

Effect of vitamin D₃ in treating hyperthyroidism in patients with graves' disease

Nermin A. Sheriba^a, Abeer A.A. Elewa^a, Maram M. Mahdy^a,
Ahmed M. Bahaa El Din^a, Nesma A. Ibrahim^a, Dina A. Marawan^a,
Tahany M. Abd El Moneim^b

^aDepartment of Internal Medicine, Ain Shams University, Cairo, Egypt, ^bDepartment of Biochemistry, Ain Shams University, Cairo, Egypt

Correspondence to Abeer A.A. Elewa, PhD,
31 Police Building, Kornish El-Nile, Al Maadi,
Cairo, Egypt Tel: + 20 122 241 2595;
e-mail: drabeerelewa@hotmail.com

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Background

Graves' disease (GD) is an autoimmune disease characterized by hyperthyroidism secondary to circulating autoantibodies. Multiple factors contributed to its etiology, including genetic and environmental factors. The role of vitamin D is well-known in calcium metabolism and skeletal homeostasis. Vitamin D was shown to be a modulator in both innate and adaptive immunity. There is a link between vitamin D deficiency and various autoimmune diseases. The prevalence of vitamin D deficiency was reported to be common in patients with GD. Interestingly, vitamin D deficiency is found to be associated with higher thyroid volume in patients with newly-onset GD. However, vitamin D deficiency relationship with GD remains a controversial issue.

Objective

The objective of this study was to evaluate the effect of vitamin D supplementation in GD with and without ophthalmopathy.

Patients and methods

A randomized prospective study was conducted on 60 adult patients with GD aged 20–40 years. Group 1 comprised 20 patients with GD receiving a daily dose of 30 mg of methimazole alone. Group 2 comprised 40 patients with GD receiving the same dose of methimazole, supplemented with intramuscular injection of vitamin D₃ 200 000 IU/month for 3 months. Patients were followed up over a 3-month duration.

Results

There was hypovitaminosis D in all participants with a percentage of vitamin D deficiency (vitamin D level: <20 ng/ml) of 73.9% in male and 54.1% in female and a vitamin D insufficiency (vitamin D level: 20–29 ng/ml) of 26.1% in male and 45.9% in female. Vitamin D was significantly correlated with thyroid volume and degree of exophthalmos. On vitamin D supplementation, group 2 had significantly lower thyroid volume and better effect on the degree of exophthalmos.

Conclusion

Vitamin D supplementation for GD has a favorable effect on thyroid volume and on the degree of exophthalmos.

Keywords:

exophthalmos, Graves' disease, vitamin D

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Introduction

Vitamin D has a well-known role in calcium metabolism and skeletal homeostasis. Recently, vitamin D proved to be a modulator in both innate and adaptive immunity [1]. Vitamin D deficiency has an established link with various autoimmune diseases, including type 1 diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. Furthermore, it has been found that the supplementation of vitamin D can prevent the onset and/or development of different kinds of autoimmune disorders in human beings and animal models [2].

Graves' disease (GD) is an autoimmune thyroid disease (AITD) characterized in its typical presentation

by association of thyrotoxicosis, goiter, and ophthalmopathy. It is a multifactorial disease caused by a complex interaction between genetic and environmental factors that lead to the loss of immune tolerance to thyroid antigens, and therefore to the initiation of an immune reaction against the thyroid [3].

Several studies discovered the association between vitamin D levels and GD [4–14]. Vitamin D deficiency is common in patients with GD and

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associated with higher thyroid volume [15,16]. Vitamin D receptor gene polymorphisms were found to be associated with the risk for GD [17].

Aim

The aim of this work was to evaluate the effect of vitamin D supplementation in GD patients with and without ophthalmopathy on the progress of their condition.

Patients and methods

A randomized open prospective study was conducted on 60 adult patients with GD aged 20–40 years who were recruited from the Endocrinology Clinic, Ain Shams University, in winter–spring periods in 2015–2016.

