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RESEARCH ARTICLE

Vitamin D in patients with Hashimoto's disease: a systematic review and meta-analysis

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Abstract

One of the most common thyroid dysfunctions is Hashimoto's disease (HD), characterized by the production of specific antibodies against thyroid gland antigens (Anti-Tg and Anti-TPO). Recent studies have suggested that vitamin D supplementation, associated with levothyroxine, may contribute to the control of this autoimmune disease. However, secondary studies on this topic, such as systematic reviews and meta-analyses, are still scarce. Thus, the present study aimed to evaluate the efficacy and safety of vitamin D in patients with HD through a systematic review with meta-analysis. Randomized clinical trials were selected on the Pubmed, Scopus, and Web of Science databases. Studies comparing groups of HD patients supplemented with vitamin D and non-supplemented HD patients were included. The following outcomes were considered: TSH, T3, T4, Anti-Tg, Anti-TPO, and adverse drug reactions. The risk of bias was performed according to the Cochrane recommendations (RoB v. 2.0), and the quality of evidence was evaluated by the GRADE system. A total of 766 studies were identified in the databases, of which 7 met the eligibility criteria. None of the studies indicated the occurrence of adverse reactions with vitamin D supplementation in any administered dosage. Supplemented patients had a significant reduction in serum TSH levels compared to the control group (mean difference = -0.180 (95% CI [-0.316 to -0.045]), p = 0.009), suggesting that thyroid function was more controlled in the intervention group. However, for the other outcomes, no statistically significant differences were observed between the groups. Additionally, most of included articles (n=5/7) had some concerns or high risk of bias, and the quality of evidence revealed a moderate confidence for almost all outcomes; so the results must be interpreted with caution. Thus, more consistent, and robust clinical trials need to be carried out to confirm the efficacy of vitamin D supplementation in patients with HD.

Keywords: Hashimoto's Disease. Systematic Review. Meta-Analysis. Vitamin D.

How to cite

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1. INTRODUCTION

Hashimoto's disease (HD) is a chronic autoimmune thyroid disease caused by genetic and environmental conditions, characterized by the production of specific antibodies against antigens of the thyroid gland (thyroperoxidase and thyroglobulin)[1-3]. This disease was first described in 1912 by Hakaru Hashimoto and represents the most common cause of hypothyroidism in adults, mainly in developed countries[1-5].

Anti-thyroperoxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) antibodies attack the thyroid follicles, impairing their functionality[2,6]. In this sense, the production of the thyroid hormones triiodothyronine (T3) and thyroxine (T4) is compromised, with a compensatory increase in thyroid-stimulating hormone (TSH) levels[2,6]. The diagnosis and monitoring of the evolution of this disease are basically carried out by measuring the aforementioned antibodies and thyroid hormones, as well as by conducting thyroid imaging examinations[2,6].

Similar to other etiologies of hypothyroidism, the main signs and symptoms are tiredness, drowsiness, weight gain, constipation, dry skin, hair loss, and hypercholesterolemia[5,6]. Additionally, the treatment of HD is initially based on the administration of low doses of fasting levothyroxine (12.5 to 25 mcg), with subsequent dosage adjustments according to the results of laboratory tests[6,7]. The goals of therapy are symptom relief and maintenance of serum TSH levels within the reference range[5-7].

Recent clinical and observational studies have suggested that vitamin D supplementation, associated with standard therapy (levothyroxine), can contribute to the control of this and other autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, due to its immunomodulatory action[8-12]. Previous studies have shown that vitamin D can suppress the autoimmune reaction and consequently reduce the serum levels of autoantibodies[13-22]. Additionally, recent meta-analyses found that patients with HD are more likely to have reduced serum vitamin D levels compared to healthy patients[23,24]. However, these meta-analyses did not evaluate the efficacy and safety of the vitamin D supplementation in patients with HD, once the authors aimed to establish the association between the serum levels in these patients compared to healthy people[23,24].

So, it is not clear whether vitamin D supplementation is, in fact, effective and safe in the treatment of HD[24]. Additionally, current guidelines did not describe the possibility of vitamin D supplementation in patients with HD[2,6]. Thus, new studies, especially systematic reviews, and meta-analyses, are necessary. Moreover, it is known that such studies have a better level of evidence compared to primary studies, as they group, synthesize, and allow a more robust critical assessment on a given subject[25]. Therefore, this study aimed to evaluate the efficacy and safety of vitamin D supplementation in patients with HD, through a systematic review and meta-analysis.

