

# STUDYING VITAMIN D SUPPLEMENTATION'S IMMUNOMODULATORY EFFECTS ON YOUNG WOMEN WITH AUTOIMMUNE TYROSIS AND HYPOVITAMINOSIS D

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## Abstract

**Background:** Preclinical and observational research have revealed the pleiotropic functions of vitamin D and suggested a positive role for it in the treatment of thyroid illness.

Examining the effects of vitamin D treatment on serum levels of TPO Ab, thyroid functions, TNF ALPHA, and IL6 as well as the effects of vitamin D supplementation on thyroid autoimmunity in patients with recently diagnosed AITD will help to shed light on the relationship between vitamin D and thyroid autoimmunity. **Materials and Methods: Setting and Design:** This study is prospective. In this study, we determined the levels of FT4, TSH, anti-TPO titre, 25(OH)D3, TNF-, and IL6 in 30 female patients with autoimmune thyroid disease based on anti-TPO levels and the presence of a vitamin D shortage at the time of diagnosis and 2 months after starting vitamin D treatment. Utilized for statistical analysis: SPSS Software 24. **Result:** TPO Ab titres were highest among AITD patients in the lowest 25(OH) D quartile that approached statistical significance ( $P = 0.005$ ) when baseline thyroid function, autoimmunity, and pro-inflammatory characteristics are split as per quartiles of serum 25-hydroxyvitamin D. TPO-Ab titres were highest in the group of people with vitamin D levels below 5.5; the mean titre value for this group was 1004; and lowest in the group of people with vitamin D levels above 13.67. This group's average value was 163.843. When divided according to the quartiles of serum 25-hydroxyvitamin D, the levels of T3, FT4, TSH, TNF ALFA, and IL6 were not statistically significant. **Conclusion:** Vitamin D treatment was discovered to have a favourable influence on the thyroid antigenicity and thyroid function in the current investigation in Vitamin D deficient participants. Vitamin D supplementation lowered thyroid antibody titres.

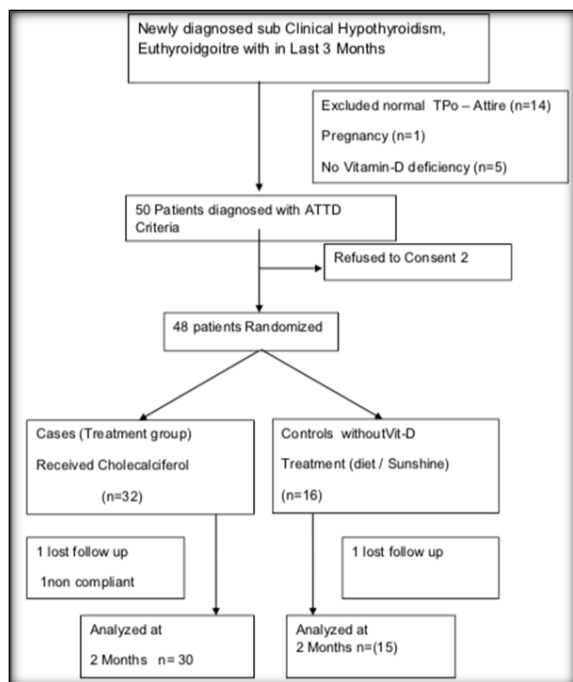
## INTRODUCTION

Worldwide, vitamin D insufficiency is becoming a bigger issue. It has been evident over the past three decades that vitamin D has a function in more than just maintaining bone health and regulating calcium homeostasis. According to recent research, vitamin D insufficiency may also play a significant role in autoimmune disorders, cancer, metabolic syndromes, cardiovascular disease, infections, and all-cause mortality in addition to its effects on the skeleton.<sup>[1]</sup> Multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), SLE, RA, inflammatory bowel disease, thyroiditis, and autoimmune gastritis are among the autoimmune diseases associated with low vitamin D levels.<sup>[2]</sup> However, it is not always obvious whether a vitamin D shortage is the disease's primary cause or merely one of its effects.