All patients were diagnosed with GD and divided by computer-generated randomization into two groups.

Group 1: 20 patients with GD received a daily dose of 30 mg of methimazole (MMI); 10 of them were diagnosed with Graves' ophthalmopathy.

Group 2: 40 patients with GD received 30 mg of MMI and were supplemented with vitamin D₃ (1,25 (OH)₂D) of 200 000 IU/month, intramuscular, for 3 months; 17 of them were diagnosed with Graves' ophthalmopathy.

Patients were followed up over a 3-month duration.

Informed consent was obtained from all participants. The study was conducted in accordance with the stipulations of the Local Ethics and Scientific Committees of Ain Shams University, and the procedures respected the ethical standards in Helsinki Declaration of 1964. A volume of 5 ml of venous blood was extracted without tourniquet after 8 h of overnight fast. Serum was separated by centrifugation and stored at -70°C until it was used.

All participants were subjected to the following:

- (1) Full medical history was taken with emphasis on hyperthyroid symptoms.
- (2) General clinical examination was performed by measuring blood pressure, pulse, temperature, and BMI
- (3) Measurement of thyroid function tests [thyroid-stimulating hormone (TSH), free T3 (FT3), and free T4 (FT4)], 25 hydroxy vitamin D (25-OHD) level at baseline and after 3 months of management, and total serum calcium and phosphorus was carried

out. For TSH, we use immunochemiluminometric assay on the Siemens ADVIA Centaur analyser (ADVIA Centaur; Bayer HealthCare LLC, Diagnostics Division, Tarrytown, New York) [18]. FT3 and FT4 levels were detected by direct equilibrium dialysis, high-pressure liquid chromatography, and tandem mass spectrometry [19]. 25-OHD level was determined by a solid-phase enzyme-linked immunosorbent assay, based on the principle of competitive binding [20]. Vitamin D deficiency was defined as a serum level of 25-OHD of less than or equal to 20 ng/ml, vitamin D insufficiency was defined as a serum level between more than 20 ng/ml and less than 30 ng/ml, and normal vitamin D deficiency as more than or equal to 30 ng/ml [21].

- (4) Neck U/S to measure baseline thyroid volume and monthly for 3 months longitudinal and transverse scans are performed to measure the depth (*D*), the width (*W*), and the length (*L*) of each lobe. The volume of the lobe is calculated by the formula V (ml) = $0.479 \times D \times W \times L$ (cm). The thyroid volume is the sum of the volumes of both lobes. The volume of the isthmus is not included. The limits of normal thyroid volume (excluding isthmus, unless its thickness is >3 mm) are 10–15 ml for female and 12–18 ml for male [22].
- (5) Thyroid scan was performed for patients with no exophthalmos to differentiate it from thyroiditis for newly diagnosed patients
- (6) Ophthalmological examination was performed at baseline and monthly for 3 months using Hertl's exophthalmometer (Good-Lite 1155 Jansen Farm Dr. Elgin, IL, USA) to assess changes in the severity of ophthalmopathy.

Exclusion criteria

Patients with chronic kidney disease, chronic liver diseases, and other endocrinological diseases such as vitamin D supplementation or any drugs affecting vitamin D level, such as steroids, antiepileptics, methotrexate, INH (isoniazid), thiazides, antacids, calcium channel blockers, and anticonvulsants, were excluded.