2. METHODS

2.1 Planning the review

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Collaboration recommendations[25,26]. This review was submitted to the PROSPERO platform (CRD42021235430).

All steps of this study, including the study selection (screening and full text appraisal), data extraction, and the quality analysis were performed by two authors independently, with a third author to solve discrepancies.

2.2 Searches and study selection

Systematic searches were conducted in PubMed (which included MEDLINE and PubMed Central databases), Scopus, and Web of Science, without limits on timeframe or language (updated on 10th October 2021). To extract the studies from these databases and remove the duplicated articles, we use the Endnote® software (v. 7.0). The full search strategies are

available in Table S1 of the Supplementary Material (DOI 10.17605/OSF.IO/9TH2G). Additionally, the reference lists of the included studies were manually searched to retrieve other relevant records. Titles and abstracts of the articles identified during the database searches and on manual search were screened for eligibility, and relevant studies were read in full. This process was performed in standardized sheets on Microsoft Excel®. The PICOS (population, intervention, control, outcomes, and study design) model was used to select potential studies for data extraction:

- P (*population*): patients diagnosed with Hashimoto's Disease (regardless of age).
- I (*intervention*): patients supplemented with vitamin D (associated or not with levothyroxine).
- C (*control*): patients not supplemented with vitamin D, placebo, or patients using other therapies.
- O (*outcomes*): serum levels of thyroid hormones (T3, T4, TSH) and antibodies (Anti-TPO and Anti-Tg) and adverse reactions.
- S (*study design*): randomized clinical trials.

Other study designs, reprint (i.e same article published in more than one journal), articles published in non-Roman characters, congress abstracts, theses and dissertations, and studies that did not assess the outcomes of interest were excluded. Studies that included pregnancy patients or other thyroid diseases (such as Graves' disease) were also excluded.

2.3 Data extraction and quality assessment

The following data were extracted by two reviewers independently, in standardized sheets on Microsoft Excel: (i) study and baseline characteristics (authors names, year of publication, country, sample size, patient age, trial duration); (ii) evaluated treatments, with detail (dosage, duration of treatment); (iii) clinical outcome results (serum levels of thyroid hormones (T3, T4, TSH) and antibodies (Anti-TPO Ab and Anti-Tg Ab) and adverse reactions). The risk of bias of the included articles was evaluated according to the Cochrane Collaboration's tool (RoB version 2.0), by two reviewers independently[25]. Additionally, the quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group[27].

2.4 Statistical analyses

Pairwise meta-analyses of randomized clinical trials were performed in *Comprehensive Meta-Analysis* v 2.2 software (Biostat, Englewood, NJ, USA). Meta-analyses for the following outcomes were performed: serum levels of T3, T4, TSH, Anti-TPO Ab, and Anti-Tg Ab. The random-effects model and the inverse variance method were used to interpolate the effect measures of each study, with a 95% confidence interval (CI). The effect sizes were the difference in means or standardized mean difference, considering that all the outcomes of interest were continuous. Results with p values of <0.05 were considered statistically significant. The meta-analyses were expressed as forest plots. The heterogeneity between the assays was estimated using the relative index of inconsistency I2 (I2>50% indicates high and significant heterogeneity). The sensitivity analysis consisted of the hypothetical sequential removal of studies from the meta-analysis. Changes in statistical methods and models were also tested.

3. RESULTS

The systematic search of the databases identified 766 records. After removing duplicates, 492 articles were selected for screening, of which 439 were excluded and 53 were read in full. A further 46 records were excluded at this point, and 7 had their data extracted[7,28-33] (Figure 1). The studies excluded after full-text reading are reported in Table S2 of the Supplementary Material, with justifications (DOI 10.17605/OSF.IO/9TH2G).

