Thieme

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

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ABSTRACT

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune disorder characterized by the destruction of thyroid cells caused by leukocytes and antibody-mediated immune processes accompanied by hypothyroidism. In recent years, evidence has emerged pointing to various roles for vitamin D, including, proliferation and differentiation of normal and cancer cells, cardiovascular function, and immunomodulation. Vitamin D deficiency has been especially demonstrated in HT patients. The aim of this study was to investigate the effect of vitamin D on circulating thyroid autoantibodies and thyroid hormones profile (T4, T3, and TSH) in females with HT. Forty-two women with HT disease were enrolled in this randomized clinical trial study and divided into vitamin D and placebo groups. Patients in the vitamin D and placebo groups received 50 000 IU vitamin D and placebo pearls, weekly for 3 months, respectively. The serum levels of 25-hydroxy vitamin D [25(OH) D], Ca^{++}ion, anti-thyroperoxidase antibody (anti-TPO Ab), anti-thyroglobulin antibody (anti-Tg Ab), T4, T3, and TSH were measured at the baseline and at the end of the study using enzyme-linked immunosorbent assays. The results of this study showed a significant reduction of anti-Tg Ab and TSH hormone in the Vitamin D group compared to the start of the study; however, there was a no significant reduction of anti-TPO Ab in the Vitamin D group compared to the placebo group ($p = 0.08$). No significant changes were observed in the serum levels of T3 and T4 hormones. Therefore, vitamin D supplementation can be helpful for alleviation of the disease activity in HT patients; however, further well controlled, large, longitudinal studies are needed to determine whether it can be introduced in clinical practice.

Introduction

Hashimoto's thyroiditis (HT) was described in 1912 by Hakaru Hashimoto [1]. It is the most common cause of hypothyroidism, recorded in 4–9.5 % of the adult population depending on race and ethnicity [2]. The disease is initiated by infiltration of inflammatory cells into the thyroid gland and production of autoantibodies against some specific thyroid antigens. These disorders trigger fibrous replacement of the thyroid follicle cells resulting in hypothyroidism [3].

The biochemical characteristic of the disease is the presence of thyroid autoantibodies against 2 major thyroid antigens, thyroid peroxidase (TPO) and thyroglobulin (Tg). In HT, anti-thyroperoxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (anti-Tg Ab) are present in more than 90 % and 80 % of the patients,

respectively [4]. TPO is a key enzyme in the synthesis of the thyroid hormones, including thyroxine (T4) and triiodothyronine (T3). The thyroid hormones are made on Tg, an intra-follicle large glycoprotein, which also serves as a source for thyroid hormones. Tg is secreted into the circulation where its estimated half-life is approximately 3 days [5].

In spite of the high prevalence of HT, its exact mechanisms responsible for the disease pathogenesis are still not completely understood. HLA (human leukocyte antigen) has been known to be involved in multiple autoimmune disorders [6]. Some of the in vitro studies have shown the possibility of certain class II alleles to bind and present thyroid-specific antigens such as TSHR or Tg peptides [7]. Inappropriate expression of HLA class II antigens by thyroid epithelial cells can initiate autoimmune responses through direct thyroid self-antigen presentation [8]..

An autoimmune response is predominantly mediated by T helper-1 (Th1) type cytokines such as TNF-α, IFN-γ, and IL-2. However, in the pathogenesis of HT, according to the cytokine mRNA pattern, both Th1 and Th2 responses are involved with a deviation toward theTh1 response [9]. TH17 is a new subset of Th cells, which, may lead to autoimmunity in animal models like HT in addition to pro-inflammatory role [10].

Anti-Tg Ab accelerates theTh1/Th2 response by increasing the uptake of autoantigens via antigen-presenting cells (APCs) [11]. Furthermore, the correlation between the anti-TPO Ab levels and the production of TNF-α and IFN-γ has been demonstrated and recently confirmed by a study indicating that anti-TPO Ab seems to promote cytokine production, including IFN-γ, TNF-α, and IL-6 [12]. Serum anti-TPO Ab and anti-Tg Ab titers correlate positively with an increased inflammatory reaction in the thyroid and development of hypothyroidism and there is a strong correlation between the echo graphic pattern and the anti-TPO Ab level in Hashimoto patients [13, 14].

1,25-Dihydroxyvitamin D3 [1,25(OH)2D3], the biologically active form of vitamin D3, not only regulates calcium metabolism in the kidney and bone, but also exerts other biological activities, including immunomodulation, via the nuclear vitamin D receptor (VDR) expressed in APCs and activated immune cells. Besides that, the expression of 1α hydroxylase, (cyp27B1), which converts 25-hydroxyvitamin D [25(OH)D] to the active form, in many of these cells supports this hypothesis that vitamin D has immunomodulation effects [15]. These findings are further confirmed by the correlation between the polymorphisms of the VDR or the cyp27B1 gene and the pathogenesis of several autoimmune diseases [16, 17]. Vitamin D has important effects on monocytes and dendritic cells, including the inhibition of inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, and IL-12. Furthermore, it inhibits DC differentiation and maturation by decreased expression of MHC class II, co-stimulatory molecule and IL-12, which in turn leads to suppression of T cell proliferation and results in a shift from Th1 to Th2 phenotype [18].

Recent epidemiological studies indicate a relationship between thyroid autoimmunity and vitamin D deficiency [19]. A study showed decrease serum levels of 25(OH)D in patients with HT and this relationship persisted after adjustment for age, sex and body mass index (BMI) [20]. There is a link between vitamin D deficiency and the presence of anti-thyroid antibodies; in other words, these antibodies were significantly more common in vitamin D deficient patients compared to those with normal vitamin D levels [21].

In addition, both lower vitamin D levels and autoimmune thyroid disease (AITD) are more common in women. It has been shown that women have higher serum anti-Tg Ab and anti-TPO Ab levels, and lower serum 25(OH)D levels than men [22]. Furthermore, the association of lower vitamin D levels with higher prevalence of AITD has been found to be significant in premenopausal, but not in postmenopausal, women [23].

It has been reported that thyroid-stimulating hormone (TSH) levels are inversely correlated with vitamin D levels independent of thyroid hormone levels [24]. Taken together, the results of previous studies suggest a possible significant association between vitamin D deficiency and hypothyroidism. In the present study, the impact of vitamin D supplementation on the thyroid function and autoantibodies titers in women with HT was explored.

Subjects and Methods

In this randomized double-blind placebo-controlled clinical trial, 42 women (aged 18–48 years) with HT disease according to clinical symptoms of hypothyroidism with elevated anti-TPO Ab (≥ 38 IU/ml) whose disease was confirmed by an endocrinologist were enrolled. They were treated with L-thyroxine (LT4) due to hypothyroidism. The subjects were selected from patients who were referred to Erfan Hospital and Imam Khomeini Hospital Complex, Tehran, Iran for Periodic examinations. The inclusion period started in October 2016 and the last person was recruited in December 2016. The study was approved by the Ethics Committee of Shahid Bheshti University Of Medical Sciences and Tehran University of Medical Sciences and registered in the Iranian registry of Clinical Trials (IRCT2016110130644N1). Written informed consent was obtained from all participants at the beginning of this study. The patients were informed of the aim and possible risks of this clinical trial and were free to leave the study at any time.

Exclusion criteria included evidence of any disease affecting the immune system balance, type 1 diabetes, multiple sclerosis, inflammatory bowel disease, and other autoimmune diseases, abnormalities of the liver enzyme function, malnutrition, BMI < 18 kg/m^2 or BMI > 40 kg/m^2, menopause, pregnancy, or lactation. Woman who used vitamin D, vitamin A, or omega-3 supplements during the past 3 months were not enrolled in the study.

Random permuted blocks were used for allocation. The participants were divided into 2 randomly allocated groups (vitamin D or placebo). Pearls containing placebo and vitamin D were coded by a third person as A and B packages, respectively. The vitamin D group received 50 000 IU of cholecalciferol [1,25(OH)2D3] weekly, and the placebo group received one placebo pearl (edible paraffin oil) per week.

The duration of the intervention was 3 months. Compliance was assessed on the last visit by pearl count (> 90 % used pearls). For all participants, sun exposure was assessed in the beginning and at end of the study. The duration of the sun exposure was assessed according to minutes/hours in a usual day.

Dietary intakes were assessed before and after the study based on 1-day recall and 2-day records, after converting food to its weights were analyzed for energy and nutrients with the Nutritionist IV software program (First Data Inc., Hearst Corp., San Bruno, CA, USA). Blood samples were collected by venipuncture before

and after the intervention. The blood samples were allowed to clot for 30 min at room temperature. After centrifugation at 1500 RPM for 10 min, the serum was separated and stored at − 80 °C until assayed. The serum levels of TSH, T4, and T3 were measured by the enzyme-linked immunosorbent assay (ELISA) method (Chemux BioScience, USA). The serum level of 25(OH)D and anti-Tg Ab and anti-TPO Ab titers were measured by the ELISA method using reagents obtained from Monobind Inc. (Lake Forest, CA, USA), and thyroid kit a-TPO Ref. 3401 from AESKU Diagnostics GmbH, Wendelsheim, Germany. The detection sensitivity of the kits was 0.67 ng/ml, 1.94 IU/ml, and 10 IU/ml, respectively. The plasma calcium level was measured using a colorimetric kit (Pars Azmun, Tehran, Iran). All samples were assayed in duplicates.

Statistical analysis

According to similar studies and assuming an alpha error of 5 % and study power of 90 %, and the possibility of attrition the sample size was determined in 21 subjects in each group using the following sample size formula:

$$n = \left[\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)\delta/d\right]2$$

The normality of data distribution was checked using the Kolmogorov–Smirnov goodness-of-fit test. For data that followed a normal distribution, the independent sample t-test and paired t-test were applied to compare the variables between the 2 groups and measures within-group, respectively.

If data did not follow a normal distribution, a parametric test was used after log transformation. Between-group and within-group comparisons for nonparametric data were done using and 2 independent sample tests (Mann–Whitney U), and 2 related sample tests (Wilcoxon) respectively. The test level for statistical significance of the differences between the 2 treatment arms was set as $p \leq 0.05$ for all tests. Analyses were performed by SPSS 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp, USA).

Results

Forty-two women with HT disease were enrolled in this study. Two subjects withdrew from the study because of drug alternation and use of corticosteroid, and 40 participants completed the study (▶ **Fig. 1S**). There was no significant difference in age, weight, body mass index, daily levothyroxine dose, and serum level of Vitamin D between the vitamin D and placebo groups at baseline (▶ **Table 1**). Similarly, no significant difference was observed in the calorie and macronutrients, except for vitamin D intake, between the 2 groups (▶ **Table 2**). The duration of exposure to sunlight was not significantly different between the groups in the beginning and at the end of the study. The mean levels of TSH, T3, T4, 25(OH) D, anti-TPO Ab, and anti-Tg Ab were also similar in both groups before supplementation (▶ **Table 3**). Neither significant adverse effects nor any complications were observed throughout the study period, and the rate of compliance was 100 %.

After supplementation, the serum levels of 25(OH) D and calcium increased significantly and the levels of TSH and anti-Tg Ab decreased significantly in the vitamin D group compared to baseline. However, in the placebo group, the serum Level of T4 decreased significantly compared to baseline. There was none significant reduction of anti-TPO Ab in Vitamin D group compared to placebo group. The levels of anti-TPO Ab and anti-Tg Ab decreased by 15.3 and 28.2 % in vitamin D-supplemented group, respectively. Vitamin D did not affect the serum levels of T3 and T4 (▶ **Table 3**). Before supplementation, the serum level of 25(OH) D had a non-significant reverse correlation with anti-TPO Ab ($r = -0.251$, $p = 0.119$) and anti-Tg Ab ($r = -0.138$, $p = 0.397$), while levothyroxine (LT4) had a significant inverse correlation with anti- TPO Ab ($r = -0.34$, $p = 0.013$) and anti-Tg Ab ($r = -0.403$, $p = 0.011$) (▶ **Fig. 1,2**).

Discussion

This study showed that vitamin D administration decreased the serum levels anti-Tg Ab ($p = 0.009$) and TSH ($p = 0.027$) significantly compared to baseline. However, no significant differences were observed between vitamin-supplemented and placebo groups. In the vitamin D group, anti-TPO Ab decreased non-significantly ($p = 0.08$) compared to the placebo group; however, we believe that if the study lasted for at least 6 months, it was possible that we obtained different results.

The results of this study are in agreement with the results of a study by Krysiak et al. in which woman with postpartum thyroiditis and vitamin D deficiency or insufficiency were treated with oral vitamin D (4000 IU daily) and (2000 IU daily), respectively, while women with normal 25-OH vitamin D levels were not treated [25]. Contrary to our study results, the effect on anti-TPO Ab titers was stronger than the effect on anti-Tg Ab titers.

Kivity et al. evaluated serum vitamin D levels in relation to anti-TPO Ab and anti-Tg Ab and reported a significantly higher prevalence of vitamin D deficiency (< 10 ng/ml) in HT patients ($p = 0.001$). As a consequence, vitamin D deficiency was found to be correlated with the presence of anti-thyroid antibodies ($p = 0.01$) [26]).

In a case-control study, Unal et al. found that anti-TPO Ab ($p = 0.003$) and anti-Tg Ab ($p = 0.02$) titers were significantly higher in vitamin D deficient subjects than in vitamin D sufficient AITD patients [27]. However, other studies did not find any association between serum anti-TPO or anti-Tg Ab levels and 25(OH)D levels in newly diagnosed HT patients [28, 29]. Effraimidis et al. conducted a longitudinal study with a 5-year follow-up period. The results

▶ **Table 1** Baseline characteristic of patients.

Characteristics	Vitamin D group	Placebo group	p-Value
Age (years)	36.4 ± 5.2	35.9 ± 7.8	0.81[a]
Body mass index (kg/m^2)	25.65 ± 5.1	27.80 ± 5.74	0.22[a]
Mean l-thyroxine dose (µg/day)	102 ± 66	113 ± 65	0.63[a]
Serum level of vitamin D (ng/ml)	25.3 ± 11.01	19.8 ± 8.8	0.084[a]

All values are expressed as mean ± (SD) or numbers.
[a] Independent sample *t*-test.

showed no correlation between serum 25(OH)D levels and the presence of anti-TPO Ab [30].

To the authors' knowledge, a few randomized controlled trials support the non-skeletal health benefits of vitamin D. We believe that this is the first clinical trial to investigate the effect of the therapeutic dose of vitamin D on circulating thyroid autoantibodies and thyroid profile (T4, T3 and TSH) in HT patients. The optimal 25(OH) D levels to prevent the onset of autoimmune diseases are still under debate [31]. The endocrine society, based on observational and clinical trials on populations high risk for vitamin D deficiency, recommends 30 ng/ml 25(OH) D as sufficient, with insufficient and deficient levels ranging from 20–29 ng/ml and less than 20 ng/ml, respectively [32]. In this study, 50 % of the subjects had deficient (< 20 ng/ml) and 75 % of them had insufficient levels (< 30 ng/ml) of vitamin D.

We decided to administer a relatively high but safe dose of vitamin D3, because administration of daily vitamin D3 (1000 IU/d or 400 IU/d) for 16 weeks showed no significant effects on the thyroid autoimmunity status compared with placebo, which may be because of the low level of the vitamin D supplementation dose [25].

