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Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis

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Abstract

Introduction: *It has been known that vitamin D has some immunomodulatory effects and in autoimmune thyroid diseases, vitamin D deficiency was more prevalent. In this study, our aim was to investigate the relationship between thyroid autoantibodies and vitamin D.*

Material and methods: *Group 1 and 2 consisted of 254 and 27 newly diagnosed Hashimoto's thyroiditis (HT) and Graves' disease (GD) cases, respectively; age-matched 124 healthy subjects were enrolled as controls (group 3). All subjects (n = 405) were evaluated for 25OHD and thyroid autoantibody [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-tg)] levels.*

Results: *Group 2 and group 1 patients had lower 25OHD levels than group 3 subjects 14.9 ±8.6 ng/ml, 19.4 ±10.1 ng/ml and 22.5 ±15.4 ng/ml, respectively ($p < 0.001$). Serum 25OHD levels inversely correlated with anti-TG ($r = –0.136$, $p = 0.025$), anti-TPO ($r = –0.176$, $p = 0.003$) and parathormone (PTH) ($r = –0.240$, $p < 0.001$). Group 2 patients had higher anti-TG and anti-TPO levels than group 1 and 3 ($p < 0.001$).*

Conclusions: *In this study, we found that patients with autoimmune thyroid disease (AITD) present with lower vitamin D levels and GD patients have higher prevalence. Since we found an inverse correlation between vitamin D levels and thyroid antibody levels, we may suggest that vitamin D deficiency is one of the potential factors in pathogenesis of autoimmune thyroid disorders.*

Key words: *vitamin D, thyroid, autoimmunity.*

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Introduction

Vitamin D is a lipid soluble vitamin which affects via vitamin D receptor (VDR). Vitamin D receptor is an intracellular receptor which belongs to the steroid/thyroid nuclear receptor family. This receptor is located in many immune cells, such as neutrophils, macrophages, dendritic cells, T and B cells. In recent years, apart from its primary role in bone and mineral homeostasis, it has been shown that vitamin D has potent immunomodulatory effects both on the innate and adaptive immune system [1-4]. Vitamin D inhibits pro-inflammatory processes by suppressing the over-activity of CD4+, Th1, Th2 and Th17 cells and the production of their related cytokines by the activation of VDR [1, 5]. Epidemiological studies have shown a relation between vitamin D deficiency and autoimmune diseases, such as rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus and autoimmune thyroiditis [6-8].

Autoimmune thyroid diseases (AITDs), including Graves' disease (GD), Hashimoto's thyroiditis (HT) and postpartum thyroiditis, are the most frequently seen autoimmune diseases affecting more than 5% of population. In recent years, there have been a few studies demonstrating an increase in vitamin D deficiency in HT [9, 10].

In this study, our aim was to compare vitamin D levels of newly diagnosed AITDs (GD and HT) and healthy controls and investigate the relation between thyroid autoantibodies and vitamin D deficiency.

Material and methods

This study was approved by the Baskent University Institutional Review Board and Ethics Committee (Project no. KA13/176) and supported by the Baskent University Research Fund. Informed consent was obtained from all patients and healthy controls.

Study population

This study population consisted of newly diagnosed AITD adult patients and controls. According to diagno-

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sis, the study population was separated into three different groups. Hashimoto's thyroiditis patients (diagnosed by elevated antithyroid peroxidase and antithyroglobulin antibodies (TPOAb, TgAb) and basal thyrotrophic hormone (TSH) as well as typical hypoechogenicity of the thyroid in high resolution sonography) were included in group 1, GD patients [diagnosed by elevated free thyroxine (fT4) and suppressed TSH levels and the presence of diffused goiter and thyroid receptor antibody (TRAb) positivity] in group 2 and controls in group 3. Patients with primary liver and renal failure, diabetes mellitus, metabolic bone disorders, hyperparathyroidism, malignancy, previously known thyroid disorders and on oral contraceptive, anticonvulsant, anti-osteoporotic therapy and other medications that might alter 25(OH)D or $1,25(OH)_2D$ metabolism and thyroid functions had been excluded from the study.

Laboratory investigation

For measuring 25(OH)D, TSH, anti-TPO and anti-tg, a blood sample was collected by venipuncture at the fasting state, the serum was separated by centrifugation and then stored at –70°C for a week until analysed.

Vitamin D: Vitamin D status was evaluated by measurement of serum 25(OH)D levels with a chemiluminescent immunoassay method (Architect i1000 system); normal range was 8.8-46.3 ng/ml (winter); and the intra-assay CV ranged from 2.6 to 4.0%. Serum 25(OH)D levels below 20 ng/ml were considered as deficiency.