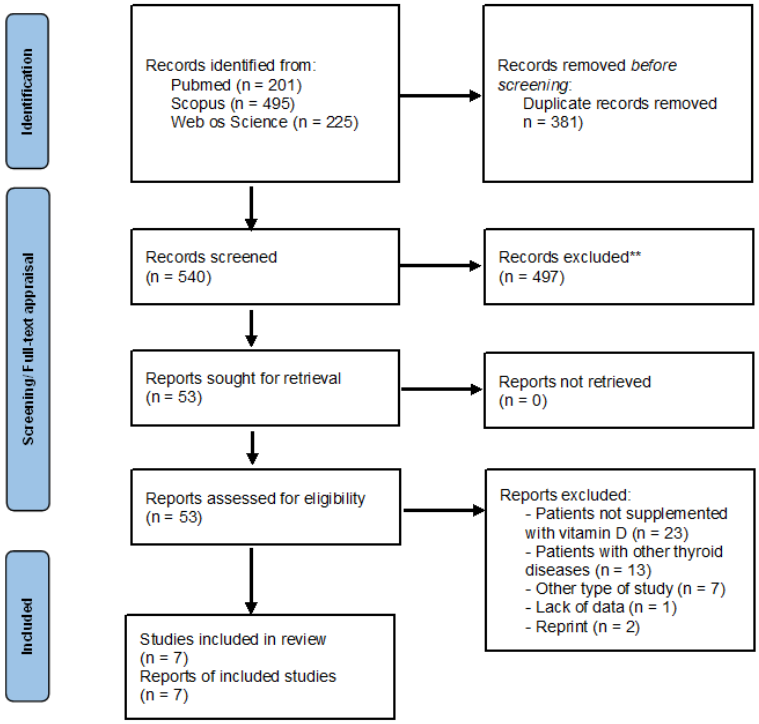

Figure 1. Flowchart of the systematic review.

As shown in Table 1, most of the included studies were multicentric and were published between 2016 and 2019. This systematic review included 566 patients, most of whom were female (71%), with ages ranging from 28 to 45 years. The dose of vitamin D supplementation ranged from 1,000 IU per day to 60,000 IU per week. A placebo was the comparator in three studies[7,28,30] and two studies used active comparators[29,32], while the other two studies did not use any comparator[31,33]. The use of levothyroxine was present in most studies; however, two of the studies did not report this information[30,32]. The shortest duration of vitamin D supplementation was 4 weeks, and the longest was 24 weeks.

Table 1. Baseline characteristics of the included studies

Author, year	Country	Interventions	Dose of Vitamin D	Duration of treatment	Dosage of Vitamin D	N	Numbers of patients using Levothyroxine	Age (years)*	Men (n, %)
Anaraki, 2017[28]	Iran	Vitamin D	50.000 IU	12 Weeks	Once a week	30	13	43.55 (1.56)	9 (30)
		Placebo	NR	12 Weeks	Once a week	26	8	44.12 (1.56)	11 (41)
Chahardoli, 2019[7]	Iran	Vitamin D	50.000 IU	12 Weeks	Once a week	21	21	36.4 (5.2)	0 (0)
		Placebo	NR	12 Weeks	Once a week	21	21	35.9 (7.8)	0 (0)
Chaudhary, 2016[29]	India	Vitamin D	60.000 IU	08 Weeks	Once a week	50	50	28.48 (6.57)	11 (22)
		Calcium carbonate	1.250 mg	08 Weeks	Once a day	50	50	27.86 (7.29)	13 (26)
Knusten, 2017[30]	Norway	Vitamin D	1.000 IU	16 Weeks	Once a day	75	NR	W= 35 (7.5) / M= 40 (9.1)	26 (31)
		Vitamin D	400 IU	16 Weeks	Once a day	69	NR	W= 36 (7.8) / M= 40 (6.6)	24 (28)
		Placebo	NR	16 Weeks	Once a day	71	NR	W= 38 (7.6) / M= 39 (7.8)	19 (23)
Krysiak, 2017[31]	Poland	No intervention	NR	24 Weeks	Once a day	18	18	35	0 (0)

Table 1. Continued...

