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Effect of Vitamin D Therapy on Hashimoto's Thyroiditis in Children with Hypovitaminosis D

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Abstract

Background

Hashimoto's thyroiditis (HT) is a common cause of thyroid diseases in children and the role of vitamin D (VD) is controversial. Therefore, the aim of this study was to investigate the influence of VD therapy on HT in children with hypovitaminosis D.

Materials and Methods

This randomized clinical trial study was conducted on 30 patients referred to Endocrine Clinic of Amirkola Children's Hospital (ACH) of Babol in Iran. The serum levels of calcium, T4, TSH, Anti thyroid peroxidase antibody (TPOAb), and Anti thyroglobulin antibody (TgAb) were checked, and ultimately the HT was diagnosed based on thyroid sonography and these findings. According to normal range of calcium>8.4 mg/dl and low level of VD, the patients were divided into deficient (<20 ng/ml), and insufficient (20-30 ng/ml) groups.

Results

The mean of anti-Tg and anti-TPO statistically decreased was 801.63±1172.29 vs. 492.38±1021.48 (p=0.01), and 728.21±1004.28 vs. 441.57±603.26 (p=0.01) before and after intervention, respectively so that this reduction was higher in 2-12 year-old patients. Moreover, the mean of thyroid volume in both right and left lobes statistically reduced was 3.97±3.18 vs. 3.21±2.67 (p=0.002), and 3.32±2.94 vs. 3.21±3.96 (p=0.008) before and after intervention, respectively so this decrease was higher in≥13 year-old children (p<0.05).

Conclusion

This study showed that the level of autoantibodies and thyroid volume were decreased, after VD intervention. Thus, it is suggested that the serum VD level should be routinely checked in these patients and when observing hypovitaminosis, an appropriate treatment and prevention with VD should be carried out to avoid recurrent VD deficiency.

Key Words: Autoimmune thyroid, Hashimoto's Thyroiditis, Thyroid volume, Vitamin D.

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1- INTRODUCTION

Hashimoto's thyroiditis (HT) as the most common clinical expression of organ-specific autoimmune disease, also called chronic lymphocytic thyroiditis, may lead to dysfunction of the thyroid gland and even subclinical or clinical hypothyroidism (1). The worldwide annual incidence of HT which is higher in women is approximately 2.2-498.4 per 100,000 (2, 3). The HT is characterized by the reactivity to one's own thyroid antigens and both T and B cell-mediated immune responses play an important role. A prominent lymphocytic infiltration happens at the thyroid tissue (4). Genetic predisposition and environmental factors including immunological activity, different pollutants, stress, exposure to high iodine concentrations, infectious diseases and various drugs are likely to play a role in the development of HT (5, 6). The pathogenesis of HT is still not fully understood (7). However, the HT is defined by an occurrence of autoantibodies typically against thyroid peroxidase and thyroglobulin, lymphocytic infiltration and hypothyroidism (8). The diagnostic hallmarks of HT are serum thyroglobulin antibody (TgAb), and thyroid peroxidase antibody (TPOAb) (9) which can be found in 80–100% of these patients (10).

A study has shown that the TgAb and TPOAb can mediate antibody-dependent cell-mediated cytotoxicity (11). Xie et al. concluded that the humoral response was important in pathogenesis of HT (12). In addition, it has been found that the immunological characteristics of TgAb and TPOAb play a role in progression of HT via regulation of immune responses (13,14). Nutritional materials including vitamin D (VD) can affect immunity function and resistance against autoimmune disorder (15). Vitamin D is a fat-soluble steroid molecule derived from the skin in the form of cholecalciferol (VD3) or from the diet in the forms of ergocalciferol (VD2) and VD3. The VD undergoes hydroxylation steps in the liver and kidneys and is changed into 25 (OH) vitamin D3 (best indicator of the body's VD status) and 1.25-dihydroxy vitamin D3 [1, 25 (OH) 2 D3], respectively (16). The active form of VD (1,25-(OH)2 D3) via connection to nuclear receptor plays important roles in physiological functions including hemostasis of calcium and phosphor, inhibition of inflammatory cytokines such as gamma-interferon, increase of epithelial cells differentiation, regulation of immunity system and other functions (17). The VD is protective in autoimmune diseases (18) and may play a role in the pathogenesis of immunity in HT (4, 19). The studies have indicated contrasting results about the effect of VD on HT. Some studies have shown the effectiveness of VD on the prevention or treatment of thyroid disease but the results of other studies were different, which was not statistically significant (4, 20). It is a challenging issue and no planning has been obtained; hence, more clinical trials are recommended to prove this issue (21). Due to the limited studies and contrast results on this issue, the current study was conducted for the first time in Iran. The aim of the present study was to determine the effect of VD therapy on Hashimoto's thyroiditis in children with hypovitaminosis D.

