

Evaluation of Vitamin D Status and its Impact on Thyroid Related Parameters in New Onset Graves' Disease- A Cross-sectional Observational Study

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Abstract

Aims and Objective: We aimed to compare serum vitamin D level in new onset Graves' disease versus age and sex matched controls. Furthermore, we assessed the correlation of vitamin D with hormonal parameters and antibody titers in Graves' disease. **Materials and Methods:** In total, 84 patients of new onset Graves' disease and 42 age and sex matched healthy individuals were recruited. Biochemical and hormonal investigations that included serum calcium, phosphorous, free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), 25 hydroxy vitamin D (25(OH)D), and parathyroid hormone (PTH) were done for all subjects. Thyrotropin receptor antibody (TRAb) was measured only for Graves' disease patients. **Results:** The patients with Graves' disease had significantly lower 25(OH)D levels (19.2 ± 8.9 ng/ml) as compared to control subjects (23.8 ± 12.5 ng/ml) ($P = 0.019$). Thyroid hormone levels, thyroid volume, and TRAb titers did not differ significantly between vitamin D deficient Graves' disease group (25(OH)D <20 ng/ml) and vitamin D non deficient Graves' disease group (25(OH)D \geq 20 ng/ml). Furthermore, serum vitamin D level did not correlate significantly with thyroid hormones, thyroid volume, or TRAb titers among Graves' disease. The odds ratio (OR) for association of vitamin D deficiency (VDD) state and Graves' disease was 1.62 (95% CI 0.77–3.41). Vitamin D sufficiency state was associated significantly with lower risk of Graves' disease (OR = 0.38, 95% CI 0.15–0.95). **Conclusion:** Serum vitamin D levels are significantly lower in new onset Graves' disease. No significant correlation between vitamin D and thyroid hormones, thyroid volume, or TRAb titers was found in these patients. VDD state is not associated with Graves' disease.

Keywords: Autoimmune thyroid disease, Graves' disease, thyroid, vitamin D

INTRODUCTION

Graves' disease is one of the common autoimmune thyroid disease encountered in routine clinical practice. With progress in research in recent years, several new molecular, immunologic, and environmental factors have been postulated in pathogenesis of Graves' disease. Vitamin D has been shown to possess immunomodulatory properties. It is worthwhile to note that key cells of immune system notably macrophages, dendritic cells, monocytes, T-, and B-lymphocytes express the vitamin D receptor (VDR) and vitamin D-activating enzyme CYP27B1. The active hormone 1,25(OH)₂D binds to VDR, thereby modulating innate and adaptive immune systems.^[1] The predominance of Th1-cell-mediated autoimmune reaction causes thyrocyte destruction and hypothyroidism in Hashimoto's thyroiditis, where as hyper reactive Th2-mediated humoral response against TSH receptor

produces stimulatory antibodies leading to hyperthyroidism in Graves' disease.^[2] 1,25(OH)₂D suppresses the proliferation, immunoglobulin production, and differentiation of B cells into plasma cells and promotes the apoptosis of immunoglobulin-producing B cells directly or indirectly mediated by helper T cells.^[3] On one hand, 1,25(OH)₂D inhibits the proliferation of Th1 cells and the production of Th1 cytokines (interferon-gamma, interleukin (IL)-2, and IL-12). While on the other, 1,25(OH)₂D enhances the development

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of Th2 cells and production of Th2 cytokines (IL-4, IL-5, and IL-10) favoring Th2 phenotype.^[3,4] Hence, the interaction of vitamin D in pathogenesis of autoimmune thyroid disease (AITD) is worth exploring.

Various studies have shown the association of vitamin D deficiency (VDD) with autoimmune diseases.^[1] In past, studies have found that vitamin D levels in patients with AITD including Hashimoto's thyroiditis and Graves' disease were lower than that in patients with non-AITDs such as toxic nodular goiter.^[5] The rates of VDD in patients with AITD are higher than that in patients with non-AITDs.^[5] However, some studies have reported no such relationship between vitamin D level and AITD.^[6,7] The number of studies exploring relationship between vitamin D level and Graves' disease are few. Yamashita H *et al.* have found that female Graves' disease patients who underwent subtotal thyroidectomy have lower serum 25(OH) D levels.^[8] It has been reported that serum vitamin D levels are decreased and associated with thyroid volume in female patients with new onset Graves' disease.^[9] Similarly, Yasuda T *et al.* found that serum vitamin D levels are lower in patients of Graves' disease without remission.^[10] However, in contrast to above studies, few studies did not report lower vitamin D status among Graves' patients.^[11,12] Hence, the relationship between vitamin D and Graves' disease is still unresolved. We aimed to compare serum vitamin D level in new onset Graves' disease versus age and sex matched controls. Furthermore, we tried to find any association of vitamin D status and Graves' disease and ascertain any correlation of serum vitamin D level with various thyroid related parameters.

