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Original Article

Relationship of Vitamin D Status with Thyroid Autoimmunity in New Onset Autoimmune Hypothyroidism

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Abstract

Background: Study of serum vitamin D level in new onset hypothyroid patients and its correlation with thyroid related parameters and antibody titers.

Objectives: We aimed to compare serum vitamin D level in new onset hypothyroid patients versus controls. Furthermore we evaluated for any association of vitamin D status with hypothyroid state and its correlation with various thyroid related parameters.

Methodology: In this cross sectional study , 61 new onset hypothyroid subjects (cases) and 40 age, sex and BMI matched healthy individuals (controls) were recruited. Measurements of serum vitamin D, thyroid hormones, thyroid peroxidase antibody (TPO-Ab), parathyroid hormone (PTH), calcium and phosphorus were done for all study participants.

Results: The mean serum vitamin D in cases (22.95±8.59 ng/ml) was significantly lower than the controls (27.9±7.85 ng/ml) ($p<0.01$). The prevalence of vitamin D deficiency was significantly higher among hypothyroid subjects than controls ($p=0.009$). Hypothyroid subjects with vitamin D deficiency group had significantly higher TSH level, greater thyroid volume and elevated anti TPO titres than those with vitamin D sufficiency. Serum vitamin D level had significant inverse correlation with anti TPO-Abtiters even after adjustment for age, sex and BMI.

Conclusion: Serum vitamin D is significantly low in new onset hypothyroid patients than healthy controls. Hypothyroid patients with vitamin D deficiency have significantly higher TSH, antibody titres and thyroid volume. A significant negative correlation was observed between serum vitamin D leveland anti TPO titres. Moreover, serum vitamin D remained an independent predictor of TPO level among hypothyroid subjects.

Keywords; Thyroid; Vitamin D; Hypothyroidism; Autoimmune Thyroid Disease; Anti TPO Antibody.

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Introduction

Vitamin D is a steroid molecule that is mainly produced in the skin and regulates the expression of many genes.[1,2]The role of vitamin D in bone mineral metabolism and maintenance of skeletal health has been known for decades, but in recent time many studies have proved its effects on extra skeletal tissue as well.[2,3,4]Theassociation between low levels of serum 25(OH)D and high incidence of several autoimmune diseases including type 1 diabetes mellitus (T1DM), rheumatoid arthritis (RA), systemic lupus erythematous, multiple sclerosis (MS), inflammatory bowel disease, and autoimmune thyroid diseases has been proved by many epidemiological studies.[1,2,5-9] Many clinical trials have demonstrated that vitamin D supplementation in humans may prevent the development of T1DM, RA or MS when given prophylactically.[1,2] Vitamin D mediates its effect through binding to vitamin Dreceptor (VDR) and thus activation of vitamin D response element in the genes.[10] The VDR are widely distributed in many human tissues including pancreas, myocardium, lymphocytes, thyroid gland etc. signifying its importance in humans.[11] Both vitamin D and thyroid hormones act through nuclear receptors and may affect each other's action as they have similar response elements on the genes and hence a lower level of vitamin D is likely to aggravate the systemic abnormalities associated with hypothyroidism.[12,13]

Autoimmune hypothyroidism has been estimated to be the most frequent endocrine autoimmune disorder and possibly affects approximately 42 million people in India[14] and the prevalence of hypothyroidism has increased markedly in the last few decades affecting even younger age groups.[15]Vitamin D is present in the serum in either of its two forms: 25hydroxyl- cholecalciferol [25(OH) D] or 1,25dihydroxy-cholecalciferol [1, 25(OH) D]. The 25(OH) D has fairly long circulating half-life of 15 days and reflects the total vitamin D content of the body.[16]Several studies have examined the relationship between low vitamin D levels and the prevalence of autoimmune thyroid disease (AITD) in humans, but the results have been conflicting.[7-9,17] Some studies have revealed good correlation between low serum 25(OH)D levels with the presence of high levels of antithyroid antibodies, abnormal thyroid function, increased thyroid volume, and increased thyroid stimulating hormone (TSH) levels,[2,7-9,12-19] while others have reported a weak or no association between low vitamin D levels and thyroid autoimmunity.[17,20-21] A recent study showed that low serum 25(OH)D levels in euthyroid patients with Hashimoto's thyroidit is were inversely correlated with serum anti-thyroid peroxidase (TPO) antibodies and that after vitamin D supplementation for four months there was a significant decrease in serum anti-TPO levels.[22] Considering the potential role of vitamin D in modulating autoimmune thyroid diseases, we undertook the present study with the aim to examine the association of vitamin D deficiency with hypothyroidism and to find out its relations with thyroid hormonal status and anti TPO antibody titers in our study population.