Statistical analysis

Data were analyzed using SPSS [ver. 18; IBM Corporation; 1111 International Business Machines Corp. (New Orchard Road Armonk, New York)]. Numerical data were tested for normality with D'Agostino–Pearson test; normally distributed data were presented as mean ± SD, and non-normally distributed data were presented as median (interquartile range). Categorical data were presented as number and percent of total. Comparative analysis of numerical data

was performed with unpaired Student's *t*-test or Mann-Whitney test depending on the normality of data. Comparative analysis of categorical data was done with χ^2 -test. Comparison of paired data was done with paired sample *t*-test and Wilcoxon's signed-rank test for parametric and nonparametric data, respectively. Data were tabulated and graphically illustrated. To evaluate the effect of vitamin D supplementation, the groups were compared regarding the degree of change of each parameter, which was calculated from the following formula:

$$\text{Degree of change } (\Delta\%) = \frac{\text{Post} - \text{pre}}{\text{Pre}} \times 100.$$

Results

Comparison between the studied groups regarding baseline demographic, clinical, and laboratory data was done; it showed no significant difference except for TSH, which is significantly lower in group 2 (Table 1). In addition, we found hypovitaminosis D in all participants, with a percentage of vitamin D deficiency (vitamin D level: <20 ng/ml) of 73.9% in male and 54.1% in female and percentage of vitamin D insufficiency (vitamin D level: 20–29 ng/ml) of 26.1% in male and 45.9% in female (Table 2). On comparing group 1 (on MMI only) with group 2 (on vitamin D and MMI) as regards the percentage of Graves' ophthalmopathy, our results revealed that 10 (50%) patients of group 1 had Graves' ophthalmopathy, in comparison with 17 (42.5%) patients in group 2, and thus the percentage of Graves' ophthalmopathy in our study was 45% (27 patients of a total of 60) (Table 3).

On comparing group 1 (on MMI) with group 2 (on vitamin D and MMI) as regards the vitamin D status among patients with Graves' ophthalmopathy, our results revealed that eight (80%) patients with Graves' ophthalmopathy in group 1 had vitamin D deficiency, whereas the remaining two (20%) had vitamin D insufficiency in comparison with 16 (94.1%) patients in Group 2 (*n*=17) with vitamin D deficiency and one (5.9%) patient with vitamin D insufficiency; therefore, the percentage of vitamin D deficiency among Graves' ophthalmopathy patients in our study was 88.9% (24 patients of 27) in comparison with 51.5% (17 patients of 33) in those with no eye signs, whereas the percentage of vitamin D insufficiency was 11.1% (three patients of 27) in comparison with 48.5% (16 patients of 33) in those with no eye signs (Table 3).

On correlating baseline vitamin D level with other measured parameters, it showed a significant negative correlation with thyroid volume ($r=-0.777$, $P=0.000$) and degree of exophthalmos in both eyes of both study groups ($r=-0.752$, $P=0.000$ for the right eye and $r=-0.763$, $P=0.000$ for the left eye), whereas a nonsignificant correlation was found with other parameters (Table 4).

Patients were followed up after 3 months of management with MMI for group 1 and MMI and vitamin D for group 2. Our results stated changes in clinical and laboratory data (thyroid function test, thyroid volume, exophthalmos, and vitamin D level) in both groups (Table 5). Details of the 3-month changes in thyroid function test, thyroid volume, and exophthalmos are illustrated in Tables 6 and 7, as FT3 showed borderline significant reduction from baseline to

Table 1 Comparison between group 1 and group 2 as regards baseline demographic, clinical, and laboratory data

Parameters	Group 1 (<i>n</i> =20)	Group 2 (<i>n</i> =40)	<i>P</i>
Age (years)	31.9±6.1	31.6±5.7	0.84
Sex [<i>N</i> (%)]			
Female	12 (60)	25 (62.5)	0.851
Male	8 (40)	15 (37.5)	
BMI (kg/m ²)	21.7±2.6	22.2±2.3	0.378
Smoking [<i>N</i> (%)]	5 (25)	9 (22.5)	0.874
Thyroid volume (ml)	42.4±8.4	44.7±8.1	0.312
Exophthalmos			
<i>n</i>	10	17	0.851
Right eye (cm)	2.4±0.4	2.6±0.3	0.151
Left eye (cm)	2.4±0.3	2.6±0.3	0.16
Ca (mg/dl)	9.4±0.3	9.5±0.3	0.242
PO ₄ (mg/dl)	3.5±0.2	3.7±0.5	0.277
Vitamin D (ng/ml)	16.7±5.2	15.2±6.2	0.340
TSH (mIU/ml)	0.005 (0.005–0.008)	0.001 (0.07–0.04)	<0.001**
FT3 (pg/ml)	13 (10.6–19.1)	15 (9.03–22.7)	0.832
FT4 (ng/dl)	5 (3.9–5.9)	5.1 (3.75–7.1)	0.371

FT3, free T3; FT4, free T4; TSH, thyroid-stimulating hormone. **Highly significant, $P<0.001$.

