SRIWIJAYA JOURNAL OF MEDICINE

Effect of Vitamin D Supplementation on Recurrence Risk in Graves' Disease Measured By The GREAT Score at Dr. Mohammad Hoesin General Hospital Palembang

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Abstract

Graves' disease is the most common cause of primary hyperthyroidism with a prevalence of approximately 0.5%, predominantly affecting women (female-to- male ratio 6–7:1) aged 35–40 years. Predictors of treatment outcomes and recurrence risk have been studied, among them the GREAT Score, which combines age, goiter size, FT4, and TRAb levels. The aim of this study was to analyze changes in the GREAT Score after the addition of vitamin D supplementation in Graves' disease patients at Dr. Mohammad Hoesin General Hospital, Palembang, within 3 months. This was a double-blind randomized clinical trial involving 30 patients with Graves' disease, both inpatients and outpatients, who met the inclusion criteria. Patients were randomly assigned into two groups: the intervention group received 10,000 IU of vitamin D, while the control group received placebo. Recurrence risk was assessed using the GREAT Score at the first and third months, and data were analyzed with SPSS v.25. Analysis using the Wilcoxon test showed no significant change in the GREAT Score for the vitamin D group (p=0.102). At the first month, the distribution was 53.3% class I, 40.0% class II, and 5.7% class III, while at the third month it was 40.0% class I, 40.0% class II, and 20.0% class III. In the placebo group, results were also not significant (p=0.480), with the first-month distribution of 33.3% class I, 40.0% class II, and 26.7% class III, and the third month 40.0% class I, 33.3% class II, and 13.3% class III. In summary, Vitamin D supplementation has no significant effect in reducing the recurrence of Graves' disease compared to placebo.

Keywords: Graves' Disease, Vitamin D, The GREAT Score, Thyroid Stimulating Hormone, Free Thyroxine

1. Introduction

Graves' disease is characterized by hyperthyroidism, grave's ophthalmopathy, and diffuse goiter.[1] A positive Thyrotropin Receptor Antibody (TRAb) is a definitive diagnosis of Graves' disease.[2] Based on the 2019 Indonesian Basic Health Research, the prevalence of hyperthyroidism in urban areas was 6.9% (TSH <0.55 mIU/L).[3] The prevalence of Graves' disease was 3% in women and 0.5% in men. The ratio of women to men is 6-7:1. Graves' disease most often occurs in people aged 35 to 40 years. 3 Graves' disease/GD is the most common cause of primary hyperthyroidism with an estimated prevalence of 0.5%. In Europe and Asia, standard treatment for Graves' disease includes the use of antithyroid drugs for the recommended duration of 12-18 months. However, the risk of recurrence is quite high (30-60%).[4]

Graves' disease is a multifactorial condition involving the interaction of genetic and environmental factors, leading to a loss of immune tolerance to thyroid antigens. Vitamin D receptor (VDR) deficiency is associated with an increased risk of this disease. Several studies have shown that patients with Graves' disease tend to have lower vitamin D levels or a higher prevalence of vitamin D deficiency,

suggesting a link between low serum vitamin D levels and Graves' disease. However, this relationship remains controversial.[5]

Vitamin D plays a vital role in maintaining calcium and phosphorus balance and bone health. It also plays a key role in non-bone diseases. Vitamin D acts as an immunomodulator. Vitamin D receptors can regulate cell proliferation, differentiation, and thyroid cell damage.[6] Vitamin D acts as an immunomodulator, playing a role in the innate and adaptive immune systems. The effects of vitamin D supplementation on Graves' disease can be found in vitamin D receptors, monocytes or macrophages, antigen-presenting cells (APCs), B cells, and T cells.[7]

