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Original Research Article

Effect of Vitamin D3 Treatment in Hyperthyroidism with Hypercalcemia

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Conflict of interest: Nil

Abstract:

Introduction: A hormone with receptors in many bodily tissues, vitamin D has been associated with reduced chronic disease risk. Vitamin D deficiency affects over a billion people. Research suggests vitamin D may help with hypothyroidism and musculoskeletal issues. Deficient vitamin D is also common in Graves' illness. Hyperthyroidism causes hypercalcemia in 0.2–4% of people.

Aim and Objectives: This research examines how vitamin D3 supplementation affects thyroid function in hyperthyrodism and hypercalcemia patients to fill information gaps.

Method: This is a prospective, randomised, single-blinded, parallel-group study which compared 12 months of vitamin D3 supplementation with that of patients receiving vitamin D3 as a complement to antithyroid medication (ATD) treatment in newly diagnosed Graves' disease (GD) patients with hypercalcemia. The study conducted a comparison between a 12-month supplementation of vitamin D3 and a control group receiving no additional vitamin D3, in conjunction with antithyroid medication. The present investigation evaluated the prevalence of hypercalcemia, the presence of thyroid-related antibodies, levels of blood calcium, markers of bone metabolism, and mineral density.

Result: Table 1 shows key characteristics of Vitamin D and ATD patients. The Vitamin D (32 males, 18 females) and ATD (26 males, 24 females) groups averaged 55.01 and 55.89 years old. Table 2 shows baseline, 6-month, and 12-month calciotropic hormone levels, especially in Vitamin D3 administration. Table 3 shows thyroid function results, with Vitamin D3 affecting FT3, FT4, and TSH more. Table 5 shows Vitamin D3's greater bone density improvement than ATD treatment.

Conclusion: The study has concluded that the adjuvant vitamin D3 is effective in the management of thyroid dysfunction and abnormal bone metabolism in hyperthyroidism.

Keywords: Hyperthyroidism, gastrointestinal symptoms, Vitamin D deficiency.

Introduction

The majority of the human body's cells and tissues have vitamin D receptors., which is why vitamin D was once thought of as a distinct hormone. Numerous studies show that vitamin D decreases the incidence of developing chronic diseases such as cardiovascular, autoimmune and infectious conditions. More than a billion people are considered to be vitamin D insufficient or deficient worldwide. People who are elderly, as well as kids and teenagers, may be at particularly high risk for vitamin D insufficiency [1].

Studies in the past showed that a decrease in serum levels of vitamin D is seen in association with hypothyroidism and may play a role in some musculoskeletal disorders. Additional research has shown that patients with Graves' illness also have low levels of serum vitamin D. There are two potential explanations for why serum levels of vitamin D are low in hypothyroid patients: first, poor vitamin D absorption from the gut and, second, possible insufficient vitamin D activation by these patient's bodies. Research done by Chaudhary et al. found that giving autoimmune thyroid disorders (AITD) patients 60,000 IU of vitamin D weekly had a positive impact on autoimmunity as seen by significantly lower TPO-Ab titers. Also, supplementing with vitamin D3 after 10 weeks significantly restored the modifications to the thyroid profile and expression of D2 (deiodinase 2) in diabetic rats [1].

By combining to the receptor of vitamin D (VDR) and the activation of VDR-responsive genes in the targeted tissues, vitamin D mediates its action. It has been found that VDR gene polymorphism and AITD are related. These methods might point to the significance of providing vitamin D to hypothyroid patients. As far as we are aware, there is no research present for examining how vitamin D administration in hypothyroid patients impacts thyroid function. The purpose of the study is to

ascertain how vitamin D administration affects the function of the thyroid in hypothyroid patients [1].

Hypercalcemia affects between 0.2% and 4% of hospital patients and those who live in the community. The amount of hypercalcemia depends on serum calcium (Ca) measurements made in patients treated in emergency departments (ED) or in free-living community individuals. Primary hyperparathyroidism and cancer-related hypercalcemia are the most common causes of hypercalcemia. If hypercalcemia is diagnosed in the context of an outpatient practice, it will affect their relative incidence, where the primary hyperparathyroidism is predominant, or in a hospital setting, where cancer-associated hypercalcemia is more common [2].

Typical signs of hyperthyroidism include sweating, irritability, weight loss despite a good appetite, palpitations without a heart condition, and goitre. The most frequent clinical symptom is hyperthyroidism with electrolyte imbalance. However, Graves' disease (GD) with hypercalcemia is uncommon, with a clinical incidence of 15-20%. It is still unknown how the treatment for thyrotoxicosis affects 25-hydroxyvitamin D (25-OHVit D) or blood calcium levels. The challenge of excluding other causes makes it difficult to give hypercalcemia patients an accurate diagnosis and treatment. A possible cause is thyrotoxicosis, which is brought on by high thyroid hormone levels and a rise in bone resorption, which causes hypercalcemia [3].

