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Efficacy of Vitamin-D Supplement on Thyroid Profile in Children with Graves' Disease

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Abstract

BACKGROUND: Many studies have shown low Vitamin-D level as a risk factor for autoimmune diseases, especially multiple sclerosis and thyroid disease. Graves' disease (GD) is an autoimmune disease caused by autoantibodies that stimulate thyroid-stimulating hormone (TSH) receptors by increasing thyroid hormone synthesis and secretion. Several studies report that many patients with autoimmune thyroid disease including GD have low Vitamin-D status.

AIM: The objective of the study was to evaluate the effect of Vitamin-D supplement on GD patients on improvement in thyroid hormone levels.

METHODS: Open random clinical trial was conducted in GD patients to determine changes in thyroid hormone to achieving normal levels between those receiving methimazole plus Vitamin-D supplementation compared with those who only received methimazole. Patients were checked for TSH receptor antibody, thyroid profile and Vitamin-D level before treatment and rechecked for thyroid profile and Vitamin-D level 3 months after treatment. t-test used to compare the drug efficacy ($p < 0.05$) in two groups.

RESULTS: From 25 children with GD accompanied by Vitamin-D deficiency with an average value of Vitamin-D was 16 ng/mL. GD children who receive methimazole with Vitamin-D supplement had elevated TSH levels in the 3rd month of therapy that was significantly different compared to GD children who received methimazole only ($p = 0.00$), and the increase of TSH was also followed by an increase in Vitamin-D levels.

CONCLUSION: All children with GD had Vitamin D deficiency, and the addition of Vitamin-D supplement to GD therapy would improve TSH faster than children who did not receive Vitamin-D supplement.

Introduction

Graves' disease (GD) is an organ-specific autoimmune disease characterized as overproduction of thyroid hormones in thyroid follicular cells resulting from the stimulation of circulating thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) [1]. GD is the most common cause of thyrotoxicosis in children and has a higher incidence in women. GD is characterized by thyrotoxicosis, hyperthyroid, and ophthalmopathy [2].

1,25-Dihydroxyvitamin D [1,25(OH)2D, calcitriol] is a steroid hormone derived from Vitamin-D, which plays an important role in maintaining an adequate level of serum calcium and phosphorus [3]. Although the biological activities of Vitamin-D are mainly manifested in the regulation of calcium-phosphorus metabolism, studies in the past 30 years indicate Vitamin-D play an important role in the immune system. Many studies have shown that low levels of Vitamin-D contribute to GD and hashimoto thyroiditis (HT) and that combining Vitamin-D with anti-thyroid drugs or thyroid hormone contributes to the treatment of autoimmune thyroid disease (AITD) by suppressing the autoimmune reaction and reducing serum levels of thyroid autoantibodies [4].

Studies assess the addition of Vitamin-D in treatment of patients with GD in Japan report that the reduction in FT4 and FT3 levels was greater in the group receiving methimazole plus Vitamin-D supplements, and they suggest to concomitant administration of Vitamin-D is useful for treating hyperthyroidism in patients with GD [5].

Many studies in adults that correlated Vitamin-D levels with GD, but in children studies that correlated Vitamin-D and GD is very limited, so we conducted a clinical trial that investigated the relationship between Vitamin-D levels and GD.

Methods

This study was an open randomized clinical trial to measure the efficacy of Vitamin-D supplementation for treat GD patient in the pediatric endocrinology clinic of H. Adam Malik General Hospital Medan, periods in

May–December 2019. This study was approved by the Ethics Committee of Faculty of Medicine, Universitas Sumatera Utara (No. 394/TGL/KEPK FK USU-RSUP HAM/2019) in accordance with the principles of the Helsinki Declaration.

The inclusion criteria are children with GD and the parents willing to participate in the study are proven by signing an informed consent sheet. The exclusion criteria are GD patients with chronic kidney disease, chronic liver disease, and patients who receive any drugs that affect Vitamin-D levels, such as steroids, antiepileptics, methotrexates, INH (isoniazid), thiazides, antacids, calium channel blockers, and anticonvulsants. This study was approved by the Health Ethics Committee of the Faculty of Medicine, University of North Sumatra and the H. Adam Malik Hospital Medan Ethics Committee. All parents or guardians of patients have been informed and asked for consent to have their children involved in this study.