Author, year	Country	Interventions	Dose of Vitamin D	Duration of treatment	Dosage of Vitamin D	N	Numbers of patients using Levothyroxine	Age (years)*	Men (n, %)
Krysiak, 2018[32]	Poland	Vitamin D	2.000 IU	24 Weeks	Once a day	16	16	34	0 (0)
		Vitamin D	4.000 IU	24 Weeks	Once a day	20	NR	35 (8)	20 (100)
		Selenomethionine	200 µg	24 Weeks	Once a day	17	NR	34 (7)	17 (100)
Simsek, 2016[33]	Turkey	Vitamin D	1.000 IU	04 Weeks	Once a day	46	5	35.8 (12)	9 (20)
		Exposure to the sun and diet control	NA	04 Weeks	Once a day	36	1	39.7 (12.6)	5 (14)

***** Data are expressed as mean and standard deviation.
Legend: N: number of patients; NR: not reported; M – men; IU: International Units; W: women.

Table 2 details the results of the selected studies, including the results of antibodies (Anti-TPO, Anti-Tg), thyroid hormones (TSH, T3, and T4), and serum levels of 25-hydroxyvitamin D (25 OHD). The studies pointed that the vitamin D was safe, once no adverse reactions were observed. However, not all studies reported all outcomes of interest.

Table 2 – Efficacy results of the included studies

Author, year	Interventions	Anti-TPO (UI/mL)*	Anti-Tg U/mL*	TSH (µIU/ml)*	T3 (ng/ml)*	T4 (ng/ml)*	25 (OH)D*
Anaraki, 2017[28]	Vitamin D	734 (102.93)	NR	NR	3.79 (0.26)	NR	9.01 (0.09) mg/dL
	Placebo	750.03 (108.71)	NR	NR	4.31 (0.27) ng/L	NR	8.85 (0.13) mg/dL
Chahardoli, 2019[7]	Vitamin D	118.1 (97.9)	140.2 (134.3)	1.83 (1.4)	1.28 (0.35)	0.94 (0.15)	NR
	Placebo	181.6 (122.5)	176.7 (167.1)	2.77 (1.9)	1.31 (0.34)	0.86 (0.12)	NR
Chaudhary, 2016[29]	Vitamin D	387 (1146)	NR	3.16 (2.07)	NR	1.27 (0.20)	95.52 (124) nmol/L
	Calcium carbonate	553.5 (1002)	NR	3.39 (2.19)	NR	1.30 (0.14)	41.61 (100.06) nmol/L
Knusten, 2017[30]	Vitamin D	147(317)	NR	2.2 (2.9)	NR	1.24 (0.15)	NR
	Vitamin D	81 (157)	NR	1.7 (0.8)	NR	1.28 (0.13)	NR
	Placebo	105 (217)	NR	2.3 (2.4)	NR	1.25 (0.13)	NR
Krysiak, 2017[31]	No intervention	1410 (425)	1212 (385)	4.5 (1.0)	3.8 (0.6)	1.1 (0.17)	47 (12) ng/ml
	Vitamin D	955 (358)	934 (415)	4.1 (1.5)	4.2 (0.6)	1.19 (0.17)	64 (10) ng/ml
Krysiak, 2018[32]	Vitamin D	638 (211)	2.7 (0.7)	3.6 (0.6)	NR	NR	NR
	Selenomethionine	649 (783)	2.6 (0.6)	3.8 (0.8)	NR	NR	NR
Simsek, 2016[33]	Vitamin D	210 (7.6-600)	NR	1.2 (0.4)	NR	NR	NR
	Exposure to the sun and diet control	166 (7.9-534)	NR	1.4 (1.3)	NR	NR	NR

***** Data are expressed as mean and standard deviation, except to the study of Simsek, 2016 (the Anti-TPO is expressed in mean, minimum and maximum values). Legend: Anti-TPO: Thyroid Peroxidase Antibody; Anti-Tg: Antithyroglobulin Antibody; TSH: Thyroid-stimulating Hormone; T3: Triiodothyronine; T4: Thyroxine; NR: not reported.

The risk of bias assessment revealed that most studies had high overall risk or some concerns (n = 5/7; 71.42%)[7,28,29,31,32]. The main domains responsible for increasing the risk of bias were randomization process, deviations from the intended interventions, and measurement of outcome. In general, these studies did not report the randomization and allocation concealment process in detail and did not report the results completely. Only two studies had a low risk of bias[30,33] (Figure 2).