Several studies have identified factors that predict the success of ATD/Antithyroid Drug therapy in patients with Graves' disease and the risk of hyperthyroidism recurrence after treatment discontinuation. Patients with a high risk of recurrence may choose alternative therapies. In 2016, the Graves' Recurrent Event After Therapy (GREAT) score was developed by the Department of Endocrinology at Amsterdam UMC to predict the risk of relapse after discontinuation of antithyroid drug (ATD) therapy at the initiation of first-line treatment. This scoring system is based on four clinical parameters: age, serum free thyroxine (fT4) concentration, thyrotropin receptor antibody (TRAb) concentration, and goiter size. The GREAT Score is categorized into three classes: Class 1 indicates mild severity, Class 2 indicates moderate severity, and Class 3 indicates severe disease. A higher class corresponds to a higher risk of recurrence.[8]

Rattanamusik et al. (January–December 2020) conducted a study involving 75 participants, comprising 41 patients with active Graves' disease and 34 in remission, and reported a 2.24- to 3.5-fold higher risk of vitamin D deficiency among Graves' disease patients compared with the general population. Similarly, Swayamsidha et al. (October 2015–September 2016) found a higher prevalence of vitamin D deficiency in patients with Graves' disease compared with healthy individuals. Garri et al., in an observational study conducted in Padang, identified low vitamin D levels accompanied by elevated interleukin-4 and thyrotropin receptor antibody (TRAb) levels in patients with Graves' disease. Furthermore, Tristan et al., in a retrospective cohort study conducted in Switzerland from 2004 to 2014 involving 741 patients with Graves' disease, demonstrated that the GREAT Score could predict the risk of relapse following antithyroid drug (ATD) therapy, with higher scores indicating a greater likelihood of relapse.[7,8,9]

This study aimed to investigate the relationship between serum vitamin D levels and the GREAT Score in patients with Graves' disease, to assess whether vitamin D status influences the risk of disease recurrence. To date, no studies have evaluated the GREAT Score in patients with Graves' disease and hypovitaminosis D. Therefore, this study was conducted to evaluate the effect of vitamin D supplementation as an adjuvant therapy in predicting the risk of recurrence among patients with Graves' disease using the GREAT Score at Dr. Mohammad Hoesin Hospital, Palembang.

2. Method

This research was structured as a double-blind, randomized clinical trial involving 30 inpatients and outpatients with Graves' disease who met the inclusion criteria. The follow-up duration was three months, data were collected by randomly

dividing patients into two groups: one group received 10,000 IU of vitamin D, while the other group received a placebo. The placebo used in this study was formulated to be identical to the vitamin D supplement in shape, content, smell, and taste. Serum vitamin D levels were initially assessed. Levels of ≥20–<30 ng/mL (≥50–<75 nmol/L) were classified as insufficient, while levels of <20 ng/mL (<50 nmol/L) were classified as deficient, and patients meeting these criteria were included in the study. Hypovitaminosis D encompasses patients with either vitamin D deficiency or insufficiency. Vitamin D supplementation can be administered at a dose of 6,000 IU, or 10,000 IU in the presence of immunological conditions. In this study, a dose of 10,000 IU of vitamin D was used, as all participants had been diagnosed with vitamin D insufficiency and deficiency. This research was conducted at the endocrine metabolic diabetes outpatient clinic of Mohammad Hoesin Regional General Hospital (RSMH) Palembang with data collection carried out from August to October 2024. The target population included all patients diagnosed all Graves' disease patients at Dr. Mohammad Hoesin Hospital, Palembang who meet the inclusion criteria and are not included in the exclusion criteria. The setting was selected due to RSMH's role as a national referral hospital, which offers a diverse population of patients with Graves' disease. This enabled the acquisition of an adequate number of cases that satisfied the inclusion and exclusion criteria.

Participants were selected through total sampling from patients who met the criteria between August and October 2024 and were monitored for three months. The inclusion criteria comprised patients over 18-60 years of age, diagnosed with uncontrolled Graves' disease and with hypovitaminosis D. Informed consent was required from patients for participation. Exclusion criteria included patients with vitamin D allergy, patients with autoimmune diseases other than Graves' disease, history of malignant disease, patients with chronic liver disorders, patients with chronic renal failure, pregnant or breastfeeding, BMI > 30 kg/m2, drugs that can affect the thyroid (amiodarone, biotin, carbamazepine, oxcarbapine, enoxaparin, heparin). Patients who discontinued treatment, died, or experienced side effects requiring discontinuation of the drug during follow-up were classified as drop-outs. Based on the sample size calculation, a minimum of 14 participants was required per group. Allowing for an estimated 10% dropout rate, the final sample size was determined to be 30.