All patients who present with neck lumps were tested for TRAb, neck ultrasound, TSH, and FT4 to diagnose GD. Then, all samples that meet the inclusion and exclusion criteria were randomly divided using simple randomization into two treatment groups; Group I received methimazole (0.25–1 mg/kg/day) with Vitamin-D supplement (2000 IU/day) and Group II: received methimazole only (0.25–1 mg/kg/day). All sample reexamined after 2 months and 3 months treatment to assess improvement in thyroid hormone and Vitamin-D level. The efficacy is assessed using increase of TSH and decrease of FT4 level. Vitamin-D values were categorized as being deficient when <20 ng/L (50 nmol/L) and insufficient between 21 and 29 ng/L (52.5–72.5 nmol/L), on the basis of Endocrinology society [6].

The data analysis is made using Statistical Package for the Social Sciences for Windows (SPSS) version 24.0, 2016, with a confidence interval at 95% and a significance rate $p < 0.05$. t-test was used to compare differences in the level of thyroid profile between Group I and Group II in this study.

Results

Study participants

There were 27 subjects met inclusion criteria in the period May–December 2019. Vitamin-D examination was incomplete in two patients, so 25 patients were included in the analysis, and then they are divided randomly into two treatment groups (Figure 1).

Basic characteristics samples in this study before intervention did not differ, with an average age of 13.5 years, the overall sample was female, and most of the samples had well nourished (Table 1).

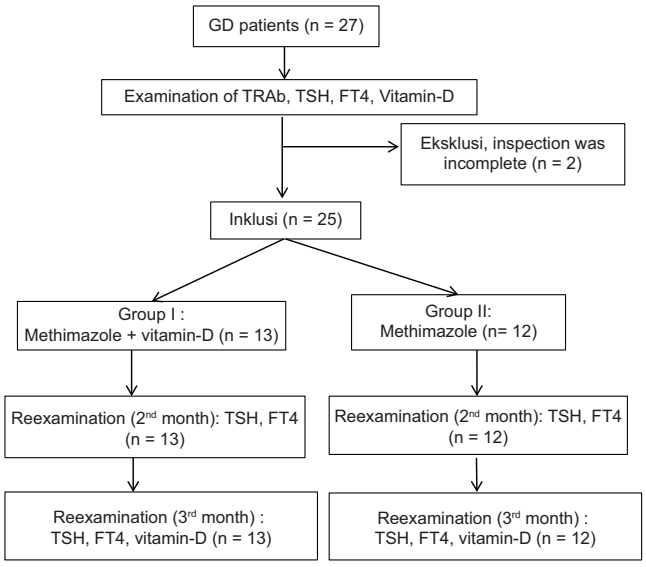

Figure 1: Study flow chart

Table 1: Baseline subject characteristics

Characteristics	Treatment group	
	Group I (n=13)	Group II (n=12)
Age (year), mean (SD)	13.8	13.2
Nutritional status, n (%)		
Well nourish	10 (52.6)	9 (47.4)
Overweight	3 (50)	3 (50)
Sex, n (%)		
Female	13 (50)	12 (50)

Table 2 shows TRAb levels, thyroid profiles (TSH, FT4), and Vitamin-D levels in the 1st month before start therapy. We found that in GD patients where there was an increase in TRAb, decrease in TSH, and increase in FT4, accompanied by Vitamin-D deficiency, there were no significant differences between the two treatment groups for TRAb levels, thyroid profile, and Vitamin-D level.

Table 2: TRAb levels, thyroid profile, and Vitamin-D levels in the 1st month

Variables	Group I (n=13)	Group II (n=12)	p*
TRAb positif (>1.75 IU/L), mean	20.4	22.4	0.05
Thyroid-stimulating hormone level, mean	0.04	0.05	0.98
FT4 level, mean	2.89	2.37	0.14
Vitamin-D deficient (<20 ng/L) mean	15.6	16.5	0.50

*t-test, TRAb: TSH receptor antibody.