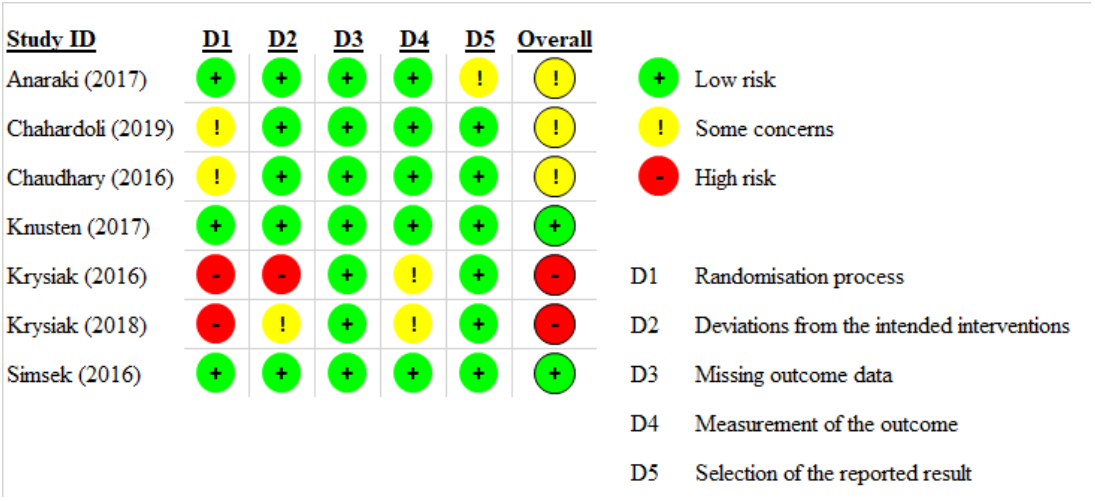

Figure 2 – Risk of bias of included studies

Considering the results reported by the seven primary studies included in this systematic review, it was possible to construct four meta-analyses for the following outcomes: TSH, T3, T4, Anti-TPO, and Anti-Tg. For the study by Knutsen et al.[30], it should be noted that the patients that received vitamin D 1,000 IU per day were considered as the intervention group.

The group that received vitamin D (intervention group) had statistically significantly lower TSH values compared to the control group (mean difference = -0.180 (95% CI [-0.316 to -0.045]), p = 0.009). This result suggests that thyroid function was more controlled in the intervention group than in the control group, but only in terms of TSH values (Figure 3). Additionally, this meta-analysis showed null heterogeneity (I2 = 0%, p = 0.575).

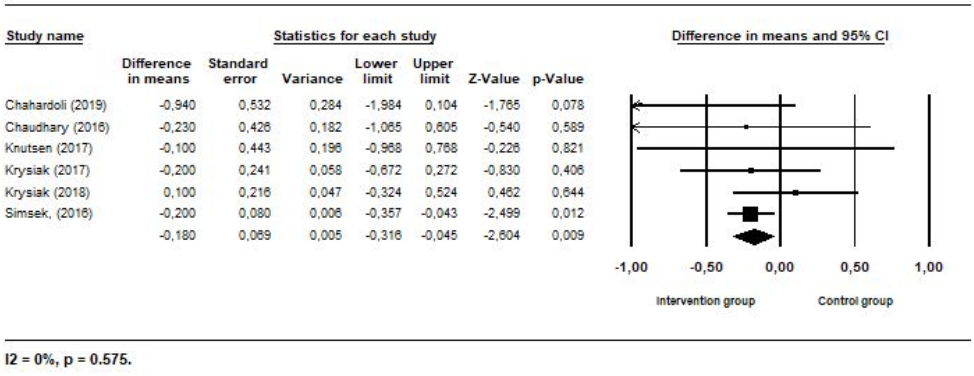

Figure 3. Forest plot for the TSH outcome (mUI/mL).

In parallel, there was no statistically significant difference between the groups regarding the values of T4 (mean difference = -0.024 (95% CI [-0.058 to 0.010]), p = 0.171) (Figure 4). The heterogeneity of this meta-analysis was also null (I2 = 0%).