Materials and Methods

This is a cross sectional study conducted in the outpatient department of Endocrinology, of a tertiary care teaching hospital of eastern India during the period from March 2017 to May 2017. Sixty one consecutive patients (39 females and 22 males) of new onset autoimmune thyroid disease (AITD) with overt hypothyroidism were recruited to our study. Any subject who was a known case of thyroid disease or was taking calcium or vitamin D supplementation, oral contraceptives, estrogen, glucocorticoids and iodine containing preparation were excluded fromthe study after taking proper medical history. 40 age, sex and BMI matched healthy individuals were taken as controls meeting the exclusion criteria during the same period. All individuals gave written informed consent for participation in the study. The study was approved by Institution ethical committee.

After overnight fasting, venous blood sample was collected under all aseptic conditions. Serum free tri-iodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH) , anti- TPO antibody, 25 OHD and PTH were measured by Electrochemiluminiscence immunoassay (ECLIA) by cobas e411 analyzer (Roche Diagnostics). Serum calcium and phosphorus were measured by Arsenazo-III, spectrometry, by Vitro 5600 analyser. All subjects underwent grey scale B mode imaging of thyroid gland by 5-12 MHz linear transducer using PHILIPS HD 7 USG machine. Parameters such as gland echogenicity and volume were noted on gray scale. A healthy thyroid gland had a medium-grey scale homogeneous echo pattern and the level of echogenicity was higher than that of surrounding muscles. The echogenicity was graded as follows, grade 1 : normal: similar to submandibular gland, hyperechoic to neckmuscles; grade 2: hypoechoic to submandibular gland, hyperechoic to neck muscles, grade 3: isohypoechoic to neck muscles.[23]The study subjects were then categorized into Euthyroid (normal FT3 and FT4 with TSH=0.45-5μIU/ml) and Overthypothyroid (cases) (Low FT3, FT4 withTSH>5μIU/ml)basedon American Thyroid Association (ATA) 2014 guideline.[24] Patients were also categorized as vitamin D sufficient (VDS) (30-100ng/ml), vitamin D insufficient (VDI) (20-30ng/ml) and vitamin D deficient (VDD) (<20ng/ml) based upon recent consensus of vitamin D classification.[2, 5]

Statistical Analysis

All continuous data were expressed as mean and standard deviation. Normality distribution of all parameters was checked using Shapiro-Wilk test. Nonparametric tests (Mann-Whitney U test) and parametric tests (Unpaired t tests) were performed to compare means between parameters as required. For comparison of means among three groups, ANOVA and Kruskalwallis tests were used for data with or without normal distribution respectively. For independent association, multiple linear regression analysis was used. For correlation analysis, Spearman's and Pearson's correlation coefficient were used for nonparametric and parametric data respectively. The data were analysed using the IBM SPSS 21 statistical software (IBM Corp., Armonk, NY, USA).

Results

The baseline parameters between cases and control subjects are summarized in [Table 1]. As expected, cases had significantly higher TSH, lower FT3 and FT4 levels in contrast to control subjects ($p<0.001$ for all). The mean anti TPO titers was significantly higher (162.94±148.66 IU/ml) as compared to controls (29.23±13.26 IU/ml), which confers to the autoimmune nature of disease. Similarly, hypothyroid subjects had greater mean thyroid volume (17.75±1.58ml) than controls (13.70±0.93ml)($p<0.001$).New onset hypothyroid subjects had significantly lower mean vitamin D levels (22.95±8.59 ng/ml) as compared to controls (27.9±7.85 ng/ml) ($p=0.005$). Moreover the prevalence of Vitamin D deficiency (VDD) was significantly higher among cases (42.62%) than controls (17.5%) ($P =0.009$).

To look for impact of vitamin D status on various thyroid related parameters among hypothyroid subjects, we divided the entire hypothyroid cohort into three groups based on mean 25 OHD levels (Group 1- VDD group, Group 2- VDI group and Group 3- VDS group).The clinical and hormonal data of three groups are summarized in Table-2.It was observed that hypothyroid subjects with VDD (Group 1) had significantly higher mean TSH and greater mean thyroid volume than other two groups ($p=0.039$ and $p= 0.001$ respectively). However we did not find any meaningful difference with regards to mean FT3and FT4 levels among three groups (p = non significant). Another noteworthy finding was the presence of significantly higher mean anti-TPO Ab titers (232.64±187.21 IU/ml) among VDD group in comparison to other two groups ($p=0.001$).