## MATERIALS AND METHODS

### Subjects and methods:

Prospective, open-label interventional trial design  
Consecutive patients between the ages of 18 and 30 who visited the department's endocrinology clinic and had recently received a subclinical hypothyroidism or euthyroid goitre diagnosis were taken into consideration. To evaluate the cases and controls as shown in figure1, a process was followed.



**Figure 1: Flowchart showing the study protocol and flow of patient**

#### Inclusion Standards

1. Women with age group between 18-30 years
2. Newly diagnosed euthyroid and subclinical hypothyroidism patients
3. Not on levothyroxine therapy
4. A vitamin D level below 20 ng/ml

#### Exclusion Standards

1. Being pregnant
2. Making pregnancy plans
3. Hypothyroidism is known and being treated
4. Patients with chronic kidney, liver, or immune deficiencies, as well as those taking long-term drugs that can affect the metabolism of thyroid hormone or vitamin D, were excluded from the study. Additionally eliminated were people who had taken vitamin D in the previous six months.

There have been 70 new cases of subclinical hypothyroidism and euthyroid goitre, of which 50 patients met the AITD criteria for vitamin D deficiency. There were 20 excluded patients, of which 14 had normal TPO-Ab titre, 5 had no Vitamin D insufficiency, and 1 was pregnant.

Out of 50 patients, two declined to provide written consent, leaving 48 patients who were randomly assigned to 16 controls and 32 cases. In 32 instances over a period of two months, there was one lost follow-up, one patient who did not comply with therapy, and one lost follow-up in 16 controls. A total of 45 patients were examined at the end of two months: 30 cases and 15 controls. The included patients were called on a separate day after 12 h fast for clinical, biochemical, and anthropometric assessment.

Cases (treatment group): AITD patients using cholecalciferol 60,000 IU (D-Rise capsules) of vitamin D once a week for eight weeks.

Serum was extracted from blood samples and kept at 80°C for biochemical analysis. TPO Ab, free tetraiodothyronine (FT4), thyroid-stimulating hormone (TSH), total T3, TNF ALFA, IL6, and 25(OH) D baseline levels were estimated.

For the duration of the trial, patients were followed up monthly in the endocrine clinic. They were examined, asked questions about side symptoms and drug compliance, collected empty sachets, and given a fresh batch of medications. Every week, patients were contacted via phone or message services to check on compliance.

After a follow-up of two months, blood samples were taken again for all the biochemical markers that were assessed at the outset.

A common questionnaire was utilised to gather data on demographics, way of life, and medical background. A history was obtained to see whether there were any systemic chronic illnesses, thyroid disorders in the past or present, past or present use of thyroid medications, previous or present use of other drugs, and any thyroid disorders in the family.

All subjects underwent thorough general and systemic examinations in accordance with the proforma. In the general examination, we searched for anthropometric measurements such as weight, height, and body mass index (BMI). We assessed height with a wall-mounted tape measure and weight with an electronic weighing scale (ELPRO, Ahmadabad).

A thyroid exam was performed to look for any goitres, and the World Health Organization's classification of goitres was used to rate them. Grade 0 goitres are nonexistent, grade 1 goitres are only palpable but not visible, and grade 2 goitres are both visible and palpable.

## RESULTS

The clinical and demographic information for the patients and controls was examined. Cases and controls had similar mean ages, heights, and weights. In comparison to controls, TPO Ab levels were significantly lower in the cases group (replacement group) (P value 0.001 vs 0.318). After receiving vitamin D medication, the mean baseline value in the cases dropped to 298.3 IU/ml from 565.77 IU/ML. TPO Ab titres changed by a median of 35.75% in patients and 11% in the control group.

Following therapy, the Free T4 increased statistically significantly from its mean baseline value of 1.27ng/dl to 1.38ng/dl with a P value of 0.001. After two months of vitamin D therapy, there is a mean difference in FT4 of 0.036.