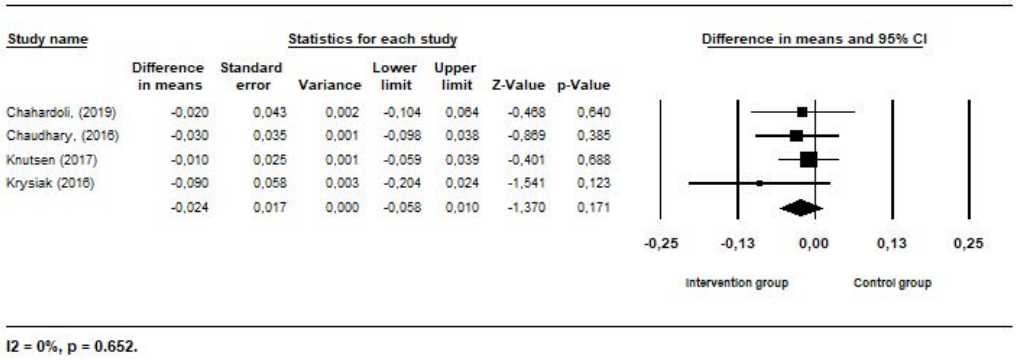

Figure 4. Forest plot for the T4 outcome (µg/dL).

For the other outcomes (Anti-Tg, Anti-TPO, and T3), the meta-analyses did not reveal statistically significant differences between the groups, and the heterogeneity was high in all of them (Figures 5 to 7). Few studies could be included for the T3 meta-analysis (n = 3), since the authors failed to report all their results (mean difference = -0.313 (95% CI [-0.664 to 0.037]), p = 0.080, I2 = 84.22%). The study by Anaraki et al.[28] was mainly responsible for the high heterogeneity; however, even with its withdrawal, the I2 still remained high (I2 = 64%).

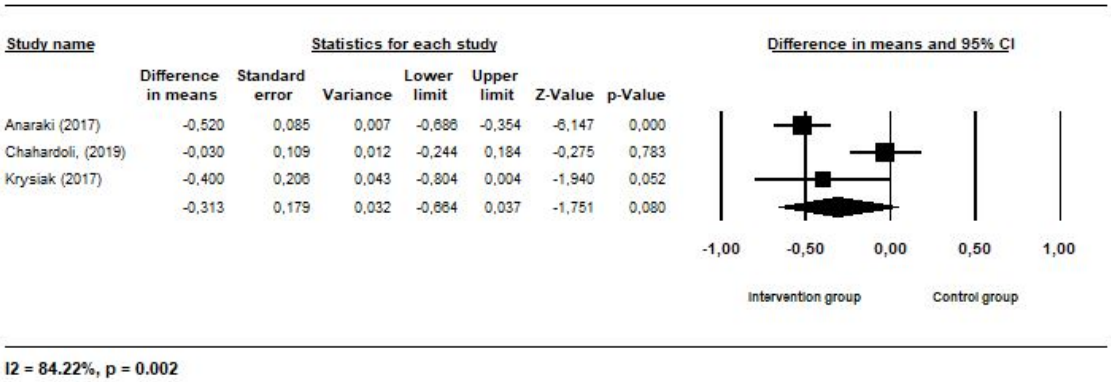

Figure 5. Forest plot for the T3 outcome (ng/mL).

The pooled effect size (standardized mean difference - SMD) for the Anti-Tg outcome was 0.187 (CI 95% [-0.309 to 0.423], p = 0.760), with a high heterogeneity (Figure 6). The sensitivity analysis showed that the study by Krysiak et al.[31] was the main study responsible for the heterogeneity in the Anti-Tg meta-analysis since its removal led to an I2 result of 33%. Similarly, for the Anti-TPO outcome, there was no difference between the groups (SMD 0.185 (CI 95% [-0.319 to 0.407], p=0.812), I2 = 67.15%) (Figure 7). The study that most contributed to the high heterogeneity of this meta-analysis was that of Krysiak et al.[32], because the I2 result was equal to 11.03% when it was removed from the analysis.

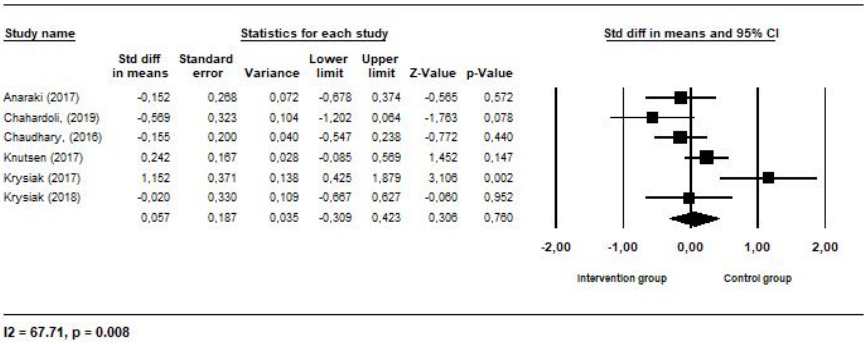

Figure 6. Forest plot for the Anti-Tg outcome (IU/mL).