Among the hypothyroid cohort, it was observed that 25 OHD level had significantly negative correlation with serum TSH ($r= -0.662$, $P< 0.001$). However, no significant correlation was observed for thyroid volume ($r= -0.087$, $P = 0.504$), FT3 ($r= 0.119$, $P = 0.361$) or FT4 ($r= 0.045$, $P = 0.073$) with 25 OHD levels. We observed that Anti TPO-Ab level correlated inversely and significantly with 25 OHD level among hypothyroid subjects ($r = -0.455$, $p<0.001$), even after adjustment for age, sex and BMI. However no such correlation was observed for control group ($r = -0.122$, $p=0.471$) (Figure 1).

Multiple linear regression analysis showed that only serum 25 OHD had a significant inverse association with Anti TPO-Ab level after being adjusted for potential confounding factors including age, BMI, FT3, FT4 and TSH (Beta= -0.321; 95% CI:-10.804 - -0.286; $p = 0.039$) (Table – 3).

While estimating the risk of hypothyroidism, we found that odds ratio for vitamin D deficiency and vitamin D insufficiency group relative to vitamin D sufficiency group were 3.095 (95%CI : 1.051 – 9.113; $p = 0.04$) and 0.787 (95%CI : 0.303 – 2.042 ; $p = 0.622$) respectively.

Table 1: Comparison of baseline parameters between case and control groups

Parameters	Case (n=61)	Control(n=40)	p value
Age(yrs.)	35.93±10.06	36.60±10.57	0.75
Sex(male/Female)	22/39	17/23	0.516
BMI (Kg/m²)	25.15±2.58	25.35±2.04	0.66
WHR	0.88±0.03	0.88±0.02	0.5
FT3(pg/ml)	1.4±0.37	3.25±0.41	<0.001
FT4(ng/dl)	0.65±0.17	1.31±0.18	<0.001
TSH(µiu/ml)	54.87±29.38	2.78±0.88	<0.001
25 OH Vitamin D (ng/ml)	22.95±8.59	27.9±7.85	0.005
S iPTH (pg/ml)	56.19±16.11	49.74±8.09	0.072
S Calcium(mg/dl)	8.68±0.63	8.8±0.30	0.138
S Phosphorus(mg/dl)	3.78±0.36	3.84±0.4	0.40
Anti TPO(IU/ml)	162.94±148.66	29.23±13.26	<0.001
Thyroid Volume(ml)	17.75±1.58	13.70±0.93	<0.001
USG Thyroid Echogenicity (Grade - 3/ 2/ 1)	56/5/0	0/0/40	<0.001
Percentage of subjects with VDD	42.62%	17.5%	0.009
Percentage of subjects with VDI	27.86%	45%	0.09
Percentage of subjects with VDS	29.5%	37.5%	0.515

Continuous data as expressed as Mean ± SD

BMI: Body mass index, WHR: Waist hip ratio, FT3: Free Tri-iodothyronine FT4: Free Tetra-iodothyronine, TSH: Thyroid stimulating hormone; 25OHD: 25 hydroxy vitamin D, iPTH: Intact parathyroid hormone TPO-Ab: Thyroid peroxidaseantibody, USG: Ultrasonography, VDD:Vitamin D deficiency, VDI: Vitamin D insufficiency, VDS: Vitamin D sufficiency.

Table 2: Comparison of parameters between different vitamin D sub-groupsamonghypothyroid subjects

Parameters	VDD(Group-1)	VDI(Group-2)	VDS(Group-3)	p value
Age(yrs.)	36.27±9.57	35.47±12	35.89±9.32	0.96
Sex(male/Female)	7/19	8/9	7/11	0.388
BMI(Kg/m²)	25.48±2.66	25.06±2.85	24.74±2.27	0.643
WHR	0.88±0.03	0.89±0.05	0.89±0.03	0.555
FT3(pg/ml)	1.41±0.43	1.40±0.288	1.39±0.38	0.973
FT4(ng/dl)	0.68±0.16	0.58±0.21	0.668±0.13	0.16
TSH(µiu/ml)	64.60±29.54	53.65±29.28	41.98±25.18*	0.039
S iPTH (pg/ml)	61.31±16.48	55.78±49.17	49.17±17.13*	0.040
S Calcium(mg/dl)	8.40±0.65	9.01±0.51	8.77±0.52	0.004
S Phosphorus(mg/dl)	3.88±0.25	3.73±0.52	3.69±0.29	0.151
Anti TPO(IU/ml)	232.64±187.21	154.33±100.85	71.84±28.43**	0.001
25-OH D (ng/ml)	14.40±2.84	24.51±1.93	33.84±2.37**	<0.001
Thyroid Volume (ml)	18.65±1.16	17.47±1.0	16.72±1.87**	0.001