2- MATERIALS AND METHODS

This randomized clinical trial (RCT) study was performed on 30 patients, referred to Endocrine Clinic of Amirkola Children's Hospital (ACH), Babol, Iran. The sample size was 30 patients selected based on the 45% reduction for autoantibodies at alpha 0.05 and power 0.8. First, all patients younger than 18 years with thyroid problems, referred to Endocrine Clinic of ACH, were selected for the present study. In the next step, to assess the changes in thyroid tissue, the thyroid sonography was performed, the

serum levels of TPOAb and TgAb were measured and then based on the above criteria, the HT was diagnosed by pediatric endocrinologist. Afterwards, the serum levels of calcium and VD were measured and finally, the patients with low levels of VD (<30 ng/ml) and normal level of calcium (>8.4 mg/dl) were included in the current study.

2-1. Criteria

Inclusion criterion was all patients younger than 18 years with thyroid disease diagnosed by pediatric endocrinologist as HT, referred to Endocrine Clinic of ACH. Exclusion criteria were patients with or without goiter with normal antibodies' levels, with HT under treatment, with certain chromosomal syndromes such as Downs, Turner, Klinefelter, and with cardiac, liver and renal diseases

2-2. Measurements

For measurement of VD, 1 ml blood was taken and serum VD level was measured using ELISA method (22).

T4: For measurement of T4, 2 ml blood sample with chemiluminescent immunoassay was taken using a Monobind kit made in USA and normal range was defined: 1-3 years (6.8-13.5 µg /dl), 3-10 years (5.5-12.8 µg /dl), >10 years (4.2-13 µg /dl) (22).

TSH and Autoantibodies: For measurement of TSH (normal range=0.5-5.5 MIU/L), anti-Tg (normal range<125 MIU/ml), anti-TPO (normal range<40 IU/ml), using luminance and Monobind kit, (made in USA), 2 ml blood sample were taken.

Ca: Serum calcium levels (normal range=8.4-11 mg/dl) were measured by methylene blue method with 1ml blood sample using MAN kit made in Iran.

2-3. Ultra-sonographic evaluation

Sonographic findings of HT display the form of echogenic heterogeneity in most patients and sometimes the hypertrophy of thyroid, formed by increasing the number of hyperplastic lymph nodes in neck (22). In this study, the ultrasonographic evaluation of the thyroid gland was performed using a Mindry 8 (made in China). Ultrasonographic features of diffuse thyroiditis were conducted using accepted standards of a heterogeneous echogenic pattern of thyroid gland or diffuse parenchymal hypo-echogenicity (23). Findings of right and left lobules were recorded in checklist. Sonographic evaluation was done by an expert sonographer in Radiology Unit of ACH.

2-4. Exercise Protocol and Supplements

2-4-1. Serological and clinical examination

According to normal calcium level (>8.4 mg/dl), and low level of VD, the patients were divided into two groups:

a) VD-deficient group (<20 ng/ml): Patients received 50,000 U VD pearl every week for 8 weeks, after that, the serum VD level was rechecked and if it reached normal range (>30 ng/ml), the patients received one pearl of VD every month till the end of study.

b) VD-insufficient group (20-30ng/ml): Patients received 50,000 U VD pearl every week for 6 weeks, then, the serum VD level was rechecked and if it reached normal range (>30 ng/ml), the patients continued to take VD once a month for 6 months. At the end of the study, autoantibodies and thyroid sonography were done again. If the VD did not reach normal range at the end of 6 and 8 weeks, the treatmentwas continued until VD returned to normal range, then, monthly treatment was started.

c) Normal range (30-100 ng/ml) (24).