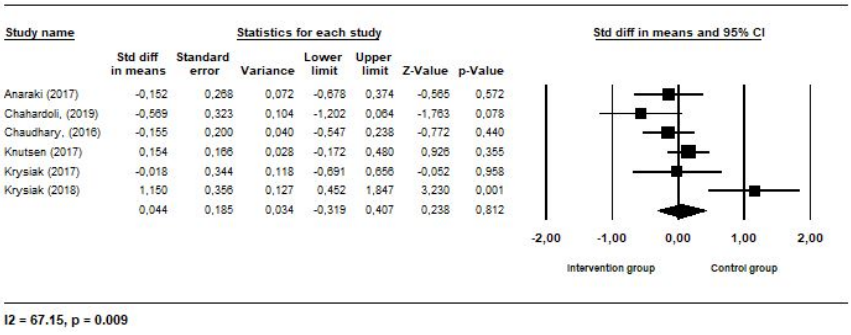

Figure 7. Forest plot for the Anti-TPO outcome (UI/mL).

Table 3 presents the results of the quality of evidence assessment (GRADE) for the evaluated outcomes: serum levels of thyroid hormones (T3, T4, TSH) and antibodies (Anti-TPO Ab and Anti-Tg Ab). In most cases, the quality of evidence revealed a moderate certainty, especially because of the risk of bias assessment. For the T3 outcome, the confidence was very low, because of other reasons too: inconsistency, once the heterogeneity was high, and imprecision, due to the wide confidence interval.

Table 3 - Evidence quality assessment (GRADE)

Certainty assessment							
N. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirect evidence**	**Imprecision**	**Other considerations**	**Certainty**
Outcome: TSH							
6	RCT	serious[a]	no serious	no serious	no serious	None	⊕⊕⊕◯ Moderate
Outcome: T4							
4	RCT	serious[a]	no serious	no serious	no serious	None	⊕⊕⊕◯ Moderate
Outcome: T3							
3	RCT	serious[a]	serious[b]	no serious	serious[c]	None	⊕◯◯◯ Very Low
Outcome: Anti-TG							
6	RCT	serious[a]	no serious	no serious	no serious	None	⊕⊕⊕◯ Moderate
Outcome: Anti-TPO							
6	RCT	serious[a]	no serious	no serious	no serious	None	⊕⊕⊕◯ Moderate

Explanations: N: number. a. Most studies had some concerns or high risk of bias. b. High heterogeneity. c. Wide confidence interval

4. DISCUSSION

The present systematic review and meta-analysis demonstrated that vitamin D supplementation promoted a serum reduction of TSH hormone in patients with Hashimoto's Disease (HD), revealing a better thyroid control compared to non-supplemented patients. However, this finding requires confirmation, since the intervention and control groups did not show statistically significant differences for the other tested substances (T3, T4, Anti-Tg, and Anti-TPO). Safety data were scarce, although the included studies did not indicate the occurrence of clinically important adverse events, suggesting that this vitamin is safe. Additionally, most studies had some concerns or high risk of bias according to the Rob 2 tool (n = 5/7), and the certainty of the evidence was moderate in most cases, according to the GRADE system; so the results of the meta-analyses should be interpreted with caution.

It is known that the reduction of TSH combined with an increase of T4 and T3 in patients with uncontrolled hypothyroidism is associated with good thyroid control[2,6]. However, the authors of the seven included primary studies did not report all the outcomes of interest, and some meta-analyses were built with only a few studies. Thus, further well-reported randomized clinical trials are necessary to confirm these findings.