With a P value of 0.210, the change in FT4 value in the control group did not reach statistical significance. After two months without therapy, the mean baseline in the control group fell to 1.23ng/dl.

TSH levels fell in the cases group compared to controls, and the P value was (0.001 vs 0.007) After receiving vitamin D medication, the mean baseline

value in cases dropped to 5.95 mIU/l from 6.46 mIU/l.

After two months without therapy, the mean baseline TSH level in the control group climbed to 7.51mIU/l. When compared to the controls, the cases group (replacement group) had considerably lower levels of the pro-inflammatory markers TNF (P value 0.001 vs 0.250). After receiving vitamin D medication, the mean baseline value in cases fell to 5.74 pg/ml from 7.54 pg/ml. The average change after two months of vitamin D therapy is 1.796. The drop in TNF levels in the control group did not reach statistical significance.

Despite a trend toward decline in IL6 when compared to controls (P value 0.051 versus 0.150), neither cases nor controls showed this shift to be statistically significant.

After therapy with vitamin D, the average baseline level of IL6 in patients reduced from 5.03 pg/ml to 4.62 pg/ml, with a mean difference of 0.411 after two months of vitamin D treatment.

TPO Ab titres were highest among AITD patients in the lowest 25(OH)D quartile that approached statistical significance (P = 0.005), when baseline thyroid function, autoimmunity, and pro-inflammatory characteristics are split as per quartiles of serum 25-hydroxyvitamin D [Table 1].

**Table 1: Baseline thyroid function, autoimmunity, TNF ALPHA and IL6 as per quartiles of serum 25-hydroxyvitamin D**

	Vitamin D	N	Mean	Std Deviation	ANOVA(F)	P Value
TPO ANTIBODIES	<5.50	7	1004.857	442.0616	5.35	0.005
	5.50-8.65	8	653.175	592.2112		
	8.65-13.67	8	445.875	287.2652		
	>13.67	7	163.843	127.8321		
	Total	30	565.777	489.8881		
T3	<5.50	7	1.2714	.30383	1.753	0.181
	5.50-8.65	8	1.0875	.11829		
	8.65-13.67	8	1.2625	.11055		
	>13.67	7	1.2186	.12760		
	Total	30	1.2077	.18606		
FT4	<5.50	7	1.2571	.16590	0.324	0.808
	5.50-8.65	8	1.2050	.31044		
	8.65-13.67	8	1.3125	.28379		
	>13.67	7	1.3271	.29222		
	Total	30	1.2743	.26179		
TSH	<5.50	7	7.5714	2.35134	0.908	0.451
	5.50-8.65	8	6.5738	2.54193		
	8.65-13.67	8	5.6313	1.84650		
	>13.67	7	6.1771	2.55008		
	Total	30	6.4627	2.32002		
TNF ALPHA	<5.50	7	9.09171	3.060645	1.118	0.360
	5.50-8.65	8	5.63550	2.627505		
	8.65-13.67	8	9.94438	10.872318		
	>13.67	7	5.42200	2.049893		
	Total	30	7.54117	6.104595		
IL6	<5.50	7	5.456857	4.4321606	0.328	0.805
	5.50-8.65	8	4.210375	4.1711866		
	8.65-13.67	8	6.498363	9.2138317		
	>13.67	7	3.867571	2.7869685		
	Total	30	5.031363	5.6136501		

TPO-Ab titres were highest in the vitamin D levels below 5.5 and below 13.67, where the mean value was 1004 and lowest in the vitamin D levels above 13.67, where the mean value was 163.843.

When divided according to the quartiles of serum 25-hydroxyvitamin D, the levels of T3, FT4, TSH, TNF ALFA, and IL6 were not statistically significant.