Parathormone: Serum PTH levels were measured with an electrochemiluminescent immunoassay method (Architect i2000 system); normal range 15-68 pg/ml; intra-assay CV 3.0-6.5%. Serum calcium (Ca) levels were measured with an enzymatic colorimetric assay (C8000 system); intra-assay and inter-assay CV were 0.5-0.6% and 0.3-0.5%, respectively.

Thyrotrophic hormone, anti-TG, and anti-TPO: TSH, anti-TG, and anti-TPO were also measured with a chemiluminescent immunoassay method (CMIA) (Architect i2000 system, Abbott, USA). The assays have intra-assay precision of 4.3%, 5.8%, and 3.2%, respectively. Positive anti-TPO, and anti-tg were defined as a value greater than 5.61 IU/ml and 4.11 IU/ml, respectively.

Statistical analyses

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS for Windows) software (version 17.0, SPSS Inc., Chicago, IL, USA). All parametric variables were given as mean ± SD or median and interquartile range according to distribution of variables. Distribution of patients was assessed by using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). The difference between categorical variables was analyzed with Chi-square test and continuous variables were analyzed with Mann-Whitney *U* test. As the vitamin D level was not normally distributed even after logarithmic transformation, the data were compared by the non-parametric Mann-Whitney *U* test. A *p*-value below 0.05 was considered to be statistically significant.

While investigating the associations between non-normally distributed and ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test.

Results

A total of 405 patients were enrolled in our study. The mean age was 44.6 ±13.5 years and 89.4% were women in the study population. There was no age difference between 3 groups ($p > 0.05$). A mean vitamin D level of all participants was 20.1 ±12 ng/ml. Patients whose serum 25(OH)D levels were below 20 ng/ml were considered as vitamin D deficient. Sixty five percent (183/281) of the AITDs patients were vitamin D deficient. When vitamin D deficient ($n = 183$) and sufficient ($n = 98$) AITDs patients were compared, anti-TG and anti-TPO levels found significantly high in the vitamin D deficient group ($p = 0.02$ and $p = 0.003$, respectively, for anti-tg and anti-TPO) (Table 1).

Group 1, group 2 and group 3 consisted of 254, 27 and 124 patients, respectively. The prevalence of vitamin D insufficiency was 63% and 85.2% in group 1 and 2, respectively. Although the levels of vitamin D were lowest in group 2 (Fig. 1), calcium and PTH levels were similar between groups. Laboratory results of study population are demonstrated in Table 2.

Table 1. Thyroid autoantibody levels according to the vitamin D status

	Vitamin D deficient group ($n = 183$)	Vitamin D sufficient group ($n = 98$)	*p* value
Vitamin D (ng/ml)	13.4 ±3.6	29.5 ±10	0.001
Anti-TG (IU/ml)	40.4 1.15-1000	19.9 1.12-1000	0.02
Anti-TPO (IU/ml)	170.9 0-1000	36.8 0.06-1000	0.003

Values are expressed as mean ÷ SD or median with interquartile range
Anti-TG – thyroglobulin antibody, anti-TPO – anti-thyroid peroxidase antibody

Table 2. Characteristics of the study population

	Group 1	Group 2	Group 3	*p* value
TSH (mIU/ml)	2.47 0.16-39.6	0.01 0.001-0.67	1.75 0.32-7.43	**< 0.001**
Anti-TG (IU/ml)	29.4 1.12-1000	71.1 1.61-1000	1.43 0.46-5.71	**< 0.001**
Anti-TPO (IU/ml)	117.68 0-1000	281.36 0-1000	0.26 0-4.78	**< 0.001**
PTH (pg/ml)	46.9 9.14-135.4	48.4 25.1-111.2	43.1 19.9-134.9	0.07
Vitamin D (ng/ml)	17.05 5.4-80	14.9 4-39	19.9 9-122.7	**< 0.001**
Ca^{2+} (mg/dl)	9.4 18.4-10.4	9.5 8.4-10.4	9.5 8.4-10.2	0.955

Values are expressed as median with interquartile range.
TSH – thyroid-stimulating hormone, anti-TG – thyroglobulin antibody, anti-TPO – anti-thyroid peroxidase antibody, PTH – parathyroid hormone, Ca – calcium

Multivariate analysis using logistic regression revealed that independent determinants of vitamin D levels were age and sex ($r = 0.17$, $p = 0.004$; $r = –0.15$, $p = 0.01$, respectively). As expected, there was a negative correlation between vitamin D and PTH levels ($r = –0.24$, $p < 0.001$). When we have investigated the association of thyroid autoantibodies, we found that there was a significant correlation between these autoantibodies and vitamin D and TSH levels (Table 3). Thyroid autoantibodies tended to be higher with lower vitamin D levels and higher TSH levels. Serum PTH levels, however, were not associated with anti-TG and anti-TPO levels.