We highlight that four of the six studies included in the TSH meta-analysis reported the use of levothyroxine associated with vitamin D[7,29,31,33]. Thus, the importance of hormone replacement for thyroid control cannot be excluded. However, the two studies[30,31] that did not report the use of levothyroxine revealed a significant reduction in TSH levels, suggesting that further studies need to be carried out to explore the real efficacy of vitamin D in HD.

Therefore, due to the scarcity of studies about this topic, the present systematic review questions whether vitamin D supplementation is necessary for all patients who have HD, or whether it is only necessary for those who have a deficiency or insufficiency of this vitamin. In the present study, it was not possible to clarify such this question, due to the limited evidence in the included studies, since only three of them mentioned the serum vitamin D dosage in the initial recruitment of the participants[28,29,31]. Additionally, it is still unclear which dose of vitamin D is ideal for these patients, since the included studies were heterogeneous in terms of the dosage.

Recently, two systematic reviews of randomized clinical trials about vitamin D in HD have been published[24,34]. One of them did not assess vitamin supplementation in patients with this disease but established a correlation between serum vitamin D levels and autoimmune hypothyroidism. Twenty-two studies were included in a pairwise meta-analysis, which revealed that patients with autoimmune thyroid diseases (including HD and Graves' disease) had lower levels of vitamin D (SMD = −0.99 [95% CI −1, 31 to −0.66]) and were more likely to have this vitamin deficiency (odds ratio (OR) = 2.99 [95% CI 1.88 to 4.74]) compared to healthy patients[24].

In parallel, the other systematic review[33] showed statistically significant differences for the levels of autoantibodies (Anti-Tg and Anti-TPO) between the intervention (vitamin D) and control (not supplemented) groups, in contrast to the present study, which did not identify differences for these outcomes. However, the patients selected in the study of Wang et al.[34] had HD or Graves' disease, revealing a more heterogeneous population compared to the present systematic review, which could compromise the results of their analysis. Additionally, despite including patients with two different thyroid diseases, the aforementioned systematic review selected fewer articles for analysis (n = 6), with a total of 344 patients, and did not evaluate other outcomes of interest, such as serum levels of thyroid hormones. Therefore, the present study contemplates more concrete and updated results about a more homogeneous population.

Additionally, a previous systematic review and meta-analysis of observational studies revealed a significant association between lower serum vitamin D and HD, compared with healthy patients (Cohen's d −0.62 (95% CI −0.89, −0.34; p<0.0001). Patients with HD had an OR of 3.21 (1.94–5.3; p<0.0001) for vitamin D deficiency (cut-off 20 ng/mL) against healthy

controls. However, this study did not evaluate the impact of the vitamin D supplementation on disease control, in terms of improvement in serum levels of thyroid hormones[23].

The present study has some limitations. Insufficient reporting of primary study results, such as the absence of the standard deviation of thyroid hormone averages, prevented all studies of the systematic review from being included in some meta-analyses. Additionally, it is not clear whether patients with HD used vitamin D only if the dosage of this substance was insufficient, as this information was not provided in all included studies. We also did not include grey literature as additional source on this review. However, despite these limitations, the present study corroborates previous investigations that point to a positive relationship between vitamin D supplementation in HD, although confirmation is necessary by conducting good-quality randomized clinical trials.

5. CONCLUSION

Considering the results obtained in this systematic review and meta-analysis, it is observed that vitamin D supplementation led to a decrease in TSH in patients with HD. However, the results of the other thyroid hormones did not show statistically significant differences, revealing conflicting evidence about the benefit of vitamin D in these patients. Additionally, the results of the meta-analyses should be interpreted with caution, once most of the included studies had some concerns or high risk of bias and the quality of evidence revealed a moderate confidence in most cases. Thus, consistent, and robust randomized clinical trials need to be carried out to confirm the real clinical implications of this vitamin in patients with HD.

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Authors' contributions

1. JMMFS contributed to study concept, study design, data collection, data interpretation, and writing of the manuscript.2. EVA contributed to data collection, data interpretation, and writing of the manuscript.3. ECOM contributed to data collection, data interpretation, and writing of the manuscript.
4. CAO contributed to data collection, data interpretation, and writing of the manuscript.5. AFB contributed to study concept, study design, data analysis, data interpretation, and reviewing of the manuscript.

SUPPLEMENTARY MATERIAL

The complementary information is available at OSF platform (DOI 10.17605/OSF.IO/9TH2G).