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Original Research

Relationship between Thyroid Volume and Baseline Vitamin D Levels in New-Onset Graves Disease

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ABSTRACT

Objective: Serum vitamin D is shown to be decreased and associated with higher thyroid volumes in Graves disease (GD). We aimed to investigate the relationship between thyroid volume and baseline serum vitamin D status in newly diagnosed GD patients.

Methods: This was a single-center cross-sectional study with a total of 61 new-onset GD patients (n=61, F: 40, M: 21) who were divided into two groups, according to baseline serum vitamin D levels, as Group-1 (vitamin D <20; n: 42) and Group-2 (vitamin D ≥20; n=19). Thyroid volume (mL) and isthmus measurements (mm) were compared between the two groups.

Results: There was an inverse correlation between the baseline serum vitamin D levels and thyroid volume, thyroid receptor autoantibodies (TRAb), free triiodothyronine (fT3), and parathyroid hormone (PTH) levels (p=0.02, r=-0.31; p=0.005, r=-0.36; p=0.04, r=-0.26; p=0.02, r=-0.32, respectively). Thyroid volume was also correlated with serum free thyroxine (fT4), fT3, TRAb, and thyroid peroxidase autoantibodies (TPOAb; p=0.001, r=0.426; p=0.001, r=0.50; p=0.04, r=0.26; p=0.001, r=0.42, respectively). Low vitamin D and high thyroglobulin antibody (TgAb) levels were significantly associated with thyroid volume based on a regression analysis (p=0.03, odds ratio [OR]:18.7, 95% confidence interval [CI]: 1.34-260.91 and p=0.04, OR: 16.6, 95% CI: 1.07-255.64, respectively).

Conclusion: Baseline serum vitamin D levels are inversely related with thyroid volumes, fT3, and TRAb levels in new-onset GD. In addition to several advantages, optimization of vitamin D levels would also be beneficial in the surveillance of these patients. However, larger scale studies are required to make further suggestions.

Keywords: Autoimmune disorders, 25 (OH) vitamin D, TRAb, Graves disease, thyroid volume

INTRODUCTION

Vitamin D is as a pro-hormone in the regulation of calcium and phosphate levels, and therefore it is particularly essential for bone and mineral metabolism. However, in recent years, many studies have been demonstrating an effect of vitamin D deficiency in several diseases, such as cancer, hypertension, cardiovascular diseases, and diabetes mellitus as well as autoimmune thyroid disorders (1). Although vitamin D levels of over 20 ng/mL are considered sufficient for its skeletal effects, values over 30 ng/mL are required to avoid manifestation of vitamin D deficiency in the organs outside the skeletal system (2).

Vitamin D mediates its effects on autoimmune disorders by triggering immune responses through its receptors on macrophages, dendritic cells, and T and B lymphocytes. Thus, the relationship between vitamin D deficiency and autoimmune thyroid disorders may also be related with vitamin D receptor (VDR) gene polymorphisms as well as environmental factors. Recently, Graves disease (GD) has been associated with vitamin D deficiency (3-6). Serum 25(OH)D levels were shown to be significantly lower and inversely correlated with thyroid volume in patients with new-onset GD compared to control subjects (7). Vitamin D deficiency was also reported to be associated with lower remission rates in GD (8, 9). In this study, we aimed to investigate the impact of baseline vitamin D levels on thyroid volume in patients with new-onset GD.

METHODS

Study Group

The patients who were admitted to the endocrinology and metabolism outpatient clinic with a diagnosis of new-onset GD were included in the study (n=61, F: 40, M: 21). The serum vitamin D levels were measured using the competitive protein--binding

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assay. The vitamin D status was defined as deficient, inadequate, and sufficient for vitamin D levels of <20 ng/mL, 20-30 ng/mL, and >30 ng/mL, respectively (1). According to the baseline serum vitamin D status at the time of diagnosis, the patients were divided into three groups: vitamin D deficient group (Group-1; n: 42, F/M: 31/11), vitamin D inadequate group (Group-2; n=10, F/M: 4/6), and vitamin D sufficient group (Group-3; n: 9, F/M: 5/4). The diagnosis of GD was based on the standard clinical criteria, thyroid function tests with autoantibody levels, and thyroid scintigraphy imaging. The serum free triiodothyronine (fT3) and free thyroxine (fT4) levels were measured using a competitive enzyme immunoassay. Serum thyroid stimulating hormone (TSH), thyroid receptor autoantibodies (TRAb), thyroid peroxidase autoantibodies (TPOAb), and thyroglobulin antibody (TgAb) levels were measured using a two-site immunoenzymetric assay. Thyroid volume (mL) and isthmus measurements (mm) were compared between each group. Thyroid volume was calculated ~~with~~ using the following standardizsed formula (10).

