Original Article

Effect of Vitamin D Supplementation on Thyroid Autoimmunity among Subjects of Autoimmune Thyroid Disease in a Coastal Province of India: A Randomized Open-label Trial

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Abstract

Objective: Hashimoto's thyroiditis (HT) is a variant of autoimmune thyroid disorders (AITD) which has been associated with vitamin D (vit-D) deficiency. However, whether vit-D supplementation is linked to reduction of thyroid autoantibodies and improvement of thyroid function is not well characterized. The present study was planned to evaluate the effect of vit-D supplementation on possible improvement of thyroid autoantibody titer and thyroid hormone profile in patients with AITD subjects. **Methods:** Twenty-three patients of HT were given weekly supplementation of 60,000 IU vit-D for 8 weeks followed by once a month for another 4 months. After 6 months of vit-D supplementation, thyroid autoantibody titer (TPO antibody) and thyroid hormone profile was rechecked. **Results:** Mean serum vit-D was increased significantly from 15.33 ± 5.71 to 41.22 ± 12.24 ng/mL (normal levels) after supplementation. There was significant increase in thyroid autoantibody titre (from 746.8 ± 332.2 to 954.1 ±4 59.8 IU/ml; $P = 0.006$) and TSH level (7.23 ± 3.16 to 3.04 ± 2.62 (mIU/L); $P = 0.01$) following 6 months of vit-D supplementation. **Conclusion:** Vitamin-D levels were low in AITD patients in eastern India and, its supplementation in HT patients increased thyroid antibody titer and there was significant reduction in serum TSH and increased in free T4.

Keywords: Anti thyroid peroxidase antibody, Hashimoto's thyroiditis, thyroid autoimmunity, Vitamin-D

Introduction

Autoimmune thyroid disease (AITD) is broadly classified into two types: Grave's disease and Hashimoto's thyroiditis (HT). HT is a polygenic in nature resulting from interplay between the genetic factor and environmental triggers, characterized by lymphocytic infiltration into the thyroid glands and thyroid specific autoantibodies.[1] HT is a typical T-cell-mediated autoimmune disease characterized clinically with diffuse thyroid swelling with presence of thyroid autoantibodies (anti thyroid peroxidase [TPO]) antibody with various form of thyroid dysfunctions.[2] Clinical manifestation is varied from overt hypothyroidism to subclinical hypothyroidism depending on the degree of immune-mediated destruction of thyroid follicular cell.

Vit-D has been demonstrated to have a role in thyroid disease. It is involved in modulating immune system, and it enhances the innate immune response while exerting the inhibitory action in adaptive immune system.[2] Nuclear vit-D receptor and the vitamin-D-activating enzyme 1α-hydroxylase (CYP27B1) is expressed in T-cell, B-cells, macrophage, and antigen-presenting cell (APC) such as dendritic cells (DCs), all are actively involved in immune response.[3] APC expresses major histocompatibility complex II antigen and costimulatory molecule, which is inhibited by vit-D; it not only prevents the maturation and differentiation of DCs but also halts their activation and

Access this article online

Quick Response Code:

Website: www.nigeriamedj.com

DOI: 10.4103/nmj.NMJ_200_20

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Submitted: 04-Jun-2020 **Revised:** 25-Jun-2020
Accepted: 04-Sep-2020 **Published:** 13-Oct-2020

How to cite this article: Behera KK, Saharia GK, Hota D, Sahoo DP, Sethy M, Srinivasan A. Effect of Vitamin D supplementation on thyroid autoimmunity among subjects of autoimmune thyroid disease in a coastal province of India: A randomized open-label trial. Niger Med J 2020;61:237-40.

survival, leading to decreased antigen presentation and T-cell activation. Vit-D modulates the DCs expression of cytokine by inhibiting the production of interleukins 12, 13 and enhancing the production of interleukin-10. Therefore, it shifts Th1, Th17 T-cell moiety to Th2 subtype. There is evidence that it also modulates the antibody production from B-cell. By and large, vit-D has the ability to suppress the adaptive immune reaction and enhance the innate immune action, which has favorable outcome for various autoimmune disorder.[3]

Efficacy of vit-D supplementation in vit-D deficient AITD is controversial. Vit-D supplementation has shown decrease in thyroid autoantibody titers as reported by some investigators while has no effect by others.[6] The present study was planned to investigate the impact and magnitude of vit-D supplementation on thyroid function in subjects with HT.