MATERIALS AND METHODS

This cross-sectional study was conducted at department of Endocrinology of a tertiary care teaching hospital (Cuttack) located at 20.46° N from October 2015 to September 2016.

Study population

A total of 84 patients (54 females and 30 males) of new onset Graves' disease without antithyroid drug intake were recruited to our study. Graves' disease was diagnosed by clinical (thyrotoxic features, diffuse goiter, and ophthalmopathy), biochemical evidence of hyperthyroidism (elevated free triiodothyronine (FT3), and free thyroxine (FT4) levels with suppressed thyroid stimulating hormone (TSH) level) and/or diffuse increased tracer uptake on Technetium 99m thyroid scintigraphy as per recommended criteria. Forty-two age and sex matched healthy individuals (18–60 years) meeting the exclusion criteria were taken as controls. To avoid influence of seasonal variation on vitamin D, we recruited controls within the same month (± 1 month) as that of cases. Exclusion criteria included patients with liver disorder, renal disorder, metabolic bone disorder, parathyroid disorder, any autoimmune diseases and chronic granulomatous disease, history of intake of calcium and vitamin D supplements within preceding 3 months, current or recent use of steroids, antitubercular drugs, antiepileptics,

ketoconazole, heparin, oral contraceptives and diuretics, pregnant, and lactating women. All study participants underwent a detailed history enquiry and clinical examination. To assess the impact of mean sun exposure duration and body area of exposure, we calculated the sun exposure index. This was calculated as hours/week the subjects spent outdoors in daylight multiplied by the percent body surface area exposed to sunlight. The type of clothing worn reflected the body surface area exposed. According to the rule of nines, the head and neck sun skin exposure accounts as 9%, each arm as 9%, each leg as 18%, and the front and back torso as 18% each.^[13]

Study definitions

We had divided the Graves' disease cohort broadly into two groups namely VDD group (25(OH)D <20 ng/ml) and non VDD group (25(OH)D \geq 20 ng/ml) from mean vitamin D levels. Further, stratification of Graves' disease cohort was done into four groups according to the mean 25(OH) D levels. They were classified as group 1 (25(OH)D <10 ng/ml), group 2 (25(OH)D = 10–20 ng/ml), group 3 (25(OH)D = 20–30 ng/ml), and group 4 (25(OH)D >30 ng/ml). To minimize bias of month of recruitment on vitamin D level, we divided the year into three periods depending on main season type namely July–September, October–February, and March–June. We included similar number of subjects from each group, that is group A [July- September (29 Graves' disease and 17 controls)], group B [October- February (24 Graves' disease and 13 controls)], and group C [March-June (31 Graves' disease and 12 controls)].

Laboratory parameters

After an overnight fast, blood samples were collected for measurements of FT3, FT4, TSH, 25-hydroxy vitamin D (25(OH)D), calcium, phosphorous, and parathyroid hormone (PTH). Thyrotropin receptor antibody (TRAb) was measured only for Graves' disease patients. Serum FT3, FT4, TSH, PTH, and serum 25(OH)D were measured using electrochemiluminescence immunoassay (ECLIA) kits (Roche diagnostics, Mannheim, Germany). ECLIA was performed using automated cobas e 411 analyzer (Roche diagnostics, Mannheim, Germany). The normal range of FT3 for this assay in a healthy population was 3.1–6.8 pmol/l. The normal reference range of FT4 for this assay was 12–22 pmol/l. The normal reference range for assay of serum TSH was 0.27–4.20 mIU/ml. The upper and lower detection limits for serum 25 OHD were 4–100 ng/ml, respectively. Serum Anti TSHR (TRAb) (Cut off >2 IU/L with functional sensitivity 0.3–40 IU/L) was measured using ECLIA kits (cobas e 411, Roche diagnostics, Germany). Serum calcium and phosphorous were measured using Vitros 5600 biochemical analyzer (Ortho-Clinical diagnostics, Inc.). Thyroid ultrasonography was done by 5–12 MHz linear transducer using PHILIPS HD 7 USG machine. Parameters such as gland echogenicity, size (volume) were noted on gray scale. The thyroid gland correct volume was obtained using ellipsoid formula after measuring maximum the longitudinal (L), anteroposterior (AP), and transverse (T) axis of both lobes ($V = L \times AP \times T \times \pi/6$). Both lobe volumes were added to get the total volume of the gland. Written informed