The independent variable in this study is vitamin D and the dependent variable is the GREAT score. In this study, eligible patients with Graves' disease will undergo blood sampling for the measurement of TRAb, FT4, TSH, and vitamin D levels during the first month. Serum vitamin D levels were quantified using the Chemiluminescent Immunoassay (CLIA) method. The 10,000 IU vitamin D capsules (Prove D3) and placebo capsules were manufactured by a pharmaceutical company distinct from the company responsible for drug distribution. Neither company was involved in the conduct or analysis of this study. The vitamin D and placebo capsules were identical in shape, size, color, taste, and odor. Blinding was maintained such that neither the investigators, supervisors, nor participants were aware of the treatment allocation. Patients were randomly assigned to one of two groups: the 10,000 IU vitamin D group or the placebo group. Allocation was carried out using sealed envelopes labeled "A" or "B," distributed by an individual not

involved in the study. The vitamin D group received 10,000 IU of vitamin D once daily in combination with antithyroid medication for three months, whereas the placebo group received a matching placebo once daily alongside antithyroid medication for the same duration. Patients were followed up at the first, second, and third months in the outpatient clinic, where clinical symptoms, adverse effects, treatment adherence, and laboratory parameters were assessed. At the end of the three-month treatment period, serum levels of free thyroxine (FT4), thyroid-stimulating hormone (TSH), and thyrotropin receptor antibodies (TRAb) were reassessed. Serum vitamin D levels were not re-evaluated, as the initial assessment was performed solely to determine the presence of hypovitaminosis D at baseline. Upon obtaining the results, the GREAT score will be calculated. The same laboratory assessments will be repeated at the third month, and the GREAT score will be reassessed based on the new results. All variables were defined operationally in accordance with established clinical guidelines and documented using standardized instruments.

This study was conducted at Dr. Mohammad Hoesin General Hospital, Palembang, from August 2024 to October 2024. It employed a double-blind randomized clinical trial design to evaluate the effectiveness of vitamin D supplementation in accelerating the achievement of euthyroidism among patients with Graves' disease in both inpatient and outpatient settings. The research ethics were approved by the Ethics Committee of Dr. Mohammad Hoesin General Hospital, Palembang, under approval number DP.04.03/D.XVIII.6.8/ETIK/242/2024. Data normality was assessed using the Shapiro–Wilk test, and numerical data that were not normally distributed were presented as median, minimum, and maximum values. Comparative analyses were performed using the Wilcoxon test, and the results are presented in tabular form.

3. Result

In this study, 46 patients with hyperthyroidism who were suspected of having Graves' disease were initially recruited. Serum TRAb and 25(OH)D vitamin D levels were measured, and 30 patients were confirmed to have Graves' disease with vitamin D deficiency. These patients were then randomly assigned into two groups: 15 patients received 10,000 IU of vitamin D supplementation, and 15 patients received a placebo for three months. Follow-up evaluations were conducted at the first and third months at the outpatient clinic of Dr. Mohammad Hoesin General Hospital, Palembang. TRAb, FT4, and TSH levels were reassessed and scored using the GREAT score. Analysis using the Wilcoxon test.

The assessment was conducted before the initiation of vitamin D administration and repeated after three months of supplementation. At the initial evaluation, 8 patients (53.3%) in the vitamin D group were classified as Class I, 6 patients (40.0%) as Class II, and 1 patient (6.7%) as Class III. After three months of treatment, reassessment showed that 6 patients (40.0%) were in Class I, 6 patients (40.0%) in Class II, and 3 patients (20.0%) in Class III. Statistical analysis using the Wilcoxon test revealed no significant difference within the vitamin D group. At the initial examination, 5 patients (33.3%) in the placebo group were classified as Class I, 6 patients (40.0%) as Class II, and 4 patients (26.7%) as Class III. After three months, reassessment showed that 5 patients (33.3%) remained in Class I, 8

patients (53.3%) in Class II, and 2 patients (13.3%) in Class III. Statistical analysis using the Wilcoxon test revealed no significant difference within the placebo group. In this study, results were obtained for both groups. In the vitamin D supplementation group, the p-value was 0.036, while in the placebo group, the p-value was 0.331. Since both p-values were greater than 0.05, it was concluded that there was no statistically significant difference between the two groups.