2-4-2. Management of hypothyroidism

The patients with subclinical

hypothyroidism (normal T4 with high TSH [>5.5 MIU/L]), and clinical hypothyroidism (low T4, according to the age, with high TSH [>5.5 MIU/L]) were treated with 3-4 µg/kg/day (22) of levothyroxine 0.1 mg tablet (Iran Hormone Inc., Tehran, Iran). T4 and TSH were checked again 1.5-2 months later (at the same time of VD testing) and then, every 3 months.

2-5. Ethical Approval

This research was approved by Ethic Committee of Babol University of Medical Sciences (MUBABOL.HRI.REC.1396.55). This clinical trial was registered in Iranian Registry of Clinical Trials (WWW.IRCT.IR), and assigned a code of IRCT20180228038900N1. Informed consent was obtained from each participant and their parents before any interview.

2-6. Statistical analysis

Data were analyzed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation [SD] (for normally distributed data). The quantitative parameters were analyzed through paired t-test. P-value <0.05 was considered statistically significant.

3- RESULTS

Of 30 patients entered in this study, 20 cases (66.7%) were female. The age ranged from 7 to 16 with the mean of 12.33±2.64 years. Among them, 16 (53.3%) patients were in age range of 2-12 years and 14 (46.7%) cases were ≥13 years. The weight range was 23-82 kg with the mean of 45.41± 25.88 kg. The height range was 125- 172 with the mean of 136.8±34.08 (**Table.1**). The parameters before intervention in children referred to Endocrine Clinic of ACH showed that the mean of calcium, TSH and T4 were 8.83± 0.25mg/dl, 26.23± 40.48 MIU/ml and 7.45± 2.41 µg /dl, respectively. As shown in **Table.2**, the results indicate that the anti-Tg and anti-TPO are significantly decreased after VD administration and this reduction is higher for anti-Tg ($p<0.05$). The mean serum VD level was lower before intervention, adjusted after intervention and finally reached to optimum level. This difference was statistically significant ($p=0.002$).

Table-1: Baseline characteristics of Hashimoto Thyroiditis patients that referred to Amirkola Children's Hospital, Iran.

Variables	Sub-group	Frequency (%)	Mean ± SD
Gender	Male	10(33.3)	-
	Female	20(66.6)	-
Age, year	2 to 12	16(53.3)	12.33±2.64
	13 and upper	14(46.7)	
Weight, kg	-	-	45.41±25.88
Height, cm	-	-	136.87 ± 34.08

SD: Standard deviation.

Table-2: Investigation of Vitamin D therapy in Auto-antibody and Vitamin D titer, before and after intervention in Thyroid patients referred to endocrinology clinic of Amirkola Children's Hospital.

Variables	Before Intervention	After Intervention	P-value
Anti-Tpo*	728.21±1004.28**	441.57±603.26	0.01
Anti-TG	801.63±1172.29	492.38±1021.48	0.01
Vit D	16.56±6.19	49.87±53.16	0.002

Anti-Tpo: Thyroid peroxidase antibody; Anti-TG: Thyroglobulin antibody, Vit D: Vitamin D. **Data was showed as mean± standard deviation.

3-2. Effect of VD on autoantibody titer according to age

As illustrated in **Table.3**, considering the effect of VD on autoantibodies based on the age, the autoantibody titers are decreased in both groups so that this reduction is higher for 2-12 year-old children.

3-3. Effect of VD on thyroid volume

As represented in **Table.4**, the mean thyroid volume in both right and left lobes is statistically reduced after VD administration.

3-4. Effect of VD on thyroid volume according to age

As displayed in **Table.4**, statistically, the mean thyroid volume is declined after VD administration so that this decrease is higher for ≥13-year-old children.