In the 2nd month after therapy, there was an increase of TSH in Groups I who treated with methimazole and Vitamin-D supplement, and decrease of FT4 in both groups. The level of TSH and FT4 in both groups did not differ significantly. However, FT4 level in Group I was decrease more greater than Group 2 (Table 3).

Table 3: Thyroid profile in the 2nd month

Variables	Group I (n=13)	Group II (n=12)	p*
Thyroid-stimulating hormone level, mean	0.08	0.05	0.29
FT4 level, mean	2.5	2.2	0.24

*t-test.

In the 3rd month of treatment, both treatment groups experienced an increase of TSH, decrease of FT4, and increase of Vitamin-D level. Statistically, there were significant differences in the increase of TSH and

Vitamin-D levels between Group I who treated with methimazole with Vitamin-D supplement and Group II who treated with methimazole only, with $p < 0.05$ (Table 4).

Table 4: Thyroid profile and Vitamin-D levels in the 3rd month

Variables	Group I (n=13)	Group II (n=12)	p*
Thyroid-stimulating hormone Level, Mean	0.14	0.06	0.00
FT4 Level, Mean	2.33	2.17	0.56
Vitamin-D level, mean	23.8	17.9	0.00

*t-test.

Increase of TSH levels in the group who received methimazole with Vitamin-D was faster compared to the group who received methimazole without Vitamin-D (Figure 2).

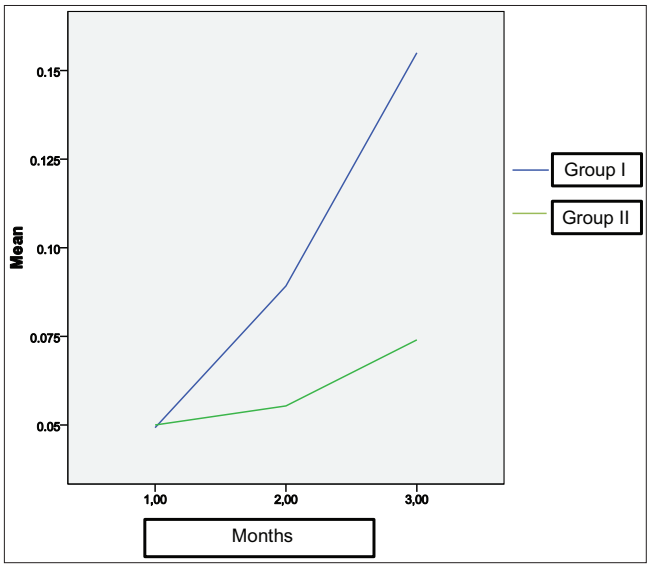

Figure 2: Thyroid-stimulating hormone comparison curves in the two treatment groups

Discussion

Vitamin-D receptors have been found in the immune system, reproductive system, endocrine system, muscles, brain, skin, and liver as well as bones, kidneys, and intestines; this proves that the role of Vitamin-D is not only limited to the skeletal system [7]. The function of Vitamin-D mainly in calcium-phosphorus metabolism, but a recent study shows that Vitamin-D also plays a role in the immune system [4]. Because Vitamin-D is an innate modulator and adaptive immunity, so Vitamin-D deficiency has a relationship with various autoimmune diseases [8]. Many studies have shown low Vitamin-D level as a risk factor of autoimmune diseases, especially multiple sclerosis and thyroid disease [9].

Thyroid disease is the most frequent endocrine disorder, including AITDs, namely, HT and GD, which occupy the main position around 5% of the population. AITDs are multifactorial diseases, where immunity influences gland infiltration by T and B cells and the production of specific autoantibodies, which are reactive to roid antigens (anti-thyroglobulin, anti-thyroid peroxidase [thyroid peroxidase antibodies], and anti-TH receptors [TRAb]) [10]. In addition, Vitamin-D supplementation has a benefit effect on the treatment of AITD by reducing levels of thyroid antibodies and suppressing autoimmune reactions. A number of previous studies have shown various relationships between Vitamin-D and AITD [11].