In a study, they evaluated the changes in blood calcium (Ca2+) concentration in relation to levels of 25-OHVit D and thyrotropin hormone receptor antibody (TRAb) in hyperthyroid patients over the course of conventional antithyroid oral medication therapy with vitamin D3. There hasn't been any research done on how more vitamin D3 affects hypercalcemia in GD. In order to determine if vitamin D3 supplementation helps GD patients recover from their digestive disruption symptoms and low serum Ca2+ levels, we also sought to characterise how antithyroid medications (ATD) changed these results [3].

The complex combination of environmental and genetic factors that results in GD is an autoimmune thyroid disease (AITD) with several causal causes. Palpitations, tachycardia, hyperhidrosis, tremors, etc; Indications of hypercalcemia rarely occur since the earliest presentations in hyperthyroidism are typical signs and symptoms of the condition. Due to the absorption of bone calcium into the blood and elevated levels of blood calcium, hyperthyroidism causes hypercalcemia [3].

Consideration of hypercalcemia is important as a PTH-independent or PTH-dependent process from a diagnostic and therapeutic point. PTH concentrations increasing in conjunction with hypercalcemia are a sign of primary, post-transplant, tertiary, or severe neonatal hyperparathyroidism, whereas hypercalcemia that is accompanied by a suppressed or low PTH concentration is indicative of PTH-independent mechanisms. Cancer-related Hypercalcemia is more common in this last group. PTH concentrations are properly decreased in hypercalcemia linked to vitamin D [2].

Understanding the mechanisms behind vitamin D-associated hypercalcemia and the value of measuring metabolites of vitamin D when vitamin-associated hypercalcemia diagnosis is made will be improved by a vitamin D metabolism review [2].

The fundamental physiologic function of vitamin D is the preserving of the normal phosphorus and calcium balance by the activity of its active metabolite, 1,25- dihydroxyvitamin D (1,25(OH)2D). Additional biological effects that 1,25 (OH)2D mediates include the control of cell division and proliferation, muscular activity, and immunological response [2].

Retaining the vitamin D formulation is one method of treating hypercalcemia caused due to hypervitaminosis D. The treatment of isotonic fluids without or with the administration of glucocorticoids and a loop diuretic like furosemide are typically helpful in lowering serum calcium levels in people who have never before experienced renal impairment. Retaining the medication may be sufficient in individuals with chronic renal failure who are taking 1-hydroxylated vitamin D analogues. It will be beneficial to administer a loop diuretic and isotonic fluids if sufficient renal function is present. In such a case, glucocorticoids will also be helpful since they decrease intestinal calcium absorption by preventing basolateral membrane calcium extrusion from enterocytes and decreasing the activity of the RNA polymerase in intestinal cells. The offending medication must be withheld from patients on hemodialysis, and a low calcium hemodialysis bath (2 mEq per litre calcium) may be used for dialysis if hypercalcemia continues [2].

There are a number of 1-hydroxylated vitamin D compounds that can be used to treat inherited rickets in their different forms as well as secondary hyperparathyroidism found in end-stage renal disease (ESRD). In the United States and Europe, these medications include doxercalciferol (Hectrol), paricalcitol (Zemplar), 1, 25(OH)2D3 (calcitriol), 1, (OH)D3 (alphacalcidol), and 22, oxacalcitriol [2].

Vitamin D has been related to a variety of autoimmune illnesses, and it has been shown to modulate both innate and adaptive immunity, according to recent studies. It was also found that

taking vitamin D supplements can stop the start and/or progression of a number of autoimmune diseases in both human and animal models [3].

In the course of treatment with vitamin D3 in addition to conventional ATDs, they measured the serum calcium levels and the metabolic index of bone. They examined the correlation between vitamin D3 treatment for hypercalcemia and hyperthyroidism as well as the morbidity rate of hypercalcemia in hyperthyroidism patients who initially have gastrointestinal symptoms [3].

