOI: 10.1007/bf03401282.

4. Ralli M, Angeletti D, Fiore M, et al. Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. *Autoimmun Rev* 2020; 19: 102649. DOI: 10.1016/j.autrev.2020.102649.

5. Bossowski A and Urban M. Serum levels of cytokines in children and adolescents with Graves' disease and non-toxic nodular goiter. *J Pediatr Endocrinol Metab* 2001; 14: 741–747. DOI: 10.1515/jpem.2001.14.6.741.

6. Štefanić M and Tokić S. Serum 25-hydoxyvitamin D concentrations in relation to Hashimoto's thyroiditis: a systematic review, meta-analysis and meta-regression of observational studies. *Eur J Nutr* 2020; 59: 859–872. DOI: 10.1007/s00394-019-01991-w.

7. Simsek Y, Cakir I, Yetmis M, et al. Effects of Vitamin D treatment on thyroid autoimmunity. *J Res Med Sci* 2016; 21: 85. DOI: 10.4103/1735-1995.192501.

8. Zhao L, Wang L and Fu B. Clinical application of calcitriol in Hashimoto's thyroiditis with hypothyroidism. *Medical Review* 2016; 22: 2410–2412.

9. Jia R. Observation on the efficacy of calcitriol combined with levothyroxine sodium tablets in Hashimoto's thyroiditis with hypothyroidism. *Journal of Medical Forum* 2020; 41: 133–135.

10. Yin H, Gu J, Guo X, et al. Application of calcitriol in hypothyroidism patients with Hashimoto's thyroiditis. *Journal of Medical Forum* 2019; 40: 140–142.

11. Han Y, Chen YJ, Li YM, et al. Effect of calcitriol treatment on Hashimoto's thyroiditis with hypothyroidism. *Chinese Clinical Research* 2015; 28: 17–19. DOI:10.13429/j.cnki.cjcr.2015.01.006.

12. Chahardoli R, Saboor-Yaraghi AA, Amouzegar A, et al. Can Supplementation

with Vitamin D Modify Thyroid Autoantibodies (Anti-TPO Ab, Anti-Tg Ab) and Thyroid Profile (T3, T4, TSH) in Hashimoto's Thyroiditis? A Double Blind, Randomized Clinical Trial. *Horm Metab Res* 2019; 51: 296–301. DOI: 10.1055/a-0856-1044.

13. Vahabi Anaraki P, Aminorroaya A, Amini M, et al. Effect of Vitamin D deficiency treatment on thyroid function and autoimmunity markers in Hashimoto's thyroiditis: A double-blind randomized placebo-controlled clinical trial. *J Res Med Sci* 2017; 22: 103. DOI: 10.4103/jrms.JRMS_1048_16.

14. Knutsen KV, Madar AA, Brekke M, et al. Effect of Vitamin D on Thyroid Autoimmunity: A Randomized, Double-Blind, Controlled Trial Among Ethnic Minorities. *J Endocr Soc* 2017; 1: 470–479. DOI: 10.1210/js.2017-00037.

15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535. DOI: 10.1136/bmj.b2535.

16. Wang S, Wu Y, Zuo Z, et al. The effect of vitamin D supplementation on thyroid autoantibody levels in the treatment of autoimmune thyroiditis: a systematic review and a meta-analysis. *Endocrine* 2018; 59: 499–505.

17. Pearce EN, Farwell AP and Braverman LE. Thyroiditis. *N Engl J Med* 2003; 348: 2646–2655. DOI: 10.1056/NEJMra021194.

18. Ajjan RA and Weetman AP. The Pathogenesis of Hashimoto's Thyroiditis: Further Developments in our Understanding. *Horm Metab Res* 2015; 47: 702–710. DOI: 10.1055/s-0035-1548832.

19. Safdari V, Alijani E, Nemati M, et al. Imbalances in T Cell-Related Transcription Factors Among Patients with Hashimoto's Thyroiditis. *Sultan Qaboos Univ Med J* 2017; 17: e174–e180. DOI: 10.18295/squmj.2016.17.02.007.

20. Ząbczyńska M, Polak K, Kozłowska K, et al. The Contribution of IgG Glycosylation to Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC) in Hashimoto's Thyroiditis: An in Vitro Model of Thyroid Autoimmunity. *Biomolecules* 2020; 10: 171. DOI: 10.3390/biom10020171.

21. Pyzik A, Grywalska E, Matyjaszek-Matuszek B, et al. Immune disorders in Hashimoto's thyroiditis: what do we know so far? *J Immunol Res* 2015; 2015: 979167. DOI: 10.1155/2015/979167.

22. Ramhøj L, Svingen T, Frädrich C, et al. Perinatal exposure to the thyroperoxidase inhibitors methimazole and amitrole perturbs thyroid hormone system signaling and alters motor activity in rat offspring. *Toxicol Lett* 2021: S0378-4274(21)00863-8. DOI: 10.1016/j.toxlet.2021.10.010.

23. Gerenova JB, Manolova IM and Tzoneva VI. Clinical significance of autoantibodies to parietal cells in patients with autoimmune thyroid diseases. *Folia Med (Plovdiv)* 2013; 55: 26–32. DOI: 10.2478/folmed-2013-0014.

24. Aliesky H, Courtney CL, Rapoport B, et al. Thyroid autoantibodies are rare in nonhuman great apes and hypothyroidism cannot be attributed to thyroid autoimmunity. *Endocrinology* 2013; 154: 4896–4907. DOI: 10.1210/en.2013-1717.

25. Li Y, Kim J, Diana T, et al. A novel bioassay for anti-thyrotrophin receptor autoantibodies detects both thyroid-blocking and stimulating activity. *Clin Exp Immunol* 2013; 173: 390–397. DOI: 10.1111/cei.12129.

26. Mattozzi S, Sabater L, Escudero D, et al. Hashimoto encephalopathy in the 21st century. *Neurology* 2020; 94: e217–e224.

27. Ercoli T, Defazio G and Muroni A. Cerebellar Syndrome Associated with Thyroid Disorders. *Cerebellum* 2019; 18: 932–940.

28. Valencia-Sanchez C, Pittock SJ, Mead-Harvey C, et al. Brain dysfunction and thyroid antibodies: autoimmune diagnosis and misdiagnosis. *Brain Commun* 2021; 3: fcaa233.

29. Ercoli T, Defazio G and Muroni A. Status epilepticus in Hashimoto's encephalopathy. *Seizure* 2019; 70: 1–5.

30. Alagarasu K. Immunomodulatory effect of vitamin D on immune response to dengue virus infection. *Vitam Horm* 2021; 117: 239–252. DOI: 10.1016/bs.vh.2021.06.001.

31. Lopez D, Al-Jaberi F, Woetmann A, et al. Macrophages Control the Bioavailability of

Vitamin D and Vitamin D-Regulated T Cell Responses. *Front Immunol* 2021; 12: 722806. DOI: 10.3389/fimmu.2021.722806.

32. Chen S, Sims GP, Chen XX, et al. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation.

J Immunol 2007; 179: 1634–1647. DOI: 10.4049/jimmunol.179.3.1634.

33. Heine G, Niesner U, Chang HD, et al. 1,25-dihydroxyvitamin D(3) promotes IL-10 production in human B cells. *Eur J Immunol* 2008; 38: 2210–2218. DOI: 10.1002/eji.200838216.