Table-3: Parameters according age before and after vitamin D therapy in Thyroid patients referred to endocrinology clinic of Amirkola Children's Hospital.

Variables	Category	2-12 years		P-value	13 years and upper		P-value
		Before Intervention	After Intervention		Before Intervention	After Intervention	
Vit D*		17.93±6.94*	42.83±9.90	<0.001	15±5.02	57.90±77.85	0.062
Anti-Tpo	Abnormal	1(6.3)**	14(87.5)	0.008	13(92.9)	1(7.1)	0.03
	Normal	15(93.8)	2(12.5)		1(7.1)	13(92.9)	
	Total	864.08±1226.64	427.23±634.47	0.08	593.50±690.75	457.96±588.89	0.03
Anti-TG	Abnormal	14(87.5)	7(43.8)	0.01	10(71.4)	7(50)	0.43
	Normal	2(12.5)	9(56.3)		4(28.6)	7(50)	
	Total	858.37±1174.91	368.09±736.34	0.01	736.77±1210.11	634.42±1308.14	0.43

vit D: Vitamin D, Anti-Tpo: Thyroid peroxidase antibody; Anti-TG: Thyroglobulin antibody. * Data was shown as mean± standard deviation. **Data was shown as frequency (percentage).

Table-4: Thyroid volume before and after vitamin D therapy in Hashimoto patients referred to endocrinology clinic of Amirkola Children's Hospital.

Variables	Category	2-12 years		P-value	13 years and upper		P-value
		Before Intervention	After Intervention		Before Intervention	After Intervention	
Thyroid Volume	Right Lobule	3.13±2.13*	2.54±1.35	0.06	4.93±3.93	3.97±3.56	0.01
		3.97±3.18		-	3.21±2.67		0.002
	Left lobule	3.17±2.17	2.84±8.16	0.1	4.86±3.99	3.86±3.64	0.02
		3.96±3.21		-	3.32±2.94		0.008

*Data was shown as mean± standard deviation.

4- DISCUSSION

The current study was conducted on 30 patients with HT referred to Endocrine Clinic of ACH. The aim of the present study was to determine the effect of VD therapy on Hashimoto's thyroiditis in children with hypovitaminosis D. The mean of thyroid autoantibodies titers was statistically decreased after VD administration in the present study. Sonmezgoz et al. suggested that the anti-TPO had inverse correlation with VD, indicating a significant role of VD in pathogenesis of HT. The result of their study concentrated on the effect and role of VD on autoantibody titers in HT patients, especially in screening and early detection (4). Like the current study, Sonmezgoz et al. and Arslan et al. showed

that the anti-TPO titer was lower in VD-normal group than in VD-deficient group, and there was an inverse correlation between VD level with anti-Tg and anti-TPO antibodies (4, 25). It is worth mentioning that in the study of Arslan et al., the VD normal range, moderate deficiency and severe deficiency were defined >20, 10-19.9 and <10 ng/ml, respectively, but in the current study, ≥ 30, 20-30, and <20 ng/ml were considered as normal, insufficient and deficient level, respectively. However, there was an inverse correlation between VD with anti-Tg and anti-TPO in most studies. Mansournia et al., concluded that the increased serum 25 hydroxy vitamin D levels were related to decreased risk of HT after adjustment for potential confounding factors so that each 5 ng/ml increase in serum 25OHD level led to about 20% decrease in HT.

In addition, they suggested that there was a positive correlation between TSH and VD while this relationship was not found for anti-TPO (26). This contradictory result could be due to the normal range of anti-TPO (<40 IU/ml) in their study. Moreover, unlike the running study, the sample size was larger in the study of Mansournia at al. and they compared the experimental groups with control group (26). Kivity et al. demonstrated that the prevalence of VD deficiency was significantly higher in patients with HT than healthy individuals (72 vs. 30.6%), and in cases with HT than non-HT patients (79 vs. 52%) (19).