consent was taken from all study participants. Institutional ethical committee clearance was taken for the study.

Statistical analysis

Descriptive statistical methods such as mean and standard deviation were applied to summarize continuous variables. Categorical data were summarized as percentages or proportions. Normality distribution of all parameters was checked using Shapiro-Wilk test. Categorical variables were compared using Chi-square test. Mann-Whitney U test and independent t tests were performed to compare means between two groups as required. Kruskal Wallis test was used for comparison of means between three or more groups. Pearson's correlation coefficient was used to analyze correlation between different parameters. A *P* value of less than 0.05 was considered statistically significant. The data were analyzed using the IBM SPSS 24 statistical software (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 84 subjects with Graves' disease and 42 age and sex matched controls were included in the study. The baseline characteristics of the study population are summarized in Table 1. The mean age of patients with Graves' disease was 35 ± 9.7 years as compared to mean age of 32.4 ± 9.7 years among controls ($P = 0.101$). As expected, Graves' disease patients had significantly elevated FT3, elevated FT4, and suppressed TSH levels in comparison to controls ($P < 0.001$) [Table 1]. The mean thyroid volume was significantly higher among Graves' disease patients (20.1 ± 10.1 cm³) as compared to controls (5.9 ± 2.0 cm³) ($P < 0.001$) [Table 1].

It was seen that mean serum 25(OH) D levels were significantly lower among Graves' disease patients (19.2 ± 9.0 ng/ml) versus controls (23.8 ± 12.5 ng/ml) ($P = 0.019$). The sun exposure index was comparable between the two groups ($P = 0.850$). Similarly, the serum calcium, phosphorous, and PTH levels did not vary significantly among Graves' disease and control groups [Table 1].

Vitamin D deficiency status and Graves' disease

The comparison of different parameters between VDD group and non VDD group are summarized in Table 2. There was no significant difference among these two subsets of Graves' disease patients with regard to mean serum FT3, serum FT4, serum TSH, and serum TRAb levels ($P =$ non significant for each parameters) [Table 2]. Furthermore, mean thyroid volumes were also comparable between VDD group and non VDD groups ($P = 0.477$).

Comparing and analyzing across four subgroups (groups 1 to 4, sub stratified by mean 25(OH) D levels as described earlier), it was seen that thyroid hormone levels (FT3, FT4, and TSH) and thyroid gland volume did not vary significantly among the described groups (*p* being non significant for each parameter). When assessing any potential difference in thyroid autoantibody status, it was seen that mean TRAb titers did not differ significantly between the four groups ($P = 0.169$), though individuals with lowest mean 25(OH) D levels that is, group 1 (25(OH)D<10 ng/ml) tended to have the highest mean TRAb titers.

Correlation between vitamin D and thyroid related parameters in Graves' disease

It was observed that serum 25(OH) D level did not correlate significantly with thyroid hormones, TRAb levels ($r = -0.08$, $P = 0.472$) and thyroid volume ($r = -0.07$, $P = 0.485$).

Table 1: Comparison of baseline characteristics of Graves' disease and control subjects in the study

