Endocrine (2020) 70:85–91
https://doi.org/10.1007/s12020-020-02274-9

ORIGINAL ARTICLE

Effect of vitamin D supplementation on TSH levels in euthyroid subjects with autoimmune thyroiditis

Alice Villa[1] · Andrea Corsello[1] · Marco Cintoni[2] · Giampaolo Papi[1] · Alfredo Pontecorvi[1] · Salvatore Maria Corsello[1] · Rosa Maria Paragliola[1]

Received: 6 January 2020 / Accepted: 16 March 2020 / Published online: 1 April 2020

Abstract

Purpose The impact of vitamin D supplementation on thyroid function is not clear and the relationship between hypovitaminosis D and autoimmune thyroiditis (ATD) incidence and evolution is still a matter of debate. The aim of this study was to retrospectively evaluate the impact of vitamin D supplementation on thyroid function in subjects with and without ATD.

Methods One hundred and ninety-eight euthyroid subjects, with diagnosis of "hypovitaminosis D" (<30 ng/mL) who had been taking supplementation therapy with cholecalciferol for different time periods, were included. They were divided in two groups according to the previous diagnosis of ATD: "ATD-neg" group including subjects without ATD [$n = 103$ (52%)]; "ATD-pos" group including subjects with a confirmed diagnosis of ATD [$n = 95$ (48%)]. For both groups, we considered TSH and 25 hydroxyvitamin D (25OHD) levels before (T0) and after (T1) cholecalciferol supplementation. We also considered the treatment duration and the monthly dose of cholecalciferol expressed as IU/month.

Results In hypovitaminosis D subjects with ATD, TSH levels significantly decreased after therapy with cholecalciferol 100.000 IU/month [mean ± SD, TSH at T0: 2.67 ± 1.21 vs. TSH at T1: 2.28 ± 0.86, $p = 0.028$]. No significant TSH variation was observed in ATD-neg group, irrespective of treatment dose and duration. As expected, 25OHD levels significantly improved with all monthly doses and especially in the group receiving 100.000 IU/month.

Conclusions Cholecalciferol supplementation improved thyroid function in euthyroid ATD-pos subjects affected with severe hypovitaminosis D. In particular, a significant reduction in TSH levels was observed in subjects with very low baseline 25OHD levels, after taking high monthly doses of cholecalciferol.

Keywords Vitamin D · Hypovitaminosis D · Thyroid function · Hashimoto's thyroiditis

Introduction

Vitamin D is a secosteroid molecule, whose primary function is bone metabolism and calcium and phosphorus homeostasis [1]. However, in the last years, extra-skeletal effects of vitamin D became relevant. The relevance of vitamin D in diseases such as hypertension, diabetes, cardiovascular diseases, autoimmune diseases, and cancer has been investigated by several authors, with most evidence suggesting a protective role of vitamin D for these conditions [2]. This can be due to the effects of vitamin D supplementation, in the setting of vitamin D deficiency, on the expression of genes involved in the pathogenesis of these diseases [3]. The determination of vitamin D status is based on the measurement of the prohormone 25 hydroxyvitamin D (25OHD) rather than on serum 1,25-dihydroxyvitamin D, which is not useful in clinical practice. Indeed, serum 25OHD is the most stable and abundant metabolite of vitamin D in human serum and has a half-life of about 3 weeks, making it the most suitable indicator of whole-body vitamin D status [4]. The definition of vitamin D deficiency or insufficiency based on 25OHD levels is still a matter of much debate. The Endocrine Society, based on observational studies and clinical trials on populations at high risk for vitamin D deficiency, applies a cutoff value of 30 ng/mL to define optimal vitamin status, while vitamin D

✉ Andrea Corsello
andreacorsello92@gmail.com

[1] Endocrinology Unit, Fondazione Policlinico "Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Largo Gemelli 8, I-00167 Rome, Italy

[2] Scuola di Specializzazione in Scienza dell'Alimentazione, Università di Roma Tor Vergata, Via Montpellier 1, I-00133 Rome, Italy

insufficiency is reported as a 25OHD of 21–29 ng/mL and vitamin D deficiency as a 25OHD <20 ng/mL [5]. More recent studies investigating the target level of 25OHD, propose a cutoff value of 20 ng/ml as "acceptable" and state that a more appropriate cutoff to define vitamin D deficiency would be lower (i.e., 12.5 ng/ml) [6].