Method

Research Design

This is prospective study which was conducted during the period of one Year with the patients who came to the outpatient department of our hospital with Graves' disease presented with hyperthyroidism and hypercalcemia. A randomised, single-blinded, parallel-group experiment compared 12 months of vitamin D3 supplementation to non-added vitamin D3 as a complement to antithyroid medication (ATD) treatment in newly diagnosed Graves' disease (GD) patients with hypercalcemia. The study considered thyroid function, TRAb tests, and medical history and clinical data were used for the study analysis. The study also analyzed the follow-up findings and analyzed the data obtained at the beginning and during the follow-up. Hyperthyroidism patients' hypercalcemia prevalence and thyroid autoimmune-related antibody indices following vitamin D3 administration were the primary goals. Blood calcium, bone markers, and mineral density were secondary objectives. TSH, fT3, fT4, and TRAb levels were abnormal with hyperthyroidism. Serum Ca^{2+} levels were increased in hypercalcemia. This thorough study examined vitamin D3's effects on hypercalcemia-afflicted GD patients throughout a specific intervention period.

Inclusion and Exclusion Criteria

Inclusion

- Patients aged group from 18 to 70 years.
- Patients with GD were diagnosed with hyperthyroidism and hypercalcemia at their initial visit and were given ATD as their therapy option.

Exclusion

- Non-hyperthyroidism disease or past hyperthyroidism
- Serum Ca2+ <2.52 mmol/L or reduced kidney function (eGFR <45 mL/min).
- Patients with tumours or malignant disease
- Patients with hyperparathyroidism disease
- Patients with hyperthyroidism crisis
- Patients with diabetes insipidus

Statistical Analysis

The statistical analysis was conducted on the complete dataset, thereby ensuring the incorporation of all gathered information. The study considered $P<0.05$ as the level of statistical significance. The analysis was conducted using SPSS 23.0 software, a widely recognised tool in the field, produced by SPSS. The programme in question is generally acknowledged for its proficiency in managing and analysing intricate statistical data, so enabling thorough and precise scrutiny of the gathered information.

Ethical Approval

The study obtained consent from each patient and the study method was approved by Ethical Committee of the concerned hospital.

Result

Table 1 compares and contrasts the most fundamental characteristics of two patient groups: those receiving vitamin D and those receiving ATD. Distributions by age and gender are shown in the table. Mean ages range from 55.01 to 55.89 years, with 32 males and 18 females in the Vitamin D group and 26 males and 24 females in the ATD group, respectively. A statistically significant age gap was found between the groups ($P = 0.867$). There appears to be no discernible age difference between the two groups, as the P value is bigger than the typically employed threshold of 0.05.

Table 1: Basic information of the two groups of patients

Groups	Age	Sex	
		Male	Female
Vitamin D group	55.01±5.08	32	18
ATD group	55.89±5.89	26	24
P value	0.867		

Two groups' baseline, 6-month, and 12-month calciotropic hormone values are shown in Table 2. Serum electrolyte, phosphate, and vitamin D (25-hydroxy) normal ranges are listed. Ca2+ and PTH levels were initially within normal limits in both groups, whereas 25-OHVit D levels were low. Ca2+ and 25-OHVit D levels rose significantly in the Vitamin D3 group over the course of a year, and PTH levels fell significantly. While 25-OHVit D levels were rather steady, Ca2+ and PTH levels dropped in the ATD group. Significant differences were seen between time points (based on F values), with the Vitamin D3 group showing more dramatic shifts. Values with low P-scores imply that the

differences being studied are not trivial. As a whole, vitamin D3 supplementation appeared to have a greater impact on calciotropic hormone levels than ATD therapy.

Table 2: Index of calciotropic hormones

Serum electrolytes	Ca2+ (mmol/L)	PTH (pg/mL)	25-OHVit D (D2+D3) (ng/mL)
Vitamin D3 group			
Baseline	3.09±0.44	29.78±6.14	25.88±8.99
6 months	2.40±0.12	51.08±9.59	59.44±9.45
12 months	2.29±0.09	47.08±7.89	98.09±6.68
ATD group			
Baseline	2.78±0.19	39.69±7.33	35.15±8.04
6 months	2.64±0.12	45.86±8.19	40.17±8.58
12 months	2.49±0.06	45.09±8.89	26.29±5.60
F values			
Vitamin D3 group	45.98	59.64	239.79
ATD group	35.77	6.39	1.99
P-values			
Vitamin D3 group	<0.001	<0.001	<0.001
ATD group	<0.001	0.002	0.061

Thyroid function findings at baseline, 6 months, and 12 months are shown in Table 3 for two groups: Vitamin D3 and ATD. Ranges of "normal" for FT3, FT4, and TSH thyroid hormone levels are presented. TSH was slightly below normal and FT3 and FT4 were within normal range at the outset for both groups. In the Vitamin D3 group, both FT3 and FT4 dropped dramatically over the course of a year, but TSH rose somewhat while still maintaining within acceptable limits. The levels of FT3 and FT4 in the ATD group dropped to within the normal range, and the levels of TSH rose. Significant changes over time are shown by F values, with Vitamin D3 leading to more pronounced shifts. The high relevance of the P values for these differences is emphasised. Overall, vitamin D3 appeared to have a greater effect on thyroid function than ATD therapy.