SL No.	Parameters	Graves' disease <i>n</i> =84	Control <i>n</i> =42	<i>P</i>
1	Age (years)	35.25±9.70	32.41±9.71	0.101
2	Sex (Male/Female)	30/54	17/25	0.697
3	Season of recruitment (group A/group B/group C)	29/24/31	17/13/12	0.639
4	BMI (kg/m ²)	19.10±2.85	21.70±2.61	<0.001
5	FT3 (pmol/l)	22.22±11.25	4.23±0.72	<0.001
6	FT4 (pmol/l)	72.64±24.80	14.73±2.40	<0.001
7	TSH (mIU/ml)	0.05±0.05	2.39±1.20	<0.001
8	TRAb (IU/l)	19.45±12.12	-	-
9	S.Ca ²⁺ (mg/dl)	9.41±0.59	9.39±0.68	0.994
10	S.Phos.(mg/dl)	4.03±0.69	3.86±0.63	0.218
11	25(OH)D(ng/ml)	19.22±8.95	23.81±12.46	0.019
12	PTH (pg/ml)	41.91±20.86	38.97±20.24	0.453
13	Sun exposure index	82.02±79.96	79.21±75.01	0.850
14	Thyroid volume (cc)	20.11±10.09	5.86±1.97	<0.001
15	Percentage subjects with severe vitamin D deficiency 25(OH)D <10 ng/ml (<i>n</i>)	10.71 (9)	9.52 (4)	0.836
16	Percentage subjects with vitamin D deficiency 25(OH)D <20 ng/ml (<i>n</i>)	59.52 (50)	47.61 (20)	0.205
17	Percentage subjects with vitamin D insufficiency 25(OH)D=20–30 ng/ml (<i>n</i>)	27.38 (23)	23.81 (10)	0.667

Continuous data are expressed as mean±S.D. BMI: Body mass index, FT3: Free triiodothyronine, FT4: Free thyroxine, PTH: parathyroid hormone, S.Ca²⁺: Serum calcium, S.Phos: Serum phosphorous, TRAb: Thyrotropin receptor antibody, TSH: Thyroid-stimulating hormone, 25(OH)D: 25-hydroxy vitamin D

Table 2: Comparison of parameters among Graves' disease subjects divided as per vitamin D deficiency status

SL No.	Parameters	VDD group n=50	Non VDD group n=34	P
1	Age (years)	36.12±10.13	33.97±9.04	0.427
2	BMI (kg/m ²)	19.15±2.58	19.02±3.24	0.847
3	FT3 (pmol/l)	22.98±12.27	21.09±9.63	0.452
4	FT4 (pmol/l)	72.67±26.14	72.59±23.06	0.964
5	TSH (mIU/ml)	0.05±0.05	0.05±0.04	0.916
6	TRAb (IU/L)	20.58±12.67	17.80±11.24	0.305
7	S.Ca ²⁺ (mg/dl)	9.31±0.55	9.55±0.65	0.090
8	S.Phos.(mg/dl)	4.19±0.70	3.78±0.62	0.006
9	25(OH)D (ng/ml)	13.49±3.91	27.65±7.47	<0.001
10	PTH (pg/ml)	49.66±22.79	30.50±9.89	<0.001
11	Thyroid volume (cc)	20.76±10.48	19.16±9.55	0.477

Data are expressed as mean±S.D. BMI: Body mass index, FT3: Free triiodothyronine, FT4: Free thyroxine, PTH: Parathyroid hormone, S.Ca²⁺: Serum calcium, S.Phos: Serum phosphorous, TRAb: Thyrotropin receptor antibody, TSH: Thyroid-stimulating hormone, VDD: Vitamin D deficiency, Non VDD: Non Vitamin D deficiency, 25(OH)D: 25-hydroxyvitamin D

Association of vitamin D status and Graves' disease

While evaluating the association between VDD status and Graves' disease, it was observed that the odd's ratio (OR) for the interaction was 1.62 (95% CI 0.77–3.41, $P = 0.205$). Interestingly, our results suggested that vitamin D sufficient status had significantly lower risk of Graves' disease [OR 0.38 (95% CI 0.15–0.95, $P = 0.034$)].

DISCUSSION

In this study, we found that serum mean 25(OH) D levels were significantly lower in new onset Graves' disease patients as compared to controls. One of the first studies that reported widespread VDD among Graves' disease patients was reported by Yamashita *et al.* from Japan involving 208 Graves' disease patients.^[8] The mean level of vitamin D in men and women Graves' disease subjects were 41.3 ± 15.0 and 31.8 ± 13.3 nmol/l, respectively in their cohort.^[8] In 2012, Yasuda *et al.* for the first time reported significantly lower mean 25(OH)D level among new onset Graves' disease female patients versus controls and suggested toward association of vitamin D and Graves' disease.^[9] The findings of low vitamin D status in Graves' disease of our study is in agreement to reports from previous studies.^[14,15] In a recently published study from Sweden, authors have reaffirmed the finding of lower vitamin D levels in Graves' disease.^[16] However, some studies have not reported similar finding of low vitamin D status among Graves' disease than control population.^[11,12] In a meta analysis to study the association of vitamin D and Graves' disease, authors concluded that the patients with Graves' disease were more likely to be deficient in vitamin D compared to the controls with a high heterogeneity.^[17] Some animal data do support the notion that vitamin D deficient state predisposes to development of Graves' disease. Misharin *et al.* observed that VDD was found