The role of vitamin D in thyroid diseases has been widely discussed. Animal studies have shown that vitamin D treatment prevents the development of autoimmune thyroiditis and improves the inflammatory status of the gland by modulating autoantibodies production and cytokines expression [7]. Furthermore, lower serum 25OHD levels have been detected in individuals with autoimmune thyroiditis (ATD) compared with healthy controls, suggesting that ATD was more likely to develop in the setting of hypovitaminosis D [8]. Consistent with this, some studies claim a significant correlation between the severity of vitamin D deficiency and thyroid volume and antibody levels [9]. However, other studies fail to find any link between these two conditions [10, 11].

The impact of vitamin D supplementation on thyroid function itself is also relatively unknown. Very few studies investigating the therapeutic effect of vitamin D on TSH levels have been reported in the literature [12]. Considering the paucity and heterogeneity of data on the correlation between vitamin D supplementation and TSH levels, in the present study we aim to retrospectively evaluate the impact of vitamin D supplementation on thyroid function.

Materials and methods

In this retrospective study, a total of 198 euthyroid subjects were included. Their medical records were collected from the archives of the Department of Endocrinology of the "Fondazione Policlinico Agostino Gemelli Hospital—IRCCS". We selected euthyroid subjects with diagnosis of "hypovitaminosis D" (25OHD <30 ng/mL) who had been taking supplementation therapy with cholecalciferol for different time periods, between January 2015 and January 2019.

Exclusion criteria were:

(1) Concomitant pregnancy;
(2) Concomitant diseases interfering with vitamin D metabolism (primary hyperparathyroidism, Cushing's syndrome);
(3) Previous thyroid surgery;
(4) Concomitant therapy with levothyroxine, methimazole, amiodarone or other medications affecting thyroid function and interfering with TSH, such as steroids, somatostatin analogues, and metformin. Subjects assuming antiepileptic drugs were also excluded since it is well-known that these drugs affect serum vitamin D levels [13];
(5) Use of supplementation different from cholecalciferol for the treatment of hypovitaminosis D.

The study population ($n = 198$) was divided in two groups based on the previous diagnosis of "autoimmune thyroiditis" (ATD): "ATD-neg" group includes subjects without ATD [$n = 103$ (52%)]; "ATD-pos" group includes subjects with a confirmed diagnosis of ATD [$n = 95$ (48%)] based on the positivity of anti-thyroperoxidase autoantibodies (TPO-Ab) and/or anti-thyroglobulin autoantibodies (Tg-Ab), associated with ultrasonographic features of thyroiditis.

For both groups we considered sex, age, TSH levels, and 25OHD levels before starting cholecalciferol supplementation (T0, baseline evaluation) and TSH levels and 25OHD levels after reaching an adequate vitamin D supplementation (T1, target evaluation), which has been considered as a 25OHD >30 ng/ml, in line with the Endocrine Society guidelines [5]. Furthermore, we also considered the interval between baseline and target evaluation (time interval), that had to be between 3 months and a maximum of 3 years, and the mean monthly dose of cholecalciferol used for treatment (expressed as IU/month).

The study was approved by the local ethics committee and carried out according to Helsinki declaration.

The primary outcome of our study was to investigate if there were significant variations in TSH values after therapy with cholecalciferol, and if there were differences between subjects with and without ATD. The secondary outcome was to investigate whether variations in TSH could be related to a specific monthly dose of cholecalciferol.

Statistical analysis

Data are presented as means ± standard deviation. The normal distribution was verified by test of Kolmogorov–Smirnov. Paired-samples-T test was used for analysis of continuous variables. Statistical significance was set at $p < 0.05$.

Results

Sample description

A total of 103 ATD-neg and 95 ATD-pos subjects were included in the statistical analysis. No significant difference in terms of age and sex was observed between the two groups. The characteristics of the study population are listed in Table 1

Table 1 Study population characteristics

Total (198 patients)							
Age							
49 ± 15							
ATD-pos				ATD-neg			*p*
48 ± 14				51 ± 14			0.13
0–25.000 IU	26.000–99.000 IU	100.000 IU	*p*	0–25.000 IU	26.000–99.000 IU	100.000 IU	*p*
50 ± 16	46 ± 13	49 ± 16	0.52	49 ± 14	51 ± 14	55 ± 16	0.14
Female sex							
180 (91%)							
ATD-pos				ATD-neg			*p*
87 (93%)				93 (88%)			0.22
0–25.000 IU	26.000–99.000 IU	100.000 IU	*p*	0–25.000 IU	26.000–99.000 IU	100.000 IU	*p*
33 (97%)	47 (92%)	7 (88%)	0.51	38 (95%)	44 (89%)	11 (79%)	0.19
BMI							
23 ± 5							
ATD-pos				ATD-neg			*p*
22 ± 4				23 ± 4			0.64
0–25.000 IU	26.000–99.000 IU	100.000 IU	*p*	0–25.000 IU	26.000–99.000 IU	100.000 IU	*p*
22 ± 2	24 ± 4	21 ± 3	0.42	23 ± 5	23 ± 3	24 ± 2	0.19

Results in ATD-neg and ATD-pos subjects together

The first statistical analysis was performed considering the entire study population (ATD-neg + ATD-pos: $n = 198$). Comparison of baseline (T0) and post-treatment (T1) TSH and 25OHD levels is shown in the Table 2. No significant variation in TSH levels ($p = 0.43$) was observed, while 25OHD levels increased from baseline to target as expected.

All subjects were then divided in three groups according to the monthly IU of vitamin D taken: 69 subjects in group 1 (0–25.000 IU/month), 81 subjects in group 2 (26.000–99.000 IU/month), and 48 subjects in group 3 (100.000 IU/month). No significant difference in TSH levels before and after treatment with vitamin D was observed in any group. As expected, 25OHD levels significantly improved with all monthly doses and especially in the group receiving 100.000 IU/month (Table 3).

To investigate the impact of the length of therapy, a further division according to the years of cholecalciferol administration was performed: 46 subjects (23.2%) up to 1 year, 96 subjects (48.5%) between 1 and 2 years, and 56 subjects (28.3%) over 2 years of therapy. TSH levels, considering the entire population (ATD-neg + ATD-pos), did not change significantly in any of the three subgroups.

Table 2 Comparison of baseline (T0) and post-treatment (T1) TSH and 25OHD levels in the entire population. (25OHD: 25 hydroxyvitamin D)

	T0	T1	*p*
TSH (mcU/ml)	1.95 ± 1.11	1.89 ± 1.10	0.43
25OHD (ng/ml)	18.75 ± 6.81	31.98 ± 8.40	<0.0001

Results in ATD-neg vs. ATD-pos subjects

To evaluate whether vitamin D therapy has a different impact on TSH according to ATD status, the two groups (ATD-neg and ATD-pos) were investigated separately. No significant change in TSH was observed in the two groups before (T0) and after (T1) treatment with vitamin D overall (Table 4).

After dividing the subjects according to the monthly IU of vitamin D as mentioned previously, no significant TSH variation was observed in ATD-neg group (Table 5). On the contrary, in ATD-pos group a significant variation in TSH levels emerges in the subgroup taking 100.000 IU/month of vitamin D ($n = 22$). In fact, TSH levels significantly decreased after therapy with cholecalciferol [mean ± SD, TSH at T0: 2.67 ± 1.21 vs. TSH at T1: 2.28 ± 0.86, $p = 0.028$] (Table 6).

After dividing the subjects according to the length of therapy, no significant difference in TSH was observed in ATD-neg or ATD-pos group (Table 7).