Table 3: Findings of Thyroid hormones level in each group

Thyroid function	FT3 (pmol/L)	FT4 (pmol/L)	TSH (IU/L)
Vitamin D3 group			
Baseline	17.59±2.48	53.85±8.11	0.029±0.025
6 months	6.69±0.39	12.08±1.48	0.87±0.59
12 months	4.89±0.69	9.78±2.15	1.39±0.69
ATD group			
Baseline	15.52±2.89	39.59±7.07	0.029±0.029
6 months	6.77±0.19	13.79±1.32	0.59±0.39
12 months	6.09±1.01	11.33±1.08	1.33±1.09
F values			
Vitamin D3 group	499.48	429.33	49.89
ATD group	299.39	265.08	29.98
P values			
Vitamin D3 group	<0.001	<0.001	<0.001
ATD group	<0.001	<0.001	<0.001

The data presented in Table 4 depicts the levels of thyroid autoantibodies in two distinct groups, namely the Vitamin D3 group and the ATD group, at three different time points: baseline, 6 months, and 12 months. Initially, both cohorts exhibited antibody levels that fell within the established normal range. During a period of 12 months, the participants assigned to the Vitamin D3 group demonstrated a notable reduction in anti-thyroid antibodies, including Anti-TPO, Anti-Tg, and TRAb. These antibody levels approached or fell within the range considered normal. On the other hand, the group receiving ATD treatment exhibited significant decreases, although their values frequently remained higher than the established normal levels. The F values demonstrate variations across different time points, with the Vitamin D3 group exhibiting more statistically significant alterations. P-values are used to indicate the level of statistical significance, highlighting that observed changes are not likely due to random chance. Essentially, it was seen that Vitamin D3 played a role in facilitating more significant reductions in autoantibody levels in comparison to ATD treatment.

Table 4: Status of thyroid anti-bodies found in each group

Anti-thyroid antibody	Anti-TPO (IU/mL)	Anti-Tg (IU/mL)	TRAb (IU/L)
Vitamin D3 group			
Baseline	65.03±22.42	129.00±15.09	5.89±1.75
6 months	39.21±10.09	59.69±8.67	1.19±089
12 months	8.39±3.32	16.07±8.49	1.08±0.14
ATD group			
Baseline	64.10±17.39	119.89±19.25	6.89±1.19
6 months	39.21±14.39	98.00±8.98	3.01±0.89
12 months	34.89±7.87	23.59±10.89	1.80±0.29
F values			
Vitamin D3 group	29.89	211.49	49.39
ATD group	8.09	104.89	46.89
P values			
Vitamin D3 group	<0.001	<0.001	<0.001
ATD group	0.001	<0.001	<0.001

Table 5 illustrates the findings of bone mineral density (BMD) measurements across various variables and groups across a span of 12 months. The study examined two distinct groups, namely Vitamin D3 and ATD. Initially, it was observed that both groups exhibited bone mineral density (BMD) readings that fell below the established normal limit. Following a period of 12 months, the group administered with Vitamin D3 showed enhancements in bone mineral density (BMD) values across all assessed sites, thereby approaching the range considered normal. In the interim, the ATD group demonstrated certain enhancements; yet, their performance continued to fall below the established standard range. The F and P values are used to determine the statistical significance of the observed changes. In general, the group receiving Vitamin D3 had more pronounced enhancements in bone mineral density (BMD) in comparison to the group receiving the placebo (ATD) throughout the duration of the trial.