In Kivity et al.'s study, VD <10 ng/ml was considered as deficiency, which was different from that in the present study. Further, they had control group but the HT patients of the current study were controlled before and after intervention. Although the running study confirmed the study of Kivity et al., it was not comparable with their study because of differences in the definition of VD ranges. In Zhang et al.'s study, the VD concentration had no correlation with increased autoantibody titer. This contrast may refer to the difference of study design and methodology in both studies. Besides, some studies have shown that the anti-TPO and anti-TG are pathologically independent to VD. It seems that anti-TPO and anti-TG are the land markers of diagnosis of HT whereas other studies have expressed that there is a relationship between anti-TPO and VD level in severe VD deficiency (4, 13, 20). The results of the current study exhibited that after VD administration, the mean of thyroid volume was statistically decreased in both right and left lobes. Zhang et al. also found no significant differences in thyroid volume by comparing groups with VD insufficiency and sufficiency (27). There was no relationship between VD and thyroid volume but larger thyroid volume was correlated with higher levels of TPOAb, representing a greater magnitude of the autoimmune inflammatory process in patients presenting larger thyroid volume. Concentrations <10 and <20 ng/ml were classified as deficiency and insufficiency, respectively (28).

In this study, considering the effect of VD on autoantibodies based on the age, the autoantibody titers decreased in both groups so that this reduction was higher for 2-12 year-old children. Venkatasamy et al. stated that 65% of HT patients were 10-12 years old and the difference in age range was not statistically significant, which was different from the present study (2-16 years) (29). Unlike our study, Botelho expressed that there was no significant difference between autoantibody and demographic variables, especially age because the age range was 18-75 years and most patients were female (92%) in their study (30). It seems that aging has no effect on the autoantibody level in adults as opposed to children. The results of the current study showed that the mean thyroid volume in both right and left

lobes was statistically reduced after VD administration so that this decrease was higher for ≥13 year-old children. Zhang et al. found no significant difference between thyroid volume with VD-normal and -deficient groups (13). Moreover, Tamer et al. expressed that no significant difference was observed between VD and thyroid volume while increased thyroid volume was correlated with TPO-Ab, which is beyond autoimmune inflammatory process in HT patients (28). Besides, in Tamer et al.'s study, the VD deficient and insufficient levels were considered as <10 and <20 ng/ml, respectively. Bozkurt et al. concluded that the severity of VD deficiency was associated with HT duration, antibodies and volume of thyroid (31), indicating that the VD may play an important role in the development and progression of HT, which needs comprehensive study. Also, in Pani et al.'s study, the TSH level and thyroid volume had statistically significant difference in two groups (32), which is similar to the current study.

Of course, most studies mentioned a difference between thyroid volume and serum VD level before intervention, but this study compared thyroid volume before and after intervention with VD therapy to solve this difference. The results of the running study demonstrated a low serum level of VD before the intervention that returned to optimum level after VD administration, which was statistically significant; while Pani et al. stated that VD deficiency was not observed before intervention (32), which is inconsistent with the present study. In the study of Kivity et al., most HT patients had serum VD level <10 ng/ml compared to control group (19). In the current study, the mean serum VD before intervention was 16 ng/ml which was slightly higher than that in Kivity et al.'s study (19).

5- CONCLUSION

The results of current study showed that the VD administration led to the decrease in autoantibodies and thyroid volume. This study also demonstrated that the correction of VD had optimal effect in HT. Thus, it is suggested that the serum VD level should be routinely checked in these patients, VD insufficiency/deficiency should be corrected and preventive treatment with VD should be considered to avoid recurrent VD deficiency. For future, it is recommended to design an RCT study with several groups, with administration of VD in both deficient group (treatment-dose group), and normal group (preventive-dose) as well as with considering other factors (as sunlight, nutrition).

6- AUTHORS' CONTRIBUTIONS

Morteza Alijanpour (Pediatric Endocrinologist) and Haji Ghorban Nooreddini (Sonographer) participated in diagnosis of patients, approved the final version and supervised the study. Mohamad Pornasrollah gathered sampling, designed the study and prepared the manuscript. Soraya Khafri, Abdolali Aghili and Shayan Alijanpour designed the study as well as prepared the manuscript, analysis and writing of manuscript.

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8- CONFLICT OF INTEREST: None.

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