Table 3 Comparison of baseline (T0) and posttreatment (T1) TSH and 25OHD levels in the entire population, divided according to monthly dose of cholecalciferol administered

	0–25.000 IU/month (69 pts)			26.000–99.000 IU/month (81 pts)			100.000 IU/month (48 pts)		
	T0	T1	*p*	T0	T1	*p*	T0	T1	*p*
TSH (mcU/ml)	1.81 ± 1.09	1.84 ± 1.13	0.76	2.02 ± 1.11	1.92 ± 1.10	0.27	2.04 ± 1.21	1.98 ± 1.05	0.72
25OHD (ng/ml)	23.94 ± 4.40	32.60 ± 7.21	<0.0001	17.71 ± 4.74	31.28 ± 9.11	<0.0001	7.09 ± 2.41	33.04 ± 8.82	<0.0001

25OHD 25 hydroxyvitamin D

Table 4 Comparison of baseline (T0) and posttreatment (T1) TSH and 25OHD levels in the two subgroups (ATD-pos and ATD-neg)

	ATD-neg (103 pts)			ATD-pos (95 pts)		
	T0	T1	*p*	T0	T1	*p*
TSH (mcU/ml)	1.79 ± 1.13	1.77 ± 1.09	0.86	2.12 ± 1.08	2.03 ± 1.10	0.33
25OHD (ng/ml)	17.82 ± 6.96	33.36 ± 9.50	<0.0001	19.76 ± 6.52	30.49 ± 6.76	<0.0001

ATD autoimmune thyroiditis, *25OHD* 25 hydroxyvitamin D

Table 5 Comparison of baseline (T0) and posttreatment (T1) TSH and 25OHD levels according to monthly dose of cholecalciferol administered in ATD-neg group

	0–25.000 IU/month (36 pts)			26.000–99.000 IU/month (41 pts)			100.000 IU/month (26 pts)		
	T0	T1	*p*	T0	T1	*p*	T0	T1	*p*
TSH (mcU/ml)	1.52 ± 1.01	1.61 ± 1.09	0.47	2.03 ± 1.19	1.88 ± 1.09	0.32	1.73 ± 1.12	1.84 ± 1.13	0.56
25OHD (ng/ml)	23.13 ± 4.53	33.01 ± 8.41	<0.0001	17.27 ± 4.39	33.06 ± 10.44	<0.0001	6.52 ± 2.52	35.09 ± 9.46	<0.0001

ATD autoimmune thyroiditis, *25OHD* 25 hydroxyvitamin D

Table 6 Comparison of baseline (T0) and posttreatment (T1) TSH and 25OHD levels according to monthly dose of cholecalciferol administered in ATD-pos group

	0–25.000 IU/month (33 pts)			26.000–99.000 IU/month (40 pts)			100.000 IU/month (22 pts)		
	T0	T1	p	T0	T1	p	T0	T1	p
TSH (mcU/ml)	2.14 ± 1.09	2.09 ± 1.14	0.78	2.02 ± 1.05	1.94 ± 1.11	0.56	2.67 ± 1.21	2.28 ± 0.86	**0.028**
25OHD (ng/ml)	24.84 ± 4.13	32.15 ± 5.65	<0.0001	18.12 ± 5.04	29.63 ± 7.42	<0.0001	8.25 ± 1.79	28.94 ± 5.90	<0.0001

ATD autoimmune thyroiditis, *25OHD* 25 hydroxyvitamin D

p-value marked in bold indicates that TSH levels significantly decreased in the subgroup taking 100.000 IU/month of cholecalciferol (statistical significance for $p < 0.05$)

Table 7 Comparison of baseline (T0) and posttreatment (T1) TSH and 25OHD levels according to the length of cholecalciferol treatment in ATD-pos group (A) and in ATD-neg group (B)

	<1 year			1–2 years			≥2 years		
	T0	T1	*p*	T0	T1	*p*	T0	T1	*p*
(A)									
TSH (mcU/ml)	2.72 ± 1.14	2.74 ± 1.24	0.91	2.09 ± 0.94	2.02 ± 0.91	0.62	1.75 ± 1.14	1.54 ± 1.08	0.19
25OHD (ng/ml)	17.12 ± 6.72	30.39 ± 6.04	<0.0001	20.76 ± 6.30	29.94 ± 29.94	<0.0001	19.82 ± 6.51	31.59 ± 7.18	<0.0001
(B)									
TSH	1.79 ± 0.95	1.75 ± 0.87	0.70	1.95 ± 1.32	1.85 ± 1.21	0.51	1.53 ± 0.90	1.68 ± 1.12	0.38
Vit D	16.62 ± 8.33	34.54 ± 8.51	<0.0001	18.96 ± 5.81	33.87 ± 10.51	<0.0001	17.09 ± 7.24	31.42 ± 8.62	<0.0001