## DISCUSSION

Worldwide, vitamin D insufficiency is becoming a bigger issue. It has been evident over the past three decades that vitamin D has a function in more than just maintaining bone health and regulating calcium homeostasis. The immune system's regulation is one of vitamin D's significant additional skeletal effects. Numerous autoimmune diseases, including rheumatoid arthritis, lupus, type 1 diabetes, Crohn's disease, ulcerative colitis, and multiple sclerosis have been associated to vitamin D deficiency. Numerous

clinical studies have revealed low vitamin D levels in patients with AITD or HT, pointing to a link between thyroid autoimmunity and vitamin D deficiency.

In this investigation, we determined the levels of FT4, TSH, anti TPO titre, 25 (OH) D3, TNF-, and IL6 in 30 female patients with autoimmune thyroid disease based on antiTPO levels, USG characteristics, and the presence of vitamin D deficiency at diagnosis and 2 months after vitamin D treatment.

We looked at how vitamin D therapy affected these variables. Following vitamin D therapy, there was a statistically significant increase in 25(OH)D3 and

FT4 levels, a significant drop in TSH, antiTPO, TSH, and TNF-, and no statistically significant change in T3, IL6 levels. Vitamin D therapy may improve thyroid antigenicity and function in autoimmune thyroid illness, as seen by the rise in FT4 levels and the declines in TSH, anti-TPO levels, and TNF-levels. The patients with early AITD who have subclinical hypothyroidism may benefit from vitamin D treatment the most.

Because AITD is more prevalent in women and our sample size is small, including both sexes in the study would make it more challenging to analyse the data. Only women were recruited for this study.

Numerous clinical studies have documented low vitamin D levels in patients with AITD or HT, demonstrating a link between thyroid autoimmunity and vitamin D deficiency.

In our research, we discovered a negative association between 25(OH)D3 and anti-TPO ( $r = 0.252$ ;  $p = 0.001$ ). Numerous research have found findings of this nature.

According to Shin et al.<sup>[3]</sup> 193 patients with no elevation and 111 patients with higher anti-thyroid antibodies both exhibited reduced serum 25(OH)D3 levels ( $p = 0.001$ ). Furthermore, in a sample of people with AITD, a negative connection ( $r = 0.252$ ;  $p = 0.001$ ) between 25(OH)D3 and anti-TPO levels was discovered after controlling for age, sex, and body mass index (BMI).

Kivity et al.<sup>[4]</sup> showed that 28 patients with HT compared to 42 patients with non-AITD (79% vs. 52%;  $p = 0.05$ ) and 50 patients with AITD compared to 98 healthy individuals (72% vs. 30.6%;  $p = 0.001$ ) had significantly higher prevalences of vitamin D deficiency (25(OH)D level 25 nmol/L). Anti-thyroid antibodies were also shown to be linked with vitamin D deficiency ( $p = 0.01$ ), indicating that vitamin D may play a role in the aetiology of AITD.

254 newly diagnosed HT and 27 GD patients had 25(OH)D levels that were lower than those of 124 healthy controls ( $p = 0.001$ ), according to research by Unal et al.<sup>[5]</sup> and serum 25(OH)D levels were negatively correlated with anti-Tg ( $r = 0.136$ ;  $p = 0.025$ ) and anti-TPO ( $r = 0.176$ ;  $p = 0.003$ ) antibodies.

Wang et al.<sup>[6]</sup> s population-based health survey of 1714 Chinese individuals likewise revealed a negative connection between 25(OH)D and anti-Tg levels in female participants ( $r = 0.121$ ;  $p = 0.014$ ).

However, several research have been unable to link HT or AITD to low vitamin D status.

The sole Indian cross-sectional study Goswami et al.<sup>[7]</sup> analysis of 642 Indian students, instructors, and staff members found only a weak inverse correlation between serum 25(OH)D and anti-TPO levels ( $r = 0.08$ ;  $p = 0.04$ ), not a link between vitamin D deficiency (25 nmol/L) and anti-TPO positive.