The main nutritional disadvantage of fat-soluble vitamin therapy may be the fact that these vitamins show their effects at high pharmacological doses, which can be toxic and may lead to adverse effects, such as hypercalcemia. In this study, the dose and supplementation duration were selected based on previous studies [33, 34]. After supplementation, the serum level of 25(OH) D increased significantly (p = 0.000). Moreover, vitamin D intake increased significantly in the vitamin D group compared to the placebo group; however, it was consistent with the study, and favorable (p = 0.035). The serum calcium level increased significantly in the intervention group in comparison with the placebo (p = 0.001); however, its levels were in the normal range (< 10.7 mg/dl).

The molecular mechanisms of the reduction of anti-thyroid Abs could be that 1,25(OH)2D3 inhibits the proliferation and promotes the apoptosis of activated B cells. Additionally, 1,25(OH)2D3 inhibit plasma cell generation and memory cell formation; subsequently, the secretion of IgG and IgM immunoglobulins by activated B cells is shown to be inhibited by vitamin D3 treatment [35]. Vitamin D also regulates regulatory B (Breg) involved in immunological tolerance by producing IL-10, IL-35, and TGF-β cytokines [36].

However, there are no conclusive results on the effect of vitamin D supplementation on the thyroid function. It has been shown that vitamin D directly inhibits Iodide uptake by thyroid follicular cells [37]. An epidemiological study reported that high vitamin D levels are associated with low TSH titers [38]. In our study, vitamin D administration decreased the concentration of TSH compared to baseline but no significant difference was observed between vitamin D-supplemented and placebo groups. A previous study showed that vitamin D modulated TSH secretion by binding to specific binding sites on Pituitary TSH-Secreting Cells [22]. Another study found

▶ **Table 2** The comparison of average intake of nutrients by 1-day recall and 2-days record, before and after the intervention.

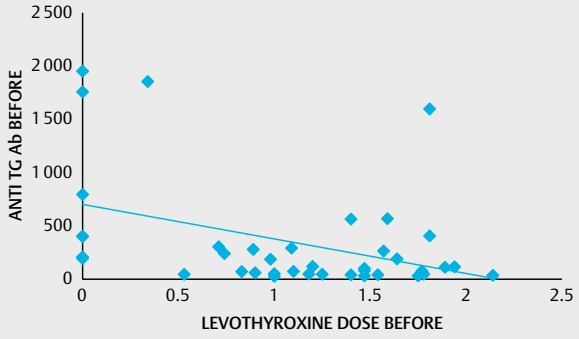
		Placebo group (n = 21)	Vitamin D group (n = 19)	p-Value[a]
Energy Cal (K)	Baseline	1812.7 ± 114.8	1871.1 ± 119.2	0.18
	after	1833.5 ± 130	1876.4 ± 127.6	0.36
	difference	20.7 ± 87.9	5.38 ± 94.6	
	p-value	0.33	0.84	
Carbohydrate (gr)	Baseline	219 ± 27.7	231.4 ± 36.8	0.29
	after	221.3 ± 33.2	235 ± 36.4	0.27
	difference	1614.4 ± 121.9	1645 ± 123.6	
	p-value	0.76	0.79	
Protein (gr)	Baseline	53.8 ± 11.7	49.8 ± 10.3	0.33
	after	51 ± 7.9	55.8 ± 9.8	0.14
	difference	− 2.8 ± 13.1	6.02 ± 14.84	
	p-value	0.38	0.17	
Fat (gr)	Baseline	82.8 ± 14	85.3 ± 13.9	0.61
	after	85.4 ± 11.8	81.5 ± 14.5	0.41
	difference	2.6 ± 15.09	− 3.86 ± 20.8	
	p-value	0.46	0.51	
Total vitamin D intake (mg)	Baseline	1.9 ± 6.45	2.97 ± 7.7	0.67
	after	0.37 ± 0.32	1.3 ± 1.8	**0.035[b]**
	difference	− 1.53 ± 6.4	− 1.6 ± 7.8	
	p-value	0.33	0.46	

[a] p < 0.05 vs. baseline value; [b] p < 0.05 vs. placebo.