Continuous data as expressed as Mean ± SD
*Comparison of parameters between Group-1 and Group-3, p<0.05.
**Comparison of parameters between Group-1 and Group-3, p<0.01.
BMI: Body mass index, WHR: Waist hip ratio, FT3: Free Tri-iodothyronine FT4: Free Tetra-iodothyronine, TSH: Thyroid stimulating hormone; 25OHD: 25 hydroxy vitamin D, iPTH: Intact parathyroid hormone TPO-Ab: Thyroid peroxidase antibody, USG: Ultrasonography, VDD: Vitamin D deficiency, VDI: Vitamin D insufficiency, VDS: Vitamin D sufficiency.

Table 3: Multiple linear regression analysis with TPO-Ab as a dependent variable among hypothyroid subjects

Parameters	Beta	95% CI	p value
Age	0.088	-2.185 - 4.773	0.459
BMI	-0.175	-23.54 - 3.404	0.140
FT3	-0.169	-173.76 - 41.226	0.222
FT4	-0.202	-404.594 - 57.079	0.137
TSH	0.190	-0.751 - 2.677	0.265
25 OH D	-0.321	-10.804 - -0.286	0.039
Thyroid volume	-0.043	-21.138 - 14.332	0.702

Discussion

AITD or Hashimoto's thyroiditis (HT) is characterized by lymphocytic infiltration in the thyroid gland and the production of pathogenic thyroid autoantibodies.[2, 25] Pathogenesis of AITD or HT is multi factorial, combining genetic, immune, environmental, and hormonal influences like vitamin D.[2, 7] In genetically predisposed individuals, the disruption of these neuroendocrine-immune interactions by environmental factors results in thyroid autoimmune dysfunction.[26]These interactions are responsible for the imbalance between type 1 T helper (Th1) and type2 T helper (Th2) immune response. The predominance of Th1-cell-mediated autoimmune reaction causes thyrocyte destruction and hypothyroidism in HT, whereas hyperreactiveTh2-mediated humoral response against TSH receptor produces stimulatory antibodies leading to hyperthyroidism in GD.[2, 17]

Several epidemiological studies have revealed that there is widespread prevalence of vitamin D deficiency of varying degrees (50-90%) in Indian population.[3] In our study, we observed that prevalence of vitamin D deficiency was significantly higher among hypothyroid subjects than the control subjects. These findings have also been reported by various authors from different population.[22,27] In another study by Tamer et al., authors reported a very high prevalence of vitamin D insufficiency (≈92%) among subjects with Hashimoto's thyroiditis.[19]

Our results showed that the mean serum 25 OHD level was significantly lower among hypothyroid subjects than controls. Similar findings have been replicated earlier by previous authors.[2, 8,18, 19] However, in contrast to it Choi et al. reported that mean serum 25 OHD level was not significantly different among overt hypothyroid, subclinical hypothyroid and euthyroid Hashimoto's thyroiditis patients.[28]

An interesting finding emerged after stratifying hypothyroid subjects into three groups based on their mean 25 OHD levels. Hypothyroid subjects with vitamin D deficiency had significantly higher TSH, thyroid volume and anti TPO-Ab titers (a marker of autoimmune response) than those without vitamin deficiency. In agreement with our findings Choi et al. observed that the prevalence of TPO-Ab positivity was significantly higher among females with vitamin D deficiency and serum vitamin D levels were significantly decreased in women with AITD relative to women without AITD.[28] Whereas Goswami et al. found no difference between groups with vitamin D <25 nmol/l and those with vitamin D >25 nmol/l in terms of TPO titers and thyroid dysfunction.[20]