Table 2 Comparison between study groups as regard the percentage of hypovitaminosis D in relation to sex

	Group 1 (on MMI only) (n=20) [N (%)]	Group 2 (on MMI and vitamin D) (n=40) [N (%)]	Total (n=60) [N (%)]
Number of men	8 (40)	15 (37.5)	23 (38.3)
Number of vitamin-D-deficient men	5 (62.5)	12 (80)	17 (73.9)
Number of vitamin-D-insufficient men	3 (37.5)	3 (20)	6 (26.1)
Number of women	12 (60)	25 (62.5)	37 (61.7)
Number of vitamin-D-deficient women	3 (25)	17 (68)	20 (54.1)
Number of vitamin-D-insufficient women	9 (75)	8 (32)	17 (45.9)

MMI, methimazole.

Table 3 Comparison between study groups as regards percentage of Graves' ophthalmopathy and associated hypovitaminosis D

	Group 1 (on MMI only) (n=20)		Group 2 (on vitamin D and MMI) (n=40)		Total GD patients (n=60)	
	With GO	Without GO	With GO	Without GO	With GO	Without GO
N	10 (50)	10 (50)	17 (42.5)	23 (57.5)	27 (45)	33 (55)
Vitamin D deficient [N (%)]	8 (80)	4 (40)	16 (94.1)	13 (56.5)	24 (88.9)	17 (51.5)
Vitamin D insufficient [N (%)]	2 (20)	6 (60)	1 (5.9)	10 (43.5)	3 (11.1)	16 (48.5)

GD, Graves' disease; GO, Graves' ophthalmopathy; MMI, MMI, methimazole.

Table 4 Correlation between baseline vitamin D level and different parameters

	Vitamin D (ng/ml)	
	Pearson's correlation	Significance (two-tailed)
Age (years)	-0.121	0.359
BMI (kg/m ²)	0.031	0.812
Ca (mg/dl)	0.139	0.291
P (mg/dl)	0.211	0.105
Baseline TSH (mIU/ml)	0.153	0.244
Baseline FT3 (pg/ml)	-0.125	0.341
Baseline FT4 (ng/dl)	-0.048	0.716
Baseline volume (ml)	-0.777**	0.000
Baseline exophthalmos of right eye (cm)	-0.752**	0.000
Baseline exophthalmos of left eye (cm)	-0.763**	0.000

FT3, free T3; FT4, free T4; TSH, thyroid-stimulating hormone. **Correlation is significant at the 0.01 level (2-tailed).

second month P -value=0.054, but insignificant reduction from the second month to the third month; FT4 showed borderline significant reduction from baseline to second month and significant reduction from the second month to the third month in group 2 compared with group 1. As regards changes in thyroid volume after vitamin D supplementation, there was a highly significant reduction from the baseline to second month and significant reduction from the second month to the third month in group 2 compared with group 1. Moreover, there was a highly significant reduction of exophthalmos from baseline to second month and significant reduction from the second month to the third month in group 2 compared with group 1.

Discussion

Our study confirms that 100% of our patients have hypovitaminosis D, as the percentage of vitamin D deficiency was 61.7% (37 patients out of 60) and vitamin D insufficiency was 38.3% (23 patients out

of 60), with a mean baseline vitamin D level of 16.7 ± 5.2 ng/ml in group 1 and 15.2 ± 6.2 ng/ml in group 2. These results are in line with the results of those who stated that there is a link between vitamin D status and AITD [14–24] and inconsistent with researches who found higher prevalence of vitamin D deficiency in non-AITD [25] and others reporting that early stages of thyroid autoimmunity are not associated with low vitamin D levels [26].

As regard Graves' ophthalmopathy, our study showed that the percentage of vitamin D deficiency in patients with Graves' ophthalmopathy was 88.9% compared with those without eye signs – 51.5% – which is in line with studies that reported that the prevalence of vitamin D deficiency in patients with Graves' ophthalmopathy was 100 versus 66.7% in those without eye signs [23].

Our results are also in line with researchers who found that hypovitaminosis D is significantly associated with

Table 5 Comparison between group 1 and group 2 as regards thyroid profile, thyroid volume, exophthalmos, and vitamin D level after 3 months

Parameters	Group 1 (on MMI only) (n=20)	Group 2 (on vitamin D and MMI) (n=40)	P
Thyroid volume (ml)	29±5.1	19.8±3	<0.001**
Exophthalmos			
Right eye (cm)	2.3±0.3	2.3±0.3	0.915
Left eye (cm)	2.3±0.3	2.3±0.2	0.778
Vitamin D (ng/ml)	16.7±5.2	43.1±6.8	<0.001**
TSH (mIU/ml)	0.02 (0.005–0.085)	0.1 (0.025–0.4)	0.008
FT3 (pg/ml)	4.60 (4.2–5.35)	4.03 (3.5–4.5)	0.001
FT4 (ng/dl)	2.00 (1.95–2.1)	1.7 (1.5–1.9)	0.001

FT3, free T3; FT4, free T4; MMI, methimazole; TSH, thyroid-stimulating hormone. **Highly significant, $P<0.001$.

Table 6 Comparison between study groups as regards the degree of change of TFT and thyroid volume

Parameters	Group 1 (MMI only)			Group 2 (vitamin D and MMI)			P-value
	Median	25th	75th	Median	25th	75th	
ΔTSH (baseline–second month)	0	0	0	0	0	0	0.256
ΔTSH (second month–third month)	343	0	962.5	632	12.5	900	0.679
ΔFT3 (baseline–second month)	–47.5	–55	–39	–57.5	–62	–45	0.054
ΔFT3 (second month–third month)	–35	–46.5	–22	–38	–48	–29	0.419
ΔFT4 (baseline–second month)	–57	–65	–49.5	–64.5	–75	–55	0.058
ΔFT4 (second month–third month)	–39	–22	–45	–53	–35	–107.5	0.002*
ΔVolume (baseline–second month)	–18	–20.5	–12.5	–42	–46.5	–37.5	<0.001**
ΔVolume (second month–third month)	–16.5	–20.5	–12.5	–24.5	–30	–18	0.006*

FT3, free T3; FT4, free T4; MMI, methimazole; TFT, thyroid function test; TSH, thyroid-stimulating hormone. *Significant, $P<0.05$. **Highly significant, $P<0.001$.

Table 7 Comparison between study groups as regard the degree of change of exophthalmos

Parameters	Group 1 (MMI only) Mean±SD	Group 2 (vitamin D and MMI) Mean±SD	P-value
ΔRight eye (baseline–second month)	–0.792±1.680	–5.681±3.161	<0.001**
ΔRight eye (second month–third month)	–2.849±2.932	–5.532±2.588	0.020*
ΔLeft eye (baseline–second month)	–1.205±1.980	–6.256±3.326	<0.001**
ΔLeft eye (second month–third month)	–2.989±2.924	–6.373±2.779	0.006*

MMI, methimazole. *Significant, $P<0.05$. **Highly significant, $P<0.001$.

ophthalmopathy in patients with Graves' hyperthyroidism (61% of patients with GD who were vitamin D deficient and 75% of those who were vitamin D insufficient had ophthalmopathy) but not Hashimoto's thyroiditis, which suggests that the pathogenesis of the eye changes in the two disorders may be different [25].

On correlating vitamin D levels with the clinical variables in the study groups, we found an insignificant inverse correlation between vitamin D levels and age ($r=-0.121$, $P=0.359$), which is agreement with some previous studies [14–23] and in disagreement with those who found that 25-OHD levels were significantly lower in the elderly patients compared with young adults [27,28], which could be explained by diminished cutaneous production of vitamin D with aging, and/or lower sun exposure [29]. Our results could be explained by the limited age group of our study between 20 and 40 years. On correlating vitamin D levels with BMI of our study

groups, we also found no significant correlation ($r=0.031$, $P=0.812$), which could also be explained by their low BMI owing to the negative effect of thyrotoxicosis on weight; this is in agreement with studies that declare no significant correlation between vitamin D level and BMI ($r=0.064$, $P=0.307$) [30]. In addition, these results are inconsistent with those who stated that obese patients had significantly lower basal 25-OHD concentrations than did age-matched control, and this could be possibly due to increased sequestration of the vitamin into subcutaneous adipose tissue [31,32].

As regards sex, we found that the percentage of vitamin D deficiency among male patients with GD was higher than that in female patients (74 vs. 54%), antagonizing some studies [23,27,33]. These findings may be because of differences in adiposity between male and female with the same BMI, as male have 10–15% less fat content than female [34].

As regards smoking as a risk factor for Graves' ophthalmopathy, our study revealed that the percentage of ophthalmopathy among smokers with Graves' hyperthyroidism was 71.4% and they were also vitamin D deficient, which is in line with studies that proved that more smokers than nonsmokers develop Graves' ophthalmopathy and smoking can be considered an independent risk factor for GD [35,36].

As regards thyroid function, we found insignificant positive correlation of baseline TSH level and baseline vitamin D level, and we also found significantly higher levels of TSH by the end of the third month in group 2, which is in agreement with many researchers [23–37]. In addition, this is inconsistent with the results of others who clarified that TSH level inversely correlated with vitamin D and suggest a significant association between hypovitaminosis D and hypothyroidism [38,39].

Moreover, we found an insignificant negative correlation of baseline FT3, FT4, and baseline vitamin D levels with a significant decrease in their levels over the end of 3 months in group 2, and this is supported by studies that proved improvement in thyroid hormones after MMI and vitamin D supplementation [37].

As regards the thyroid volume, our study revealed a significant inverse correlation between baseline vitamin D level and baseline thyroid volume ($r=-0.777$, $P=0.000$), which goes in line with other studies [16].

Furthermore, we noticed a highly significant reduction in thyroid volume during the course of follow-up in both groups. The degree of this reduction was found to be more in group 2 who received MMI and vitamin D supplementation, with a highly significant difference from the baseline to the second month ($P<0.001$) and a significant difference from the second month to the third month.

To our knowledge, so far no other practical trials were done to evaluate the effect of vitamin D supplementation on thyroid volume.

Regarding exophthalmos, we found an inverse correlation with baseline vitamin D level in the right eye ($r=-0.752$, $P=0.000$) and left eye ($r=-0.763$, $P=0.000$), which is consistent with researchers who stated the same findings [23]. In addition, we noticed significant reduction in exophthalmos in both eyes of group 1 and highly significant reduction in both eyes of group 2. The

degree of this reduction is obviously noted in group 2 with a highly significant difference from the baseline to the second month ($P<0.001$) and significant difference from the second month to the third month in both eyes.

Conclusion

In GD, vitamin D supplementation in addition to MMI improve thyroid function test, thyroid volume, and degree of ophthalmopathy in patients with hypovitaminosis D.

Recommendations

Further studies are needed to evaluate the effect of vitamin D supplementation in GD patients with sufficient vitamin D, as well as trials of different formulations to find out the most effective supplementary dose.

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Conflicts of interest

There are no conflicts of interest.

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