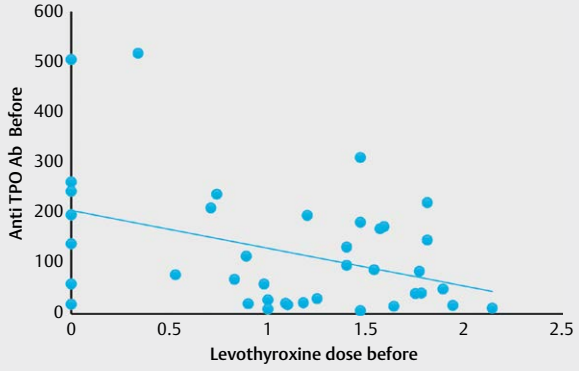
▶ **Table 3** The effect of vitamin D supplementation on anti-TPO Ab, anti-Tg Ab, T3, T4, TSH, calcium, and 25(OH)D in women with Hashimoto's thyroiditis.

	Vitamin D group	Placebo group	p-value
	Anti-TPO Ab (U/ml)		
Baseline	131.4 ± 108	174.1 ± 141.8	0.3
after	118.1 ± 97.9	181.6 ± 122.5	0.08
p-value	0.18	0.79	
	Thyroglobulin antibodies (U/ml)		
Baseline	192.6 ± 161.8	182.5 ± 153.9	0.83
after	140.2 ± 134.3	176.7 ± 167.1	0.45
p-value	**0.009**[a]	0.68	
	Thyrotropin (μIU/ml)		
Baseline	3 ± 2.09	2.56 ± 1.36	0.75
after	1.83 ± 1.4	2.77 ± 1.9	0.47
p-value	**0.027**[a]	0.58	
	T4 (μg/dl)		
Baseline	11.35 ± 1.82	12.1 ± 1.99	0.18
after	10.7 ± 1.58	11.1 ± 1.52	0.4
p-value	0.17	**0.008**[a]	
	T3 (ng/ml)		
Baseline	1.28 ± 0.34	1.32 ± 0.37	0.72
after	1.28 ± 0.35	1.31 ± 0.34	0.77
p-value	0.99	0.90	
	Calcium (mg/dl)		
Baseline	9.28 ± 0.93	9.39 ± 0.94	0.70
after	10.27 ± 0.43	9.91 ± 1.5	0.39
p-value	**0.000**[a]	0.094	
	25-Hydroxyvitamin D (ng/ml)		
Baseline	25.38 ± 11.02	19.8 ± 8.81	0.08
after	50.16 ± 14.98	22.03 ± 9.45	**0.000**[b]
p-value	**0.000**[a]	0.056	

[a] $p < 0.05$ vs. baseline value; [b] $p < 0.05$ vs. placebo.



▶ **Fig. 1** Reverse correlation between anti-Tg Ab and levothyroxine.



▶ **Fig. 2** Reverse correlation between anti-TPO Ab and levothyroxine.

that vitamin D significantly suppressed TSH secretion in the basal state [39]. The T4 levels increased significantly in the placebo group while TSH showed a non-significant opposite trend, which could be due to use of LT4. Although patients were on stable replacement therapy, their past history of LT4 consumption was not available for comparison between the 2 groups.

We also controlled some potential confounding variables, such as age, sex, BMI, LT4 dose, sun exposure, and dietary intake.

This study has some limitations. First, because of a short follow-up period, longer treatment for at least 6 months is required to show the clinical effects of vitamin D on the thyroid function. Second, the small sample size of the study might be the reason for the null effect of vitamin D supplementation on other factors. It would be better to include a group of patients that have never taken L-thyroxine or have taken it at doses ≤ 1.0 μg/kg/day, and exclude individuals whose thyroid destruction was relatively high to respond any intervention.

Longitudinal clinical trials are needed to confirm the beneficial effects of vitamin D on the thyroid function. We suggest that when diagnosing patients with HT, vitamin D levels can be evaluated and proper treatment is administered, if any deficiency is seen.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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