Thyroid Volume (mL)=0.479×[Right lobe depth × width × length(cm)]+0.479 × [Left lobe depth × width × length(cm)]

Thyroid ultrasonography imaging for the calculation of thyroid volumes (mL) and isthmus measurements (mm) were performed by the same physician using Logic 7, General Electric, Milwaukee, Wiskonsin. Patients with a history of thyroidectomy, renal disease, hepatic disease, or malignancy or those under medications that affect vitamin D status and having prior replacement of vitamin D in the last 6 months were excluded from the study. The patients younger than 18 years and older than 75 years were also not included in the study groups.

This study was approved by the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital on 17.06.2016 (2016/16) and written informed consent was obtained from all patients. All procedures were performed in accordance with the Declaration of Helsinki.

Statistical Analysis

The distribution of variables was evaluated using the Kolmogorov-Smirnov test and a histogram analysis. The mean±standard error of the mean (SEM) and frequency values are reported for each data. The three groups were compared using ANOVA, Kruskal-Wallis, and Mann-Whitney U tests, with the post-hoc Bonferroni adjustment as appropriate: for statistically significant results. Categorical variables were processed using the chi-square test. The Pearson and Spearman correlation analysis was performed for normally and non-normally distributed data, respectively. A statistical significance was accepted at a p value of <0.05. Statistical calculations were performed using the Statistical Package for Social Sciences 22.0 software (SPSS IBM Corp.; Armonk, New York, USA).

RESULTS

A total of 61 patients were included in the study (F: 40, M: 21). The serum TSH levels were below 0.005 μIU/mL, and the fT4 and fT3 levels were above upper limit of normal (1.71 ng/dL, 4.4 pg/mL) in all the patients. The mean age and vitamin D levels of the patients were 34.8±1.2 years (18-61) and 13.8±1.3 (2.5-39), respectively, (mean±SEM [min-max]). The distribution of the clinical features according to vitamin D levels are shown in Table 1. Thyroid volumes and isthmus measurements did not show significant difference according to the baseline serum vitamin D levels at the time of diagnosis (p=0.8 and p=0.1, respectively; Table 1).

Table 1. Distribution of clinical features according to the vitamin D status

	Group-1 (vit D <20 ng/mL)	Group-2 (vit D >20 ng/mL)	p
Age (mean±SEM)	36.2±1.5	35.1±2.0	0.05
BMI	23.7±0.7	22.5±3.1	0.3
fT4	4.4±0.3	4.3±0.7	0.9
fT3	15.2±1.3	13.7±2.3	0.6
TRAb	9.4±1.4	9.1±4.5	0.5
TPOAb	335.6±38.6	317.9±89.7	0.5
TgAb	573±170	606±434	0.6
vit D	7.9±4.6	26.6±3.5	0.001
Ca	9.5±0.6	9.7±0.14	0.3
P	3.7±0.1	4.1±0.2	0.2
PTH	52±2.2	35.1±4.1	0.05
Thyroid Volume (mL)	31.9±2.7	26.8±5.0	0.3
Isthmus (mm)	4.8±0.4	3.7±0.8	0.1

BMI: body mass index, fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; Ca: calcium, P: phosphorus; PTH: parathyroid hormone; SEM: standard error mean

The presence of Graves ophthalmopathy was similar between the three groups (p=0.7). Thyroid volume was higher in males and in patients with body mass index (BMI) >25 (p=0.001 and 0.04, respectively). The thyroid volume did not show significant difference according to presence of Graves ophthalmopathy (Table 2).