According to Effraimidis et al.<sup>[8]</sup> from Amsterdam, neither participants with a genetic predisposition for AITD nor seroconverts with de novo development of anti-TPO antibodies had 25(OH)D levels that were lower than those of controls or AIRD cases. Different

cut-off levels used to define vitamin D deficiency or insufficiency, inter-assay and inter-laboratory variability in 25(OH)D measurements, and limitations in study design, such as cross-sectional studies with a small subject population and the potential for selection bias, as well as the heterogeneity of the study population and the variety of methods used for the diagnosis of AITD, all contribute to the varying results of studies.

Recently published research that examined the benefits of vitamin D supplementation for HT or AITD are few in number.

Mazokopakis et al.<sup>[9]</sup> Both Chaudhary et al.<sup>[10]</sup> and Simsek et al.<sup>[11]</sup> observed vitamin D3 treatment in vitamin D-deficient patients, and both investigations, which are comparable to our study, showed a significant drop in blood anti-TPO levels.

Serum 25(OH)D levels in 218 euthyroid HT patients were found to be negatively linked with anti-TPO levels, according to Mazokopakis et al. When compared to HT patients who did not have a vitamin D deficiency (25(OH)D level 75 nmol/L), anti-TPO levels were likewise noticeably higher in vitamin D-deficient HT patients. In 186 patients with vitamin D deficiency, blood anti-TPO levels significantly decreased (20.3%) after 4 months of oral vitamin D3 therapy (1200–4000 IU/day).

Study from India by Chaudhary et al.<sup>[10]</sup> examined 100 newly diagnosed AITD patients and discovered that those with the lowest 25(OH)D quartile had the greatest anti-TPO levels ( $p = 0.084$ ). When compared to patients who did not receive vitamin D supplementation, patients who got vitamin D3 supplementation at 60,000 IU per week for 8 weeks experienced a substantial decrease in anti-TPO levels at the 3-month follow-up (46.73% vs. 16.6%;  $p = 0.028$ ). The proportion of those who responded (25% decline in anti-TPO level) was higher in the vitamin D supplementation group (68% vs. 44%;  $p = 0.015$ ). When comparing treatment and control groups, subgroup analysis showed that only individuals with baseline serum TSH 10 mIU/L had a substantial drop in TPO Ab titres (relative to baseline).

Simsek et al study 's ( $p = 0.02$  and  $p = 0.03$ , respectively) showed that vitamin D therapy at 1000 IU/day for a month significantly reduced the levels of anti-TPO and anti-Tg in AITD patients with a 25(OH)D level 50 nmol/L. Anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-Tg) antibodies can be found in serum, there can be varying degrees of thyroid hypofunction, and intrathyroidal infiltration of B and T lymphocytes with CD4+ is a characteristic feature of HT, a typical T-cell-mediated autoimmune disease. Vitamin D plays a significant role in immune system modulation, enhancing the innate immune response while inhibiting the adaptive

The immunomodulatory effects of 1,25(OH)2D3 on T cells have been demonstrated in in vitro experiments.<sup>[12,13]</sup> Vitamin D and vitamin D receptor deficiency may boost the Th1-mediated immune response. By preventing Th1 cells from growing and

functioning, the active form of vitamin D treatment has shown promise in treating autoimmune illnesses. Vitamin D can decrease the autoimmune process at various HT stages, lower Th1 cell cytokine production, and activate Th1 cell antigenicity generated by cytokines. The production of thyroid antibodies that respond with thyroid antigens may be decreased by vitamin D in its biologically active form.

TNF- and IL1, two proinflammatory cytokines, can influence apoptosis that is connected to immunity. Studies using thyroid cell culture have demonstrated that TNF-, IL-1, and IFN- can cause apoptosis.<sup>[14]</sup> Through local immune cell release, proinflammatory cytokines like IL-6, IL-1, and TNF- may exacerbate cell damage and hasten the course of the disease. Vitamin D deficiency can result in an increase in the secretion of proinflammatory cytokines including IL-6, IL-1, and TNF-, which can lead to increased cell damage in HT patients because vitamin D can influence the immune system's production of proinflammatory cytokines.<sup>[15]</sup>

In this investigation, serum TNF- levels were lowered after vitamin D administration, achieving a statistically significant difference. Although not statistically significant, IL-6 levels are trending downward as compared to pre-treatment readings. According to our findings, vitamin D treatment had an impact on the levels of inflammatory cytokines including TNF- and IL-6 in the body of patients with vitamin D deficiency and autoimmune thyroid disease.

Treatment with vitamin D can reduce the tissue-level release of cytokines from immune cells as well as their production. The beneficial effects of vitamin D treatment on individuals with autoimmune thyroid disease that we observed in our trial may have happened at both the tissue and systemic levels. Effects caused by additional cytokines or by mechanisms that were not examined in this study. Studies have revealed a relationship between TNF-, IL-6, and anti-TPO as well as between TNF- and HT.<sup>[16,17,18]</sup>

The effect of vitamin D treatment on thyroid function and the levels of thyroid autoantibodies, TNF-, IL-6, and IL-1 in individuals with autoimmune thyroiditis was examined by Fettah Acibucu et al.<sup>[19]</sup> There was a statistically significant difference (p 0.05) between the pre- and post-treatment levels of FT4, TSH, anti-TPO, anti-TG, PTH, and ALP. Following vitamin D therapy, 25 (OH) D3 and FT4 levels statistically significantly increased, and TSH, antiTPO, antiTG, PTH, and ALP levels significantly decreased—findings that are analogous to those from our trial. This study's positive effect on thyroid antigenicity was explained by cytokines released from immune cells at the tissue level, and their secretion can be decreased with vitamin D treatment. In contrast to our study, post-vitamin D treatment, no significant difference was noted in TNF-, IL-6, and IL-1 levels. The present investigation supports the significance of vitamin D in causing this drop by demonstrating a

decrease in TPO Ab titres in patients with subclinical hypothyroidism (who did not receive levothyroxine). This study emphasises the necessity of additional long-term vitamin D interventions to determine whether the decrease in TPO Ab titres results in a slowed progression of subclinical to overt primary hypothyroidism or in inducing remission of hypothyroidism as evidenced by stopping or reducing the dose of levothyroxine, which would be a more clinically relevant outcome.

Due to expanding knowledge of vitamin D's significance for bone health and further skeletal consequences, vitamin D insufficiency is becoming a global health issue. Improved vitamin D status may result from the addition of vitamin D to commonly consumed foods like edible oil. No histological evidence of HT was taken; AITD was predicated on serum TPO Ab titre greater than the upper limit of normal, thyroiditis evidence from our lab and/or HRUSG, and so on.

## CONCLUSION

Vitamin D supplementation reduced thyroid antibody titres in the current study's patients who were vitamin D deficient, and vitamin D treatment was found to have a favourable impact on thyroid antigenicity and thyroid function.

This study supports the significance of vitamin D in causing this reduction by demonstrating decreased levels of TPO Ab titre, TNF ALPHA, and IL6 in patients with subclinical hypothyroidism (who did not get levothyroxine).

The preventive and therapeutic potential of vitamin D in thyroid illnesses is still up for debate, however, given there is only a hazy causal association and scant evidence from interventional trials.

To find out whether people with low 25(OH)D levels are more likely to develop AITD and to shed light on the effectiveness and use of vitamin D as a treatment for these thyroid conditions, long-term, randomised controlled trials are necessary.

Small sample size and short follow-up time are the study's limitations.

### List of used abbreviations

NILM Negative for intraepithelial lesion/malignancy  
ASCUS Atypical squamous cell of undetermined significance

ASCUS-H Atypical squamous cell— cannot exclude HSIL

LSIL Low grade squamous intraepithelial lesion  
HSIL High grade squamous intraepithelial lesion.

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