The link between vitamin D and autoimmunity may be explained in terms of the anti-inflammatory and immunomodulatoryfunctions of Vitamin D.[22,29] The vitamin-D activating enzyme1α-hydroxylase (CYP27B1) and the nuclear vitamin D receptor (VDR) are expressed in most immune cells,including T cells, B cells, and antigen-presenting cells(APCs) such as macrophages and dendritic cells (DCs), highlighting the potential role of vitaminD in the immune system and in the pathogenesis of autoimmune diseases.[2, 30,31] The active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)2D], inhibits the adaptive immune system. 1,25(OH)2D suppresses the proliferation, differentiation of B cells into plasma cells and immunoglobulin production and promotes the apoptosis of immunoglobulin-producingB cells directly or indirectly mediated by helper Tcells.[1, 32] In addition, 1,25(OH)2D inhibits the proliferation of Th1cells and the production of Th1 cytokines, such asinterferon-gamma, interleukin (IL)-2, and IL-12.[2, 22] 1,25(OH)2D enhances the development of Th2 cells by exerting a direct effect on native CD4+ cells or byacting on APC/DC and thus facilitating the production of Th2 cytokines, such as IL-4, IL-5, and IL-10,which move T differentiation in favor of the Th2phenotype. 1,25(OH)2D also induces CD4+CD25+regulatory T cells that produce IL-10, which leads to blocked development of Th1 cells and inhibitedsecretion of IL-17 by T-effector cells.[2, 29] Recently, several genetic studies demonstrated an association between susceptibility to thyroid autoimmunity and gene polymorphisms of numerous proteins and enzymes associated with vitamin D functions, including VDR, vitamin D binding protein (DBP), 1α-hydroxylase(CYP27B1) and 25-hydroxylase (CYP2R1). [2, 7,29]

We observed that serum 25 OHD levels had a significant negative correlation with anti TPO antibody titers. Bozkurt et al. demonstrated that the severity of25(OH)D deficiency correlated with the duration ofHT, thyroid volume, and antibody levels, suggesting a potential role of 25(OH)D in the development of HT and/or its progression to hypothyroidism.[8]Similar findings have been reported earlier by different authors, who also showed a negative correlation between 25 OHD and TPO-Ab levels in AITD or HT.[18, 22, 28]In our study we found a statistically significant inverse correlation between serum 25 OHD and TSH levels among hypothyroid subjects. Similar to our observation, few studies have also reported an inverse relationship between 25(OH)D and TSH levels in HT, suggesting the association between low vitamin D status and thyrocyte damage.[2, 8,19, 32, 33] However it is unclear whether the low 25 (OH) D levels observed in AITD or HT are the result of the autoimmune disease process or part of its cause.[2, 8, 18, 23]

In this study, during the analysis for association between serum 25 OHD and various thyroid related parameters, we observed a significant inverse association between serum 25 OHD and Anti TPO-Ab levels after adjustment for potential confounding factors, among hypothyroid subjects. This is in agreement with the findings of Mansournia et al., who suggested that higher serum 25 hydroxy-vitamin D levels were associated with decreased risk of HT.[32]Furthermore, in our study, the odds of hypothyroidism with the vitamin D deficient group were significantly higher than odds in the Vitamin D sufficient group. Mansournia et al. in their study showed that vitamin D deficiency status was an independent predictor of hypothyroidstate[32] which further reinforces our findings.

Limitations of the study

The study population was small and hence generalization of result cannot be made. Another limitation of our study is that the observed association between vitamin D and HT cannot be interpreted as the causal effect of vitamin D on HT due to cross-sectional nature of study. The low vitamin D levels may be a consequence of HT rather than its risk factor. Hence further large scale studies are needed to further clarify the matter. It would be interesting to see whether improving vitamin D status has any influence on hypothyroid status.

Conclusion

In our study, across the three subgroups, patients in vitamin D deficient subgroups had significantly higher TSH and anti-TPO titers than the other two subgroups. It was also observed that vitamin D deficient subjects had significantly higher thyroid volume than subjects in vitamin D sufficient group. A significant negative correlation was observed between serum levels of Vitamin D with TSH and anti TPO among case subjects suggesting definite link between low vitamin D and autoimmune hypothyroidism. Moreover vitamin D remained an independent predictor of TPO level and vitamin D deficiency status was associated with higher odds of hypothyroidism. However, further randomized controlled and prospective studies are needed to investigate whether low vitamin D levels is a causal factor in the pathogenesis of autoimmune thyroid disease and whether vitamin D supplementation would be helpful in patients with HT.

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