Subjects and Methods

Objectives

The study was aimed to evaluate the effect of vit-D supplementation to the HT patients with Vit-D deficiency with subclinical hypothyroidism.

The objective was to study the effect of vit-D supplementation on thyroid autoantibody (anti-TPO antibody) titer and thyroid hormone profile (thyroid-stimulating hormone [TSH] and free T4) in patients with HT with subclinical hypothyroid state.

The study was jointly carried out by the Departments of Endocrinology and Biochemistry, All India Institute of Medical Sciences, Bhubaneswar, India.

Participants

Patients with thyroid disorder attending the endocrinology clinic of All India Institute of Medical Sciences, Bhubaneswar (India), were screened for eligibility. The inclusion criteria were patients of either sex between 18 and 65 years of age, having thyroid autoantibody more than 60 units/mL, TSH levels between 5.5 and <10 (normal, 0.34–5.5 μIU/mL), and normal free T4 (0.89–176 ng/dL).

Women planning to conceive, all patients with infertility, psychiatric disorders, severe cardiovascular, liver and renal disease, on treatment with steroid hormones, and antiepileptic or glucocorticoids were excluded from the study.

The study was initiated following the approval of the Institutional Ethics Committee (protocol number T/IM-F/17-18/4.) of All India Institute of Medical Sciences, Bhubaneswar (India), and the trial was registered at clinicaltrials.gov (registration no. CTRI/2018/02/012176).

Study design, randomization, and blinding

The study was a prospective, randomized, open-label trial. Out of 51 screened, 23 patients completed the study.

Intervention

The eligible patients were administered 60,000 IU of vit-D3 orally once a week for initial 8 weeks followed by once a month for next 4 months.

Assessment of clinical and biochemical endpoints

Levels of vit-D, TSH, free T4, and anti-TPO antibody were measured at baseline and at 6 months by chemiluminescent immunoassay system.

Statistics

To calculate a change of 200U/ml of anti-TPO antibody levels following 6 month of vit-D therapy, a sample size of 22 was required. The standard deviation (SD) assumed was 500. The α and β errors allowed were 5% and 20%, respectively. Continuous variables were expressed as mean and SDs and analyzed using Student's *t*-tests. All tests were 2-sided and $P < 0.05$ was considered statistically significant.

Results

The mean age, height, weight, and body mass index (BMI) were 35.5 ± 11.0, 153.0 ± 6.2, 56.1 ± 12.1, and 25.2 ± 7.7, respectively [Table 1].

Table 2 depicts the change in values of anti-TPO antibody, TSH, vit-D, and free T4 levels before and after 6 months of vit-D administration. There was significant increase ($P = 0.001$) in the anti-TPO antibody, vit-D, and free T4 levels. However, the TSH showed a significant reduction after 6 months of vit-D therapy.

The plasma vit-D levels (25-OH vit-D) after 6 months of therapy was normalized in 20 cases (87%). Moreover, 3 (13%) still remained in the mild deficiency states, but no one in the moderate or severe deficiency levels.

Table 1: Demographic profile

Characteristics	HT (*n*=23)
Age	35.50±11.03
Sex	
Male	1
Female	22
Height (cm)	153.02±6.12
Wight (kg)	56.09±120.9
BMI (kg/m^2)	25.2±7.7

HT – Hashimoto's thyroiditis, BMI – Body mass index

Table 2: Depicts the change in values of anti- thyroid peroxidase antibody, thyroid-stimulating hormone, Vitamin-D and free T4 levels before and after 6 months of Vitamin-D administration

Parameters	Before Vitamin-D	6 month after Vitamin-D	*P*
Anti-TPO Ab (U/mL)	746.84±332.24	954.09±459.76	0.001
TSH (mIU/L)	7.23±3.16	3.04±2.62	0.001
25(OH) Vit-D	15.33±5.71	41.22±12.24	0.001
Free T4 (ng/dL)	0.9±0.29	1.11±0.198	0.005

n=23. TPO – Thyroid peroxidase, 25(OH) Vit-D – 25-hydroxy Vitamin D, TSH – Thyroid-stimulating hormone

Table 3: Status of Vitamin-D in Hashimoto's thyroiditis subjects

Serum 25 (OH) D	Base line	6 month
	15.33±5.71	38.03±12.24
Normal (≥30 ng/mL) (%)	1 (4.34)	20 (86.95)
Mild deficiency (20-29.9 ng/mL)	6 (26.8)	3 (13.05)
Moderate deficiency (10-19.9 ng/mL)	11 (47.82)	0
Severe deficiency (<10 ng/mL)	5 (21.73)	0

Values are *n* (%). 25(OH) Vit-D – 25-hydroxy Vitamin D

Discussion

Table 3 shows the status of vit-D in HT subjects. Adequate vit-D was observed in only 1 case (4%), while 22 cases (96%) were deficient. Six months after supplementation, 20 (87%) subjects had normal levels, whereas 3 (13%) had mild vit-D deficiency. Various studies have reported an association between vit-D deficiency to be more common in subjects with HT than in controls.[7,8] Another study by Kivity *et al*. had reported prevalence of vit-D deficiency in 28 patients with HT compared to 42 patients with non-AITD (79% vs. 52%; $P < 0.05$). Vitamin-D level was an independent factor affecting the presence of TPO antibody in HT patients.[9] Some studies, however, had failed to find an association between low vitamin D status and HT. A study by Goswami *et al*. from India revealed no association between Vit-D deficiency (<25 nmol/L) and anti-TPO positivity, but only a weak inverse correlation between serum 25 (OH) D and anti-TPO levels in 642 students, teachers, and staff from India ($r = -0.08$; $P = 0.04$).[6] Effraimidis *et al*. found no association between low vit-D levels and early stage of thyroid autoimmunity in their study among euthyroid subjects with genetic susceptibility for AITD.[10]

After 6 months of vit-D supplementation, it was observed that a there was a significant increase in anti-TPO antibody titer. A few studies had investigated whether vit-D supplementation is beneficial in HT. Chaudhary *et al*.[4] and Mazokopakis *et al*.[7] had reported marked decrease in TPO antibody after vit-D supplementation; however, no relationship was observed by Knutsen *et al*.[11]

The exact cause of increase in thyroid autoantibodies following vit-D supplementation is not known. However the TPO antibody titer may increase due to the on going autoimmune destruction of thyroid follicular cell by T-lymphocytes as a natural process in the initial stage of HT.[12] Further research in large sample size is needed to find out the cause.

The present study showed a significant reduction in TSH and increase in FT4 following vit-D supplementation [Table 2]. TSH levels were inversely correlated with vit-D levels independent of plasma thyroid hormone levels.[13] A population-based study showed that high vit-D status in younger individuals is associated with low circulating TSH which was independently of the age, sex, BMI, serum anti-TPO Ab, and/or thyroglobulin antibody.[14] Serum vit-D was significantly lower in hypothyroid patients than in controls ($t = -11.128$, $P < 0.001$), suggesting that there might be a significant association between hypovitaminosis-D and hypothyroidism.[15]

A study by Talaei and coworkers (2018) had shown that vit-D supplementation among hypothyroid patients for 12 weeks caused reduction in serum TSH levels compared to placebo, but it did not alter serum T3 or T4.[16]

Limitations of the present study include the open-labeled design of randomized clinical trials, lack of placebo arm, a relatively smaller sample size, and shorter follow-up duration.

Conclusion

Vit-D deficiency is significantly common in HT patients in Eastern India and its supplementation in these patients did not show any beneficial effect on thyroid autoimmunity as evidenced by a significant increase in circulating anti-TPO antibody titers though there is significant reduction in the TSH levels.

Roles played by the individual authors

i. KKB: conceptualized the study and protocol writing and monitored the study progress, provided the patients, and edited the final draft
ii. GKS**:** contributed in biochemical estimation
iii. DPS and AS: Statistical inputs and data analysis
iv. DH: manuscript correction and editing the final daft
v. MS: verification of accuracy of laboratory data.

Acknowledgments

The authors acknowledge Dr. Madhusmita Sahu, Senior Resident, Department of Endocrinology. for data entry and Ms. Shweta, staff nurse for collecting the blood samples for vit-D estimation.

Financial support and sponsorship

The study was funded by All India Institute of Medical Sciences, Bhubaneswar.

Conflicts of interest

There are no conflicts of interest.

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