This study was found that all GD patients were accompanied by Vitamin-D deficiency, where the Vitamin-D levels of all samples were <20 ng/mL or an average of 16 ng/mL in both treatment groups. As already explained, that Vitamin-D has immunomodulatory activity. Therefore, Vitamin-D can suppress the immune system in GD [5].

The study conducted in Hungary reported that there is association between hyperthyroidism and Vitamin-D found, where deficiency of Vitamin-D was significantly higher in patients with hyperthyroid (Vitamin-D levels <10 ng/mL) than in healthy people who were the same as age, as well as in patients with hyperthyroidism compared with patients with non-AITD [12]. The study conducted in Turkey is the only study conducted in the pediatric population, reported that higher levels of Vitamin-D deficiency (<15 ng/mL) in children with newly diagnosed hyperthyroidism compared to sex-appropriate control groups and age [13].

Hyperthyroidism in patients with GD is mainly due to the production of autoantibodies that bind to receptors for thyrotropin (TSH) in thyroid cells [5]. GD is the most common cause of hyperthyroidism in children and adolescents [14]. Thyrotoxicosis is a general term that indicates an increase in levels of T3 (triiodothyronine) and or T4 (thyroxine) with any cause, whereas hyperthyroidism is a result of a thyrotoxicosis state due to increased thyroid hormone production [15].

In the present study, we sought to clarify whether supplemental administration of Vitamin-D influences the treatment course of patients with GD. We found that in patients who were treated with both methimazole and Vitamin-D supplement, FT4 was decrease more rapidly compared with the levels in patients treated with methimazole alone in the 2nd and 3rd months of therapy, although the difference in FT4 levels between the two groups was not significantly different. Serum levels of TSH showed a reciprocal increase, and the rate of this increase was more rapid in Group B. The rapid decrease of FT4 in Group I may, therefore, be due to decrease in thyroid hormone production by the addition of Vitamin-D supplement. However, the dose of methimazole in both groups is still in the therapeutic dose range, we cannot completely rule out the possibility that the physicians decreased methimazole doses more rapidly in patients treated with methimazole alone.

As described in the introduction, it has recently been shown that Vitamin-D has immunomodulatory

activity. However, TRAb values after treatment were not measured in our study. Study conducted in Japan assess the effect of Vitamin-D supplementation on GD reported that there were no differences in TRAb levels in patients who received methimazole alone or with Vitamin-D supplementation. There may be several possibilities for the mechanism of antithyroid action of Vitamin-D. The first is a decrease in TSH receptors numbers. The second is an acceleration in the metabolism or a decrease in the biosynthesis of thyroid hormones. The third is vitamin-D has a direct effect on TRAb. At this moment, we are uncertain as to which one is most likely. However, recent studies using cultured rat thyroid cells strongly suggest direct antithyroid action of vitamin-D [16].

This study has several weaknesses. First, we did not evaluate TRAb levels after Vitamin-D supplementation and also adjustment dosage of methimazole during the period of therapy, although the dosage of methimazole is still in the dosage range. Second, this study only assessed Vitamin-D, but no assessed about daily habits patients like exposed to sunlight as one of the main sources of Vitamin-D. Third, the subjects are too small so it is difficult to generalized. There is a need for multicenter advanced study with more subjects so that it can be applied to all children with GD.

Conclusion

Hyperthyroidism in patients with GD is mainly due to the production of autoantibodies that bind to TSH receptors on thyroid cells. Many studies have stated that low Vitamin-D status is a risk factor for autoimmune disease. In this study, we found that all children with GD had Vitamin-D deficiency, and the addition of Vitamin-D supplement to GD therapy would improve the thyroid profile of GD children faster than children with GD who did not receive Vitamin-D supplement. However, further research with large samples and long monitoring is needed to assess the effect of supplementation on the autoimmune disease process.

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