FT4 levels in both groups showed no statistically significant changes. After one month of treatment, the median FT4 level in the vitamin D group was 1.81 (0.85–4.40) ng/dL, while in the placebo group it was 2.18 (1.00–20.20) ng/dL. After three months of treatment, the median FT4 level in the vitamin D group was 1.76 (0.68–4.22) ng/dL, compared to 2.14 (0.54–3.30) ng/dL in the placebo group. Statistical analysis using the Wilcoxon test revealed no significant differences in FT4 levels before and after treatment in either group ($p > 0.05$).

Table 1. Characteristics of Research Subjects (NA=30)

Variable	Vitamin D (n =15)	Placebo (n =15)
Gender (n, %)		
Man	5 (33.3%)	3 (20%)
Woman	10 (66.7%)	12 (80%)
BMI (kg/m^2)		
< 18.5	6 (40 %)	8 (53.3%)
18.5-22.9	6 (40 %)	7 (46.7%)
23-24.9	3 (20%)	0 (0%)
Treatment History (n, %)		
PTU	11 (73.3%)	10 (66.7%)
Metimazole	4 (26.7%)	5 (33.3%)
Comorbid Disease (n, %)		
Hypertension	4 (26.7%)	2 (13.3%)
Diabetes	2 (13.3%)	2 (13.3%)
Smoke	4 (26.7%)	2 (13.3%)

Table 2. Treatment Outcomes in Both Groups

TSH Titer	**Month 1**	**Month 3**	**p value**	**Month 1**	**Month 3**	**p value**
	0.0009	0.018	0.331	0.0006	0.1028	0.036
FT4 Titer	**Month 1**	**Month 3**	**p value**	**Month 1**	**Month 3**	**p value**
	2.18	2.14	0.140	1.81	1.76	0.712
TRAB Titer	**Month 1 Frequency (n/%)**	**Month 3 Frequency (n/%)**	**p value**	**Month 1 Frequency (n/%)**	**Month 3 Frequency (n/%)**	**p value**
Class 1	7/ 46.7%	8/ 53.3%		10/ 66.7%	10/ 66.7%	
Class 2	5/ 33.3%	3/ 20.0%	1.00	2/ 13.3%	2/ 13.3%	1.00
Class 3	3/ 20.0%	4/ 26.7%		3/ 20.0%	3/ 20.0%	
GREAT Score	**Month 1 Frequency (n/%)**	**Month 3 Frequency (n/%)**	**p value**	**Month 1 Frequency (n/%)**	**Month 3 Frequency (n/%)**	**p value**
Class I	5/ 33.3%	5/ 33.3%		8/ 53.3%	6/ 40.0%	
Class II	6/ 40.0%	3/ 53.3%	0.480	6/ 40.0%	2/ 40.0%	0.102
Class III	4/ 26.7%	2/ 13.3%		1/ 5.7%	3/ 20.0%	

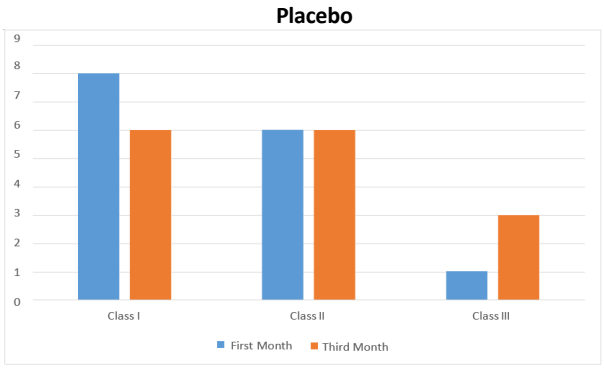

Figure 1. The GREAT Scores in the vitamin D group

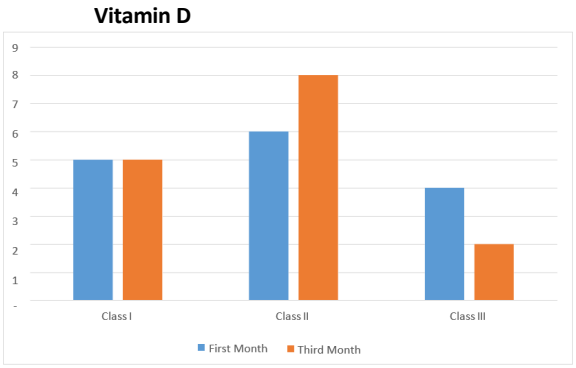

Figure 2. The GREAT Scores in the placebo group

In the TSH analysis, after one month of treatment, the median TSH level in the vitamin D group was 0.0006 (0.0001–1.2480) µIU/mL, while in the placebo group it was 0.0009 (0.0001–0.8828) µIU/mL. After three months of treatment, the median TSH level in the vitamin D group increased to 0.1028 (0.0001–2.2000) µIU/mL, whereas in the placebo group it was 0.018 (0.0001–3.9061) µIU/mL. Statistical analysis using the Wilcoxon test revealed a significant change in the vitamin D group, while no significant difference was observed in the placebo group.

4. Discussion

The autoimmune condition Graves' disease is characterized by ophthalmopathy, widespread thyroid enlargement, and hyperthyroidism.[7] The disorder is brought on by autoantibodies stimulating TSH receptors, which causes the thyroid to secrete too much hormone. Even with successful antithyroid treatment, recurrence is still frequent.

Because of its immunomodulatory properties, vitamin D has drawn more attention. It may lessen autoimmune processes by promoting regulatory immunological activity and suppressing proinflammatory cytokines. Despite the fact that vitamin D insufficiency is commonly seen in Graves' disease, its exact therapeutic impact is still unknown.[8]

Recurrence can be accurately predicted using the GREAT Score, which takes into account goiter size, FT4, TRAb, and age. [9] The risk of relapse is higher in younger patients with large goiter volumes and elevated FT4 and TRAb levels. [10] However, neither the GREAT Score nor the likelihood of recurrence was significantly changed by vitamin D administration, according to this study.

These findings are supported by earlier research. According to research by Chen et al. (2025) and Cho et al. (2020), vitamin D supplementation did not significantly reduce the risk of recurrence.[12,13] Similarly, Taskent, Planck, and Xu found that although vitamin D insufficiency is associated with the onset of disease, relapse rates are not always altered by supplementation.[5, 14, 15] The current study's brief duration and small sample size might have made it more difficult to identify long-term immunologic effects.

Overall, rather than being a major component in remission, Current evidence suggests limited short-term immunological impact. Higher dosages and longer intervention times are probably needed for its action in regulating TRAb activity and thyroid function in order to get quantifiable therapeutic results.[16]

Several risk factors predicting relapse after ATD discontinuation have

been reported. A recent systematic review and meta-analysis identified younger age, large goiter, smoking, female gender, severe biochemical disease, and higher antibody levels before ATD treatment as risk factors for relapse. Other risk factors, such as T3 levels, currently lack clinical evidence that they directly alter the effectiveness of vitamin D supplementation in Graves' disease, although thyroid hormones (including T3/T4) can influence vitamin D metabolism and calcium status.[12]

According to other study, the GREAT score has been shown to have strong validity and is a useful method for assessing the risk of relapse in Graves' disease, which may influence treatment strategies.[11] The GREAT score is calculated by considering four factors: age, FT4 levels, TRAb levels, and goiter size.[12]

Age is an important determinant in predicting relapse of Graves' disease. Physiologically, younger individuals tend to have more active and responsive immune systems. This heightened immune activity may hinder the resolution of autoimmune processes, contributing to the long-term persistence of the disease. Consequently, achieving sustained remission after discontinuation of antithyroid therapy becomes more challenging. Therefore, younger patients are at a higher risk of relapse compared to older individuals, whose immunological activity tends to decline with age, thereby increasing the likelihood of achieving remission.[13,14] In addition to age, free thyroid hormone levels, particularly free T4 (FT4), also have significant predictive value for the risk of relapse. FT4 directly reflects excessive thyroid hormone secretion due to autoimmune stimulation. High FT4 levels at diagnosis reflect a more severe degree of hyperthyroidism, indicating that the thyroid gland is in a state of hyperactivity that is difficult to control with pharmacological therapy alone. This condition correlates with an increased likelihood of relapse, as higher FT4 levels mean that achieving long-term stability of thyroid function is more difficult. Therefore, FT4 is not merely a biochemical parameter but also an important indicator of disease severity and resistance to therapeutic control.[13,14]

The immunological aspect of Graves' disease is clearly reflected in the levels of Thyrotropin Receptor Antibody (TRAb), the primary pathogenetic antibody in the disease. TRAb works by abnormally stimulating the TSH receptor, thereby stimulating the continuous production of thyroid hormone. The higher the levels of TRAb in the patient's circulation, the greater the ongoing autoimmune activity. This condition indicates that the immunological process has not been resolved and has the potential to persist, ultimately triggering a high risk of relapse after therapy is discontinued. Thus, TRAb is not only a diagnostic biomarker but also serves as a crucial prognostic indicator in predicting the clinical course of Graves' disease.[15,16]

Another equally significant contributing factor is the volume of the thyroid gland, or goiter. Thyroid volume reflects the amount of tissue that can be targeted by TRAb stimulation. A larger thyroid gland, however, presents a greater surface area for thyroid follicular cells, which can produce excess hormones. This makes Graves' disease more difficult to control, both through pharmacological and definitive therapy. Furthermore, significant thyroid enlargement is often associated with longer-standing disease and more intense levels of autoimmune activity. Therefore, a large goiter is a consistent factor in increasing the likelihood of relapse.[15,16]

Vitamin D plays a crucial role in modulating immune responses and has been implicated in the pathogenesis of various autoimmune diseases. By suppressing interleukin-12 (IL-12), a cytokine that promotes Th1 polarization, vitamin D indirectly shifts the T-cell balance from a Th1- to a Th2-dominant profile. In $CD4^+$ T-cell responses, vitamin D directly decreases the production of Th1 cytokines (IL-2 and IFN-γ) while enhancing the secretion of Th2 cytokines (IL-4). This immunomodulatory effect suggests that vitamin D may help attenuate autoimmune activity. Moreover, the Th1 chemokine CXCL10, known to play a critical role in the pathogenesis of Graves' disease, can be inhibited by vitamin D analogs, which have been shown to suppress CXCL10 production in thyroid cells.[13]

The absence of a significant effect of vitamin D on GREAT scores may be explained by the study's findings, which also demonstrated that changes in FT4 levels and goiter size in the vitamin D supplementation group were not significant, similar to those observed in the placebo group. This indicates that participants had a comparable likelihood of experiencing relapse regardless of vitamin D supplementation. These findings are consistent with the study by Cho *et al.*, which also reported no significant association between vitamin D supplementation and relapse of Graves' disease.[9] This study has several limitations, including a relatively small sample size, a short study duration, and the potential confounding effect of morning sunlight exposure, which may influence participants' vitamin D levels. These factors could affect the validity of the findings and limit the study's ability to provide a comprehensive understanding of the impact of vitamin D supplementation on Graves' disease. Future research with a longer follow-up period and better control of confounding factors related to vitamin D deficiency is recommended. Such studies may provide stronger evidence to support the potential role of vitamin D supplementation in patients with Graves' disease and vitamin D deficiency.

5. Conclusion

In this double-blind randomized controlled trial, vitamin D supplementation (10,000 IU/day for 3 months) did not significantly change the GREAT Score or biochemical parameters in Graves' disease patients. Further large-scale trials with longer follow-up and direct recurrence endpoints are warranted.

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