Table 3. Correlation between thyroid autoantibodies and vitamin D and TSH levels

	Vitamin D	TSH
Anti-TG		
r	–0.13	0.144
p	0.025	0.018
Anti-TPO		
r	–0.17	0.21
p	0.003	0.001

TSH – thyroid-stimulating hormone, anti-TG – thyroglobulin antibody, anti-TPO – anti-thyroid peroxidase antibody

Discussion

In this case-control study, patients with autoimmune thyroid diseases (HT and GD) had lower 25(OH)D levels than healthy subjects and vitamin D levels were the lowest in GD patients. Since we have known from our previous and other Turkish studies that vitamin D deficiency has been a prevalent health problem in our country, we adopted a cutoff level of vitamin D level as 20 ng/ml [21-23]. According to this cutoff value, 60.7% of our study population had vitamin D deficiency.

It has been known that vitamin D deficiency is not correlated with severity of hyperthyroidism [24, 25], and antithyroid drugs have immunosuppressive effects. In addition, thyroid hormones relatively affect renal activity of 1α-hydroxlase and plasma $1,25(OH)_2D$ levels [26, 27]. For these reasons, only newly diagnosed AITDs patients were included and we measured 25(OH)D level instead of $1,25(OH)_2D$ in our study.

Autoimmune thyroid diseases are relatively common organ-specific autoimmune disorders that cause diseases ranging in severity from hypothyroidism (HT) to hyperthyroidism (GD) [28]. The effects of various environmental factors and the intrinsic genetic predisposition of an individual may lead to a loss of self-tolerance and contribute to the initiation of AITDs. In pathological conditions like thyroiditis, infiltrating lymphocytes, cell surface expression of MHCII, Fas-mediated apoptosis and cytokines re-

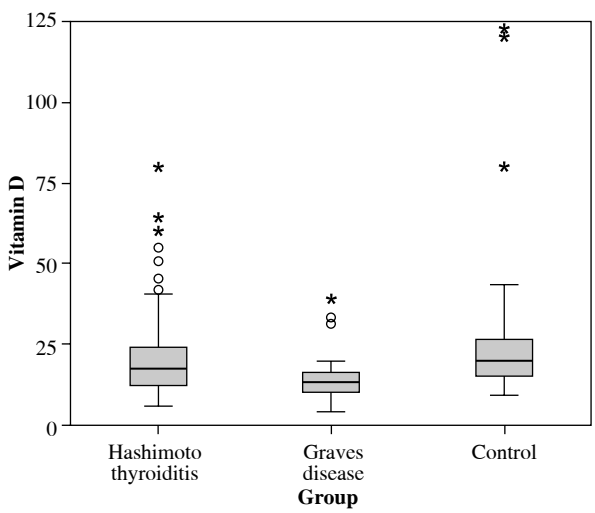

Fig. 1. Vitamin D levels in each group

leased from both immune cells and thyrocytes contribute to amplification and progression of AITD [29-34]. According to this theory, as a result of defective suppressor T cells, Th (CD4) cells are able to activate and cooperate with B lymphocytes. B lymphocytes activated by T lymphocytes produce antibodies that react with thyroid antigens. Studies on HT and GD patients had reported low vitamin D levels [9, 10, 35, 36]. Consistent with the literature, we found a lower vitamin D level in patients with autoimmune thyroiditis (GD group and HT group) than in controls. In addition, this is the first study that found a statistically significant negative correlation between serum 25(OH)D and anti-TPO, anti-TG levels in both HT and GD patients.

Conclusions

Our findings indicate that patients with AITD present with lower vitamin D levels and GD patients have higher prevalence. Since we found an inverse correlation between vitamin D levels and thyroid antibody levels, we might speculate that there might exist a casual relationship. However, these findings do not clarify whether treatment with vitamin D has any beneficial effect on progression or remission of AITD. So, further studies specifically designed to evaluate the beneficial effect of vitamin D supplementation on AITD are needed.

The authors declare no conflict of interest.

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