Table 5: The result of BMD

Variable	L2–4	Femoral neck	Trochanter major	Total hip
T value				
Normal range	Low bone mass: −2.4 to −1.0, Osteoporosis: <−2.5			
Vitamin D3 group				
Base line	−2.89±0.10	−2.79±0.22	−2.59±0.21	−2.89±0.25
12 months	−1.68±0.27	−1.61±0.39	−1.69±0.49	−2.09±0.11
ATD group				
Base line	−2.88±0.29	−2.59±0.19	−2.69±0.19	−2.88±0.19
12 months	−2.55±0.26	−2.19±0.45	−2.29±0.29	−2.39±0.19
F value				
Vitamin D3 group	119.39	55.33	19.05	69.58
ATD group	6.54	5.32	9.89	16.57
P value				
Vitamin D3 group	<0.001	<0.001	0.001	<0.001
ATD group	0.02	0.022	0.0054	0.001
Z value				
Normal range	≤−2.0			
Vitamin D3 group				
Base line	−2.29±0.17	−2.28±0.45	−2.59±0.29	−2.39±0.12
12 months	−1.84±0.01	−1.49±0.15	−1.59±0.04	−1.69±0.15
ATD group				
Base line	−2.29±0.02	−2.65±0.08	−2.07±0.08	−2.29±0.24
12 months	−2.03±0.07	−2.11±0.03	−1.69±0.39	−1.79±0.23
F value				
Vitamin D3 group	12.89	6.89	17.09	17.89
ATD group	24.69	80.892	1.8	2.59
P value				
Vitamin D3 group	0.189	0.199	0.129	0.044
ATD group	0.089	0.011	0.389	0.199

Discussion

In 2017, a study was conducted with the aim of assessing the effect of supplementation of vitamin D in GD in patients with or without ophthalmopathy. 60 adult indi with GD between the ages of 20 and 40 participated in this randomized prospective research. Twenty GD patients from Group 1 were given a daily dosage of 30 mg of methimazole. Group 2 was made up of 40 GD patients who received the same dose of methimazole in addition to 200,000 IU of vitamin D3 given intramuscularly every month for three months. Three months were spent monitoring the patients. All participants had hypovitaminosis D, with 54.1% of women and 73.9% of men having vitamin D deficiency and 45.9% of women and 26.1% of men having vitamin D insufficiency. Significant correlations between exophthalmos severity and vitamin D and thyroid volume were found. Group 2 had a considerably smaller volume of thyroid and a better impact on the degree of exophthalmos after taking supplementation of vitamin D. The study concluded that vitamin D supplementation for GD has a favourable effect on the degree of exophthalmos and thyroid volume [5].

A study was conducted previously on cases of thyrotoxicosis-related hypercalcemia and described serial biochemical results over the course of hyperthyroidism treatment. Although thyrotoxicosis-related hypercalcemia is well reported, the mechanism underlying the hypercalcemia is not well understood. The first patient showed a complicated medical history with multiple suspicions of recurring hyperparathyroidism, breast cancer, hypercalcemia that had spread, and thyrotoxicosis that had been previously treated. The first two reasons were ruled out by suppression of parathyroid hormone level, negative computed tomography scans, and negative bone scans. After 131I ablation of the thyroid gland, the levels of parathyroid hormone and 1,25-dihydroxyvitamin D3 returned to normal whereas serum thyroxine and calcium levels decreased. The study concluded thyrotoxicosis should be a possibility for doctors to rule out when diagnosing hypercalcemia [4].

A study was done to find out how levels of iodine and vitamin D intake in the Korean population are affected by thyroid autoimmune dysfunction and disease. The Korea National Health and Nutrition Examination study, which was the first research in Korea to examine both blood 25-hydroxy vitamin D levels and urine concentration of iodine (UICs), provided the data for this population-based investigation., UIC, Thyroid function testing and serum 25(OH)D were performed on a total of 4183 participants in the study. The deficiency of Vitamin D had a higher prevalence of anti-thyroid peroxidase antibody (TPOAb) positivity than vitamin D sufficient and insufficient groups. The iodine-deficient group had a significantly increased rate of TPOAb positive. Iodine excess individuals and TPOAb negative participants both had significantly higher rates of thyroid dysfunction than the other groups overall. Excessive iodine consumption was substantially linked to a high incidence of thyroid dysfunction in persons who were both TPOAb negative and were in the group with deficient vitamin D. The correlation between iodine intake and thyroid dysfunction vanished in people with total and TPOAb negative status in the vitamin D inadequate and sufficient groups. This concluded that this national research discovered a strong correlation between a high incidence of thyroid autoimmune disease and dysfunction and low vitamin D levels in persons who consumed too much iodine. These findings may clarify the possible advantages of vitamin D supplements in TPOAb-negative individuals who consume large amounts of iodine [6].

A study was conducted in the past to determine the status of blood 25-hydroxyvitamin D (25(OH)D) and evaluate the predictability of the outcome. 25(OH)D, free thyroxine, phosphorus, free triiodothyronine, parathyroid hormone, calcium, thyroid stimulating hormone, and creatinine serum levels were assessed prior to medication. As a standard control group, 60 healthy individuals with comparable BMIs and ages were recruited. Results from post-treatment follow-up showed that 25.00% of the patients had therapeutic failure. Patients who experienced therapeutic failure were found to have considerably lower serum 25(OH)D levels. Deