The Effects of Vitamin D Supplementation on Thyroid Function in Hypothyroid Patients: A Randomized, Double-blind, Placebo-controlled Trial

Afsaneh Talaei, Fariba Ghorbani, Zatollah Asemi[1]

Endocrinology and Metabolism Research Center, Department of Internal Medicine, School of Medicine, Arak University of Medical Sciences, Arak, [1]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

Abstract

Background: Data on the effects of vitamin D supplementation on thyroid function in hypothyroid patients are scarce. **Objective:** This study was done to evaluate the effects of vitamin D supplementation on thyroid function in hypothyroid patients. **Material and Methods:** This randomized double-blind, placebo-controlled trial was conducted on 201 hypothyroid patients aged 20–60 years old. Subjects were randomly assigned into two groups to intake either 50,000 IU vitamin D supplements (n = 102) or placebo (n = 99) weekly for 12 weeks. Markers of related with thyroid function were assessed at first and 12 weeks after the intervention. **Results:** After 12 weeks of intervention, compared to the placebo, vitamin D supplementation resulted in significant increases in serum 25-hydroxyvitamin D (+26.5 ± 11.6 vs. 0.0 ± 0.0 ng/mL, $P < 0.001$) and calcium (+0.4 ± 0.7 vs. 0.1 ± 0.6 mg/dL, $P = 0.002$), and a significant decrease in serum thyroid-stimulating hormone (TSH) levels (−0.4 ± 0.6 vs. +0.1 ± 2.0 µIU/mL, $P = 0.02$). A trend towards a greater decrease in serum parathyroid hormone (PTH) levels was observed in vitamin D group compared to placebo group (−3.8 vs. +1.9, $P = 0.07$). We did not observe any significant changes in serum T3, T4, alkaline phosphatase (ALP) and albumin levels following supplementation of vitamin D compared with the placebo. **Conclusion:** Overall, the current study demonstrated that vitamin D supplementation among hypothyroid patients for 12 weeks improved serum TSH and calcium concentrations compared with the placebo, but it did not alter serum T3, T4, ALP, PTH, and albumin levels.

Keywords: Hypothyroid, thyroid function, vitamin D supplementation

Background

The presence of vitamin D receptors in most tissues and cells in the human body leads to that vitamin D was considered as a unique hormone.[1] Several studies have demonstrated that vitamin D has an effect in decreasing the risk of chronic illnesses including autoimmune, infectious and cardiovascular diseases.[2–4] It has been estimated that more than one billion people worldwide have vitamin D deficiency or insufficiency.[5] The prevalence of 25(OH)D deficiency was reported as 81.3% among children in the south of Iran.[6] Elderly people as well as children and young adults are potentially at high risk for vitamin D deficiency.[7]

Several studies have reported low serum levels of vitamin D in hypothyroid patients which in turn may lead to some musculoskeletal complaints in these patients.[8,9] Other studies have demonstrated that the patients with Graves' disease also have low serum levels of vitamin D.[10,11] There are two mechanisms that may explain why serum levels of vitamin D is low in hypothyroid patients; one is that the low levels of vitamin D may be due to poor absorption of vitamin D from the intestine and the other is the body of these patients may not activate vitamin D properly.[8] In a study by Chaudhary *et al*.[12] was seen that administration of 60,000 IU vitamin D weekly in autoimmune thyroid disorders (AITD) had a favorable effect on autoimmunity as evidenced by significant reductions in TPO-Ab titers. In addition, vitamin D3 intake after 10 weeks in diabetic rats greatly corrected the alterations in thyroid profile and D2 (deiodinase 2) expression.[13]

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Address for correspondence: Dr. Afsaneh Talaei,
Endocrinology and Metabolism Research Cente,
Arak University of Medical Sciences, Arak, Iran.
E-mail: afsanehtalaeii@yahoo.com

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Vitamin D mediates its effect through binding to vitamin D receptor (VDR) and activation of VDR-responsive genes in the target tissues.[8] VDR gene polymorphism was found to associate with AITD.[8] These mechanisms might suggest the importance of vitamin D administration in hypothyroid patients. To our knowledge, no reports are available evaluating the effects of vitamin D administration on thyroid function in hypothyroid patients. This study is aimed to determine the effects of vitamin D supplementation on thyroid function in hypothyroid patients.

Procedure

Trial design

This was a 12-week randomized, double-blind, placebo-controlled clinical trial.

Participants

Participants of this study were 201 hypothyroid patients which were selected from subjects attending the endocrinology service of Arak University of Medical Sciences (AUMS) from October 2015 to December 2015. Patients aged 20–60 years old were stable for more than one year on their levothyroxine dose and thyroid-stimulating hormone (TSH) level was at 0.5–5 mIU/L without need to change the levothyroxine dose.

Ethics statements

This research was done in accordance with the Declaration of Helsinki and informed consent was received from all subjects. The research was approved by the ethics committee of AUMS and was registered in the Iranian website for registration of clinical trials (http://www.irct.ir: IRCT2016022325895N2).

Study design

At first, subjects were randomly divided into two groups by random permuted blocks to receive either 50,000 IU vitamin D supplement ($n = 102$) or placebo ($n = 99$) weekly for 12 weeks. Vitamin D capsules and its placebos (paraffin) were provided by Zahravi Pharmaceutical Company (Tabriz, Iran) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. At the onset of the study, subjects were requested to keep their habitual diet and routine levels of physical activity throughout the study period as well as not to take any medications that might affect their reproductive physiology during treatment.

Treatment adherence

Compliance to the consumption of supplement and placebo was examined by bringing the containers of the capsules as well as by the measurement of serum 25-hydroxyvitamin D concentrations.

Assessment of anthropometric measures

Anthropometric measures including height, weight (Seca, Hamburg, Germany) and body mass index (BMI) were quantified at the onset and at the end of the study.

Assessment of outcomes

The primary outcome variables were thyroid function including serum T3, T4 and TSH in the current study. The secondary outcome variables were serum calcium, ALP, PTH and albumin.

Biochemical assessment

Twelve-hour fasting blood samples were taken by venipuncture at weeks 0 and 12 at the reference laboratory. Blood samples were taken according to a standard protocol and immediately centrifuged (Hettich D-78532, Tuttlingen, Germany). Then, the samples were stored at −80°C until analysis at the AUMS reference laboratory. Serum 25-OH-D was measured using the enzyme immunoassay method (DRG, Marburg, Germany) with inter- and intra-assay coefficient variations (CVs) of 9.7 and 4.7%, respectively. Measurement of total tetraiodothyronine (TT4) and triiodothyronine (TT3) were done using the radioimmunoassay (RIA) method, and TSH was measured by immunoenzymometric assay (IEMA) using commercial kits (Izotop, Budapest, Hungary). Intra- and inter-assay CVs were 3.3 and 6.2% for TT4, 6.7 and 7.8% for TT3 and 3.9 and 7.1% for TSH, respectively.

Randomization

Randomization assignment was conducted using computer-generated random numbers as blindness by a trained midwife at clinic.

Statistical methods

To evaluate normal distribution of variables, we performed the Kolmogrov–Smirnov test. To detect differences in the general characteristics between the two groups, we used independent samples Student's *t*-test and Mann–Whitney U test based on normal or abnormal distribution. Paired *t*-test also was applied to compare values within groups. To demonstrate the effect of vitamin D supplementation on thyroid function, one-way variance analysis ANOVA was applied. To control the effect of confounders including baseline values of biochemical parameters, age and BMI at baseline, we applied analysis of covariance (ANCOVA). A P value < 0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

At the study baseline, we recruited 220 participants; however, 19 subjects were excluded from the study because of not meeting inclusion criteria. In the current study, 201 subjects [vitamin D ($n = 102$) and placebo ($n = 99$)] completed the trial [Figure 1]. On average, the rate of compliance in the present study was high, such that 100% of capsules were taken throughout the study in both groups. No side effects were reported following the consumption of vitamin D supplements in participants throughout the study. Totally, 58% of the patients were vitamin D deficient as described when vitamin D is less than 20 ng/ml.

Mean age, baseline weight and BMI, and end-of-trial weight and BMI were not significantly different between the two groups [Table 1].

After 12 weeks of intervention, compared with the placebo, vitamin D supplementation resulted in significant increases in serum 25-hydroxyvitamin D (+26.5 ± 11.6 vs. 0.0 ± 0.0 ng/mL, $P < 0.001$) and calcium (+0.4 ± 0.7 vs. 0.1 ± 0.6 mg/dL, $P = 0.002$), and a significant decrease in serum TSH levels (−0.4 ± 0.6 vs. +0.1 ± 2.0 µIU/mL, $P = 0.02$). A trend towards a greater decrease in serum PTH levels was observed in the vitamin D group compared with the placebo group (−3.8 vs. +1.9, $P = 0.07$). We did not observe any significant change in serum T3, T4, ALP and albumin levels following supplementation of vitamin D compared with the placebo [Table 2].

Adjustments for baseline values of biochemical variables, age and BMI at baseline did not influence our findings, except for serum ALP ($P = 0.02$) and albumin levels ($P = 0.04$) [Table 3].

Discussion

We found that vitamin D supplementation among hypothyroid patients for 12 weeks improved serum TSH and calcium concentrations compared with the placebo, but it did not alter serum T3, T4 levels. To our knowledge, this trial is the first evaluating the effects of vitamin D supplementation on thyroid function among subjects with hypothyroid.

Vitamin D is well known for its primary role in bone and mineral metabolism, and it has been recently shown that its deficiency is associated with many diseases such as cardiovascular disease, cancer, infection, adiposity as well as osteoporosis.[14] Also, it has been proved that low concentrations of serum vitamin D is associated with autoimmune diseases.[2] In addition, vitamin D deficiency is a global problem throughout the world.[7] It has been estimated that more than one billion people in the world have vitamin D deficiency or insufficiency.[7]

The prevalence of vitamin D deficiency in adult population has been reported to be 9–70% with a higher prevalence in Asian countries.[15,16] A study from Japan including 200 patients with Graves' disease demonstrated that 40% of women and 20% of men had vitamin D deficiency.[17] Some other studies have indicated that patients with Graves' disease also have low levels of vitamin D.[18] According to these findings, the present study showed that the prevalence of vitamin D deficiency was high in hypothyroid patients. Vitamin D supplementation significantly decreased TSH levels but had no significant effect on T4 or T3 concentrations. These results suggested that there may be a significant relationship between vitamin D deficiency and hypothyroidism. According to

Table 1: General characteristics of study participants

	Placebo group (n=99)	Vitamin D group (n=102)	P^1
Age (y)	36.8±11.1	38.2±12.0	0.40
Height (cm)	160.7±2.9	161.3±4.2	0.30
Weight at study baseline (kg)	75.0±13.7	76.2±11.9	0.50
Weight at end-of-trial (kg)	75.1±13.7	76.3±11.8	0.53
Weight change (kg)	0.1±0.8	0.1±0.7	0.46
BMI at study baseline (kg/m^2)	29.0±5.2	29.3±4.9	0.62
BMI at end-of-trial (kg/m^2)	29.1±5.2	29.4±4.8	0.65
BMI change (kg/m^2)	0.1±0.3	0.1±0.3	0.59

Data are mean±SDs. [1]Obtained from independent *t*-test

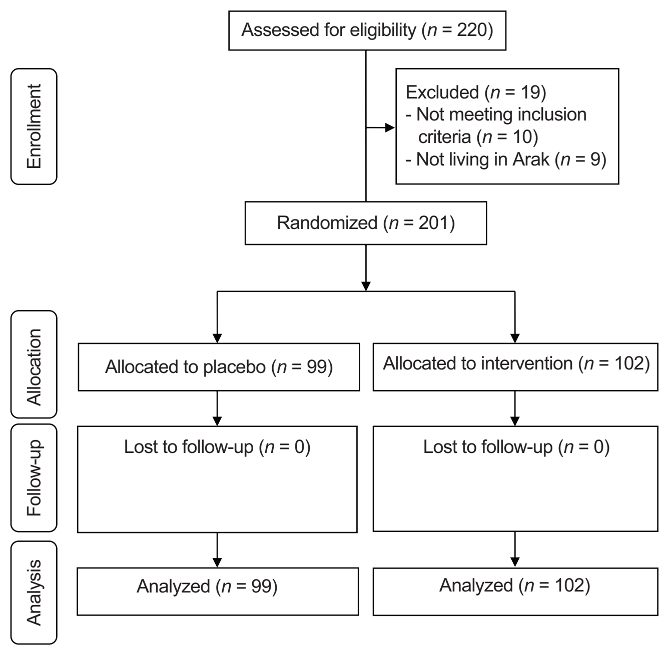

Figure 1: Summary of patient flow diagram

Table 2: The effect of vitamin D supplementation on thyroid function in hypothyroid patients[1]

	Placebo group (n=99)			Vitamin D group (n=102)			P^2
	Baseline	End-of-trial	Change	Baseline	End-of-trial	Change	
Vitamin D (ng/mL)	16.4±8.7	16.4±8.7	0.0±0.0	17.1±7.8	43.7±11.3	26.5±11.6	<0.001
TSH (mIU/L)	2.7±1.3	2.8±1.4	0.1±2.0	2.6±1.4	2.2±1.4	-0.4±0.6	0.02
T3 (µg/dL)	1.7±0.4	1.6±0.4	-0.1±0.5	1.7±0.5	1.7±0.5	0.01±0.6	0.23
T4 (µg/dL)	8.7±2.3	8.4±2.4	-0.3±2.7	8.5±2.3	8.7±2.2	0.2±3.0	0.22
Calcium (mg/dL)	8.7±0.5	8.9±0.5	0.1±0.6	8.8±0.4	9.2±0.5	0.4±0.7	0.002
ALP (mg/dL)	131.2±45.5	128.4±45.7	-2.8±63.7	130.8±44.6	143.1±51.0	12.3±66.6	0.10
PTH (pg/mL)	38.6±15.7	40.5±14.7	1.9±22.4	41.7±15.9	37.9±13.9	-3.8±21.8	0.07
Albumin (mg/dL)	4.2±0.4	4.2±0.4	0.01±0.6	4.3±0.4	4.3±0.4	0.01±0.6	0.98

[1]All values are means±SDs. [2]Obtained from repeated measures ANOVA test. ALP: Alkaline phosphatase, PTH: Parathyroid hormone, TSH: Thyroid-stimulating hormone

Table 3: Adjusted changes in thyroid function in hypothyroid patients[1]

	Placebo group (*n*=99)	Vitamin D group (*n*=102)	*P*[2]
Vitamin D (ng/mL)	-0.1±0.8	26.6±0.8	<0.001
TSH (mIU/L)	0.1±0.1	-0.4±0.1	0.005
T3 (µg/dL)	-0.1±0.04	-0.003±0.04	0.29
T4 (µg/dL)	-0.3±0.2	0.1±0.2	0.23
Calcium (mg/dL)	0.1±0.04	0.4±0.04	<0.001
ALP (mg/dL)	-2.9±4.9	12.4±4.7	0.02
PTH (pg/mL)	0.2±1.5	-2.1±1.4	0.26
Albumin (mg/dL)	-0.05±0.04	0.07±0.04	0.04

[1]All values are means±SEs. [2]Obtained from ANCOVA test adjusted for baseline values, age and BMI at baseline. ALP: Alkaline phosphatase, PTH: Parathyroid hormone

our results, some studies have reported the prevalence of vitamin D insufficiency in Hashimoto's disease (92%) was significantly higher than in healthy controls (63%).[19] Furthermore, Mackawy *et al*.[8] concluded that the patients with hypothyroidism suffered from hypovitaminosis D and there was a positive significant correlation between serum level of vitamin D with thyroid hormones and a negative significant correlation with TSH levels and suggested that the deficiency of serum levels of vitamin D was significantly associated with the degree and severity of hypothyroidism. There are two explanations for this association. First, the low levels of vitamin D may be due to poor absorption of vitamin D from the intestine.[8] Second, the body may not activate vitamin D properly.[8]

It has been known that both vitamin D and thyroid hormone bind to similar receptors called steroid hormone receptors. Some polymorphisms in VDR gene were shown to predispose people to autoimmune thyroid disease including Graves' disease and Hashimoto's thyroiditis.[20,21] Some previous studies have demonstrated that vitamin D modulates pituitary TSH secretion by binding to specific binding sites.[22] Smith *et al*.[23] found that vitamin D administration significantly suppressed TSH secretion in the basal state. He also showed that serum TSH levels of middle-aged and elderly women were higher than those of same-age men.[23] This result may indicate that TSH secretion is regulated by sex hormones, genetic susceptibility or environmental factors, which may also mediate the relationship between vitamin D status and serum TSH level.[24] In addition, another study found that circulating estrogen could induce serum TSH suppression in males by acting on pituitary, and vitamin D has been shown to have an important role in estrogen synthesis of both female and male gonads.[25]

Conclusion

Overall, the current study demonstrated that vitamin D supplementation among hypothyroid patients for 12 weeks improved serum TSH and calcium concentrations compared with the placebo, but it did not alter serum T3 and T4 levels.

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Conflicts of interest

There are no conflicts of interest.

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