There was a positive correlation between thyroid volume and serum fT4, fT3, TRAb, TPOAb, and TgAb levels (p=0.001, r=0.426; p=0.001, r=0.50; p=0.04, r=0.26; p=0.001, r=0.42; p=0.001 r=0.42; respectively; Table 3). There was an inverse correlation between serum vitamin D levels and thyroid volume, TRAb, fT3, and parathyroid hormone (PTH) levels (p=0.02, r=-0.31; p=0.005, r=-0.36; p=0.04, r=-0.26; p=0.02, r=-0.32; respectively; Table 4).

Low baseline vitamin D and high TgAb levels were significantly associated with higher thyroid volume in a logistic regression analysis (p=0.03, odds ratio [OR]: 18.7, 95% confidence interval [CI]:1.34-260.91; p=0.04, OR: 16.6, 95% CI: 1.07-255.64, respectively; Table 5).

DISCUSSION

The major effect of vitamin D is on the regulation of bone and mineral homeostasis; however, it has been recently shown that hypovitaminosis D is also associated with extraskeletal disorders,

Table 2. Relationship of thyroid volume with categorical variables

	Thyroid Volume (mean±SEM)	p
Gender		
Female	25±2.8	0.001
Male	40±2.7	
Ophthalmopathy		
Absent	28.7±2.5	0.1
Present	35.8±4.3	
Age, years		
<40	31.1±2.8	0.8
>40	30.2±3.4	
BMI		
<25	28.3±2.5	0.04
>25	39.4±5.2	

Chi-square; SEM: standard error mean; BMI: body mass index

Table 3. Correlation of thyroid volume and isthmus thickness with clinical features

	Thyroid Volume		Isthmus Thickness	
	p	r	p	r
Age, years	0.7	0.04	0.6	0.07
BMI	0.2	0.15	0.04	0.27
fT4	0.001	0.45	0.001	0.52
fT3	0.001	0.50	0.001	0.55
TRAb	0.04	0.26	0.001	0.40
TPOAb	0.001	0.42	0.1	0.21
TgAb	0.001	0.42	0.8	-0.02
Vit D	0.02	-0.31	0.3	-0.12
Ca	0.1	0.21	0.6	0.06
PTH	0.3	0.13	0.9	-0.004
P	0.7	0.03	0.1	-0.21

Pearson, Spearman; BMI: body mass index; fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; Ca: calcium; P: phosphorus; PTH: parathyroid hormone

Table 4. Correlation of vit D levels with clinical features

	Vit D	
	p	r
Age, years	0.1	-0.11
BMI	0.7	-0.04
fT4	0.2	-0.16
fT3	0.04	-0.26
TRAb	0.01	-0.33
TPOAb	0.1	-0.11
TgAb	0.1	-0.11
Thyroid volume	0.02	-0.31
Ca	0.1	0.21
PTH	0.02	-0.32
P	0.04	0.28

BMI: body mass index; fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; Ca: calcium, P: phosphorus; PTH: parathyroid hormone

Table 5. Logistic regression analysis of risk factors asociatedassociated with thyroid volume

	Thyroid volume		
	p	OR	CI 95%
Vitamin D	0.03	18.7	1.34-260.91
Age, years	0.8	1.19	0.19-7.2
BMI	0.1	0.14	0.18-1.11
Gender	0.002	142.85	0.0-0.15
fT4	0.5	0.38	0.01-9.33
fT3	0.1	13.9	0.68-285,67
TRAb	0.4	0.30	0.02-4.25
TPOAb	0.4	0.47	0.07-3.04
TgAb	0.04	16.6	1.07-255.64

BMI: body mass index; fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; PTH: parathyroid hormone; OD: odds ratio; CI: confidence interval

such as hypertension, diabetes mellitus, malignancy, cardiovascular and autoimmune thyroid diseases (1). Vitamin D regulates inflammatory cytokine production and inhibits the proliferation of proinflammatory cells through its receptors on lymphocytes and macrophages (11). The effects of vitamin D on monocytes and macrophages is in favor of activating the innate immune system;, however, there is an inhibitory effect on the acquired immune response (12). These effects represent the immunomodulatory action, which results in an association between vitamin D deficiency and autoimmune disorders. Vitamin D inhibits the production of Th1 cells by suppressing the function of interleukin (IL)-2, IL-12, and interferon (IFN)-γ and stimulating IL-4, thereby shifting the polarization of T cells towards the Th2 phenotype (13). The decrease in this inhibitory effect on Th1 production is related to an increase in the autoimmune thyroid disorders with vitamin D deficiency (1).