to modulate Graves' hyperthyroidism induced in BALB/c mice by thyrotropin receptor immunization.^[18] In this study, BALB/c mice on a vitamin D deficient diet were more likely to develop persistent hyperthyroidism than other mice receiving adequate vitamin D supply.^[18]

In our study, we found no statistical difference in terms of thyroid hormones, thyroid volume, or antibody titers (serum TRAb) between VDD and non VDD groups. Only one previous study has looked into the difference of thyroid related parameters between two Graves' disease groups stratified on basis of mean serum vitamin D level (25(OH)D <20 ng/ml group versus 25(OH)D >20 ng/ml group)^[19] The authors noted that the two groups had no significant difference in terms of thyroid hormone status. They also reported that 100% of their Graves' disease patients were TRAb positive when 25(OH)D level <20 ng/ml as compared to 37.50% of patients were TRAb positive when 25(OH)D level >20 ng/ml.^[19] Among our cohort, patients with lowest vitamin D levels (subgroup with 25(OH)D <10 ng/ml) tended to have the highest mean TRAb titers. Zhang *et al.* have noted lower mean 25(OH)D levels among TRAb positive Graves' disease patients in comparison to TRAb negative Graves' disease patients.^[15] Our results show that serum vitamin D level do not correlate with thyroid hormones, thyroid volume, and TRAb levels in Graves' disease. Yasuda *et al.* showed no association between serum 25(OH) D levels and thyroid function tests or TRAb levels.^[9] Two recently published studies also did not report any correlation of serum vitamin D level with thyroid hormones and thyroid auto-antibody titers.^[12,16,19] However, in contrast to these findings, two studies have showed significant inverse correlation between vitamin D levels and TRAb titers in Graves' disease.^[14,15] From review of above findings, it seems that thyroid hormones are perhaps not affected by vitamin D status in Graves' disease. The relationship between vitamin D level and antibody titers need further clarification, though at present most of studies fail to report any significant correlation between these two parameters.

Ma *et al.* have reported that lower serum 25(OH) D levels was associated with an increased risk of Graves' disease after adjustment for age, TSH, and thyroid auto-antibodies (OR = 1.09, 95% CI–1.03–1.15 $P = 0.001$).^[14] However, in our study, VDD status was not significantly associated with Graves' disease. Therefore, an interesting finding of our study was that vitamin D sufficiency state was shown to be associated with significantly lower risk of Graves' disease. A recent study has reported that elevated 25-hydroxyvitamin D levels at the time of anti thyroid drug discontinuation (HR, 0.933; 95% CI, 0.876–0.993) was identified as a protective factor for the recurrence of Graves' disease.^[20] Hence, vitamin D sufficiency state may be protective against Graves' disease, but analysis of data from larger population would be needed to affirm these findings. It would be also interesting to see the influence of vitamin D supplementation of status on Graves' disease in future prospective studies.

Our study has few limitations. We did not assess daily total dietary calcium, vitamin D, and phytate intake that may have affected vitamin D status. Serum 25(OH) D assay was done only once for each person. Being a cross-sectional study causality between VDD and risk of Graves' disease cannot be made. Finally, our sample size was small, and hence, future large scale studies are essential to further clarify the findings.

CONCLUSION

Vitamin D levels are significantly lower in new onset Graves' disease. However, no correlation was observed between vitamin D and thyroid hormones, thyroid volume, or TRAb titers in Graves' disease. Similarly, no meaningful difference existed in terms of any thyroid related parameters between VDD and non deficiency groups. VDD status was not significantly associated with Graves' disease.

Presentation at a meeting

This study was presented at the Endocrine society of India annual conference, ESICON 2017 held from 13th to 15th October, 2017 at Thiruvananthapuram, Kerala, India.

Consent

Written informed consent was obtained from the study subjects for publication of study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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