ATD autoimmune thyroiditis, *25OHD* 25 hydroxyvitamin D

Discussion

This study shows that in euthyroid subjects with autoimmune thyroiditis (i.e., with positive antithyroid antibodies, ATD-pos group) and hypovitaminosis D, TSH levels decrease significantly after reaching target levels of 25OHD with high monthly doses of vitamin D (i.e., 100.000 IU/month). We considered as endpoint target levels of 25OHD >30 ng/ml, regardless of the time intercurrent to reach this target. Interestingly, the variation of 25OHD levels between T0 and T1 seems to have contributed to the TSH reduction in this subgroup.

We enrolled only euthyroid subjects in order to avoid possible confounding factors such as substitutive therapy with levothyroxine for hypothyroidism, or antithyroid drugs treatment for hyperthyroidism.

It is well-known that ATD is a chronic condition associated with an increased risk of developing primary hypothyroidism. The observation that TSH decreased after reaching target 25OHD levels can be considered a "beneficial" effect of cholecalciferol therapy. Interestingly, the role of cholecalciferol in slowing down the risk of developing hypothyroidism in Hashimoto's thyroiditis has recently been pointed out by some authors. Ucan et al. [14] claimed a positive effect of cholecalciferol treatment on patients with Hashimoto's thyroiditis, showing that 25OHD levels are significantly lower in this condition and that cholecalciferol administration determines a decrease in autoantibodies levels, an increase in HDL levels and a decrease in thyroid volume. Therefore, the treatment of hypovitaminosis D seems to slow down the development of hypothyroidism and to decrease the cardiovascular risks.

In our study, TSH levels decreased in ATD-pos subjects after cholecalciferol supplementation of 100.000 IU/month, whereas no significant variation of TSH was observed in ATD-neg group after the same treatment. Thus, our findings, on the one hand suggest that cholecalciferol is "more effective" in subjects "at higher risk" to develop hypothyroidism, on the other hand it supports the hypothesis of a relevant role of cholecalciferol in the regulation of autoimmune mechanisms. The latter is an indirect inference, since our study considered serum TSH concentrations, rather than thyroid autoantibodies.

On this topic, few studies are currently available in the literature. A recent double-blind randomized clinical trial [15] investigated the effect of the therapeutic dose of vitamin D on circulating thyroid autoantibodies and thyroid profile in Hashimoto's thyroiditis patients treated with levothyroxine and found a significant reduction in TSH and Tg-Ab levels in the cholecalciferol-treated group. Two other double-blind randomized placebo-controlled trials, quite similar to each other in the study design, gave opposite results [16, 17]. However, the short duration of the follow-up and the different size of the groups analyzed, could have contributed to not univocal results. Furthermore, fixed doses of cholecalciferol were used. From this point of view, some strengths of our study were the recruitment of a large series of subjects who were not on levothyroxine therapy and the decision to divide them also on the basis of vitamin D intake, which allowed to highlight a significant correlation between cholecalciferol intake and TSH levels. However, the main limitation of our study is related to its retrospective nature.

Furthermore, differently from the above-mentioned trials, in our study we did not consider TPO-Ab and Tg-Ab levels, and we preferred to focus on TSH determinations. In fact, since in clinical practice we normally avoid repeating thyroid autoantibodies dosage in known cases of Hashimoto's thyroiditis, it would have been problematic to carry out a retrospective study taking into account this variable. Furthermore, the significance of autoantibodies levels in Hashimoto's thyroiditis evolution is still questionable. Certainly, autoantibodies variations are unrelated to TSH variations. On the contrary, TSH measurement is quoted as the gold standard to evaluate thyroid function.

The reduction in TSH levels during cholecalciferol therapy could be the result of different processes. An improved thyroid function or a reduction of disease activity due to an anti-inflammatory/immunomodulatory action of vitamin D can be supposed. In fact, vitamin D regulates the differentiation and the activation of CD4+ T lymphocytes, thus preventing the development of an autoimmune response [18]. Moreover, $1,25(OH)_2D$ reduces the number of antigen-presenting cells, has a direct immunosuppressive effect on dendritic cells, and reduces the production of cytokines [19]. Furthermore, vitamin D could influence the thyroid gland through a direct action on the central nervous system and the thyrotropes. The existence of a relationship between vitamin D and pituitary secretion of TSH had already been documented in the 80s, when Sar found that vitamin D receptors are present in rat thyrotropes and argued that vitamin D influences TSH secretion of pituitary thyrotropes by binding to specific sites [20]. More recently, high vitamin D status was found to be significantly associated with low circulating TSH levels both in young individuals [21] and in middle-aged or elderly men [22], thus confirming a close relationship between vitamin D and serum TSH levels.

The most significant finding in this study is the relationship between target vitamin D levels (at T1) and TSH reduction in the group of subjects with ATD and hypovitaminosis D who have been treated with a higher monthly dose of cholecalciferol. Of note, 25OHD levels at T1 were not different in the three subgroups of ATD-pos subjects receiving three different monthly doses (Table 5), whereas the subgroup taking 100.000 IU/month started from lower levels of 25OHD and higher TSH at T0. Interestingly, we have not observed

significant differences in age, sex, or BMI between the three subgroups that could explain the higher TSH. Thus, we could speculate that the higher baseline TSH in the subgroup taking 100.000 IU/month might be secondary to the very low baseline 25OHD levels and that the reduction of TSH levels was somewhat related to the variation of vitamin D levels between T0 and T1. These results overall, suggest that subjects with ATD and severe vitamin D deficiency might benefit more (in terms of reduced TSH levels) from vitamin D supplementation and in particular from relatively high doses of cholecalciferol (i.e., 100.000 IU/month). In our opinion this is a particularly interesting finding, which had never been reported previously.

Conclusions

In conclusion, the results of the present study suggest that therapy with cholecalciferol may improve thyroid function in euthyroid subjects with ATD and severe hypovitaminosis D. In particular, a significant reduction in TSH levels can be observed in subjects with very low vitamin D levels at baseline (i.e., <10 ng/ml), taking high monthly doses of cholecalciferol (i.e., 100.000 IU/month). Our results open new perspectives toward a more rational use of vitamin D supplementation in subjects affected with ATD. However, clinical trials, free from the methodological bias common to retrospective studies, are needed in order to investigate further the role of vitamin D supplementation in either the prevention or the improvement of ATD and more information with regard to the best formulation, dose and timing of supplementation are also needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. M. Umar, K. S. Sastry, A. I. Chouchane, Role of vitamin D beyond the skeletal function: a review of the molecular and clinical studies. Int. J. Mol. Sci. **19**(6), (2018). https://doi.org/10.3390/ijms19061618
2. Y.H. Lai, T.C. Fang, The pleiotropic effect of vitamin d. ISRN Nephrol. **2013**, 898125 (2013). https://doi.org/10.5402/2013/898125
3. A. Hossein-nezhad, A. Spira, M.F. Holick, Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. PLoS ONE **8**(3), e58725 (2013). https://doi.org/10.1371/journal.pone.0058725
4. T.D. Thacher, B.L. Clarke, Vitamin D insufficiency. Mayo Clin. Proc. **86**(1), 50–60 (2011). https://doi.org/10.4065/mcp.2010.0567
5. M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon, D.A. Hanley, R.P. Heaney, M.H. Murad, C.M. Weaver, S. Endocrine, Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. **96**(7), 1911–1930 (2011). https://doi.org/10.1210/jc.2011-0385
6. J.E. Manson, P.M. Brannon, C.J. Rosen, C.L. Taylor, Vitamin D deficiency—is there really a pandemic? N. Engl. J. Med. **375**(19), 1817–1820 (2016). https://doi.org/10.1056/NEJMp1608005
7. F. Baeke, T. Takiishi, H. Korf, C. Gysemans, C. Mathieu, Vitamin D: modulator of the immune system. Curr. Opin. Pharmacol. **10** (4), 482–496 (2010). https://doi.org/10.1016/j.coph.2010.04.001
8. J. Wang, S. Lv, G. Chen, C. Gao, J. He, H. Zhong, Y. Xu, Meta-analysis of the association between vitamin D and autoimmune thyroid disease. Nutrients **7**(4), 2485–2498 (2015). https://doi.org/10.3390/nu7042485
9. N.C. Bozkurt, B. Karbek, B. Ucan, M. Sahin, E. Cakal, M. Ozbek, T. Delibasi, The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocr. Pract. **19**(3), 479–484 (2013). https://doi.org/10.4158/EP12376.OR
10. G. Effraimidis, K. Badenhoop, J.G. Tijssen, W.M. Wiersinga, Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. Eur. J. Endocrinol. **167**(1), 43–48 (2012). https://doi.org/10.1530/EJE-12-0048
11. F. D'Aurizio, D. Villalta, P. Metus, P. Doretto, R. Tozzoli, Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? Autoimmun. Rev. **14**(5), 363–369 (2015). https://doi.org/10.1016/j.autrev.2014.10.008
12. D. Kim, The role of vitamin D in thyroid diseases. Int. J. Mol. Sci. **18**(9) (2017). https://doi.org/10.3390/ijms18091949
13. B. Menon, C.V. Harinarayan, The effect of anti epileptic drug therapy on serum 25-hydroxyvitamin D and parameters of calcium and bone metabolism–a longitudinal study. Seizure **19**(3), 153–158 (2010). https://doi.org/10.1016/j.seizure.2010.01.006
14. B. Ucan, M. Sahin, M. Sayki Arslan, N. Colak Bozkurt, M. Kizilgul, A. Gungunes, E. Cakal, M. Ozbek, Vitamin D treatment in patients with hashimoto's thyroiditis may decrease the development of hypothyroidism. Int J. Vitam. Nutr. Res **86**(1-2), 9–17 (2016). https://doi.org/10.1024/0300-9831/a000269
15. R. Chahardoli, A.A. Saboor-Yaraghi, A. Amouzegar, D. Khalili, A.Z. Vakili, F. Azizi, 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 **51**(5), 296–301 (2019). https://doi.org/10.1055/a-0856-1044
16. P. Vahabi Anaraki, A. Aminorroaya, M. Amini, F. Momeni, A. Feizi, B. Iraj, A. Tabatabaei, 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. **22**, 103 (2017). https://doi.org/10.4103/jrms.JRMS_1048_16
17. A. Talaei, F. Ghorbani, Z. Asemi, The effects of vitamin D supplementation on thyroid function in hypothyroid patients: a randomized, double-blind, placebo-controlled trial. Indian J. Endocrinol. Metab. **22**(5), 584–588 (2018). https://doi.org/10.4103/ijem.IJEM_603_17
18. M.T. Cantorna, L. Snyder, Y.D. Lin, L. Yang, Vitamin D and 1,25 (OH)2D regulation of T cells. Nutrients **7**(4), 3011–3021 (2015). https://doi.org/10.3390/nu7043011
19. M. Barragan, M. Good, J.K. Kolls, Regulation of dendritic cell function by vitamin D. Nutrients **7**(9), 8127–8151 (2015). https://doi.org/10.3390/nu7095383

20. M. Sar, W.E. Stumpf, H.F. DeLuca, Thyrotropes in the pituitary are target cells for 1,25 dihydroxy vitamin D3. Cell Tissue Res. **209**(1), 161–166 (1980). https://doi.org/10.1007/bf00219932
21. L.O. Chailurkit, W. Aekplakorn, B. Ongphiphadhanakul, High vitamin D status in younger individuals is associated with low circulating thyrotropin. Thyroid **23**(1), 25–30 (2013). https://doi.org/10.1089/thy.2012.0001
22. Q. Zhang, Z. Wang, M. Sun, M. Cao, Z. Zhu, Q. Fu, Y. Gao, J. Mao, Y. Li, Y. Shi, F. Yang, S. Zheng, W. Tang, Y. Duan, X. Huang, W. He, T. Yang, Association of high vitamin d status with low circulating thyroid-stimulating hormone independent of thyroid hormone levels in middle-aged and elderly males. Int. J. Endocrinol. **2014**, 631819 (2014). https://doi.org/10.1155/2014/631819