The relationship between low vitamin D levels and GD has been previously reported (14, 15). GD is characterized by a loss of im-

mune tolerance to thyroid antigens leading to the inflammation of thyroid gland (3). Thus, the decreased inhibitory effect on the immune system caused by hypovitaminosis D is thought to act as a further reinforcement in the development of GD. Vitamin D levels were shown to be decreased and related with thyroid volume in patients with new-onset GD (7). Furthermore, lower levels of vitamin D were reported to be associated with lower rates of remission in patients with GD (8). To the best of our knowledge, this is the first study investigating the change in thyroid volumes according to the baseline serum vitamin D levels among patients with new-onset GD. In our study, the mean thyroid volume and isthmus measurements did not show significant difference between the three groups according to the vitamin D status. However, thyroid volumes had an inclination to be higher in patients with lower vitamin D levels revealing a negative correlation between the two parameters. In contrast, thyroid volumes showed positive correlation with thyroid hormones and autoantibody levels. Higher autoantibody levels causing enhanced stimulation of thyroxine synthesis, accompanied with a further increase in the volume of thyroid gland, is the possible explanation of this relation.

In an animal in vivo autoimmune thyroiditis model, vitamin D treatment is shown to reduce the severity of inflammatory lesions in the thyroid gland (16). It is also reported that lower vitamin D levels are associated with higher thyroid autoantibody levels (17, 18). In our study, there was an inverse correlation between baseline vitamin D levels and serum TRAb titers. This may be associated with the lack of an inhibitory action on the immune system due to decreased vitamin D levels. In our study, there was a tendency to higher fT3 levels in patients with lower levels of vitamin D, which may be related with the increased TRAb titers and further stimulation of the inflammatory changes in the thyroid gland.

In addition to vitamin D deficiency due to environmental factors, vitamin D receptor (VDR) polymorphism is also reported to be an important cofactor in the development of GD (19). In a recent meta-analysis, significant difference in the association of vitamin D levels and GD has been reported in African and Asian patients, while no significant difference was found in the European population (20). These differences might be related with the VDR polymorphisms among different ethnic populations. The increased prevalence of autoimmune thyroid disorders according to VDR polymorphisms has been reported in several studies (19, 21). The most common polymorphisms are reported as ApaI and FokI polymorphisms in Hashimoto disease and TaqI polymorphism in GD (22). In a study performed in the Turkish population, TaqI and FokI genotypes were shown to be associated with higher prevalence of Hashimoto thyroiditis (23). Despite the negative correlation of vitamin D and thyroid volumes, the lack of difference in the mean thyroid volumes between the three groups in our study may be due to the presence of these polymorphisms; however, further studies are needed to demonstrate the VDR genotypes related with GD in the Turkish population.

In our study, thyroid volume was higher in male patients accompanied with higher BMI values, which was also related with an increased gland size. There was no significant difference in the rates of ophthalmopathy development according to the vitamin D levels, and the thyroid volumes were similar in patients with and without Graves ophthalmopathy. Previous studies have shown that there was no difference in the severity of GD according to the vitamin D status (7, 24). However, higher fT3 and TRAb levels were observed with lower vitamin D levels in our study. Nevertheless, the ophthalmopathy presence was similar between the three groups. The higher fT3 and TRAb levels may also be the reason for lower remission rates of GD in vitamin D deficiency, which has been previously reported (8).

The limitation to our study is that it was a single-center cross-sectional study with a limited number of patients. Prospective larger scale studies with vitamin D treatment and follow-up for the onset of remission are needed to make definitive suggestions. Studies of vitamin D receptor polymorphisms associated with GD among different population groups would also be beneficial for further conclusions.

CONCLUSION

Vitamin D deficiency is an important risk factor in the development of autoimmune thyroid disorders. Baseline serum vitamin D levels are inversely related to fT3, TRAb levels, and thyroid volumes, which are related to the adverse outcomes in GD. Therefore, in addition to several advantages, optimization of vitamin D levels would also be beneficial on the surveillance of these patients. However, larger scale studies on different ethnic populations are required to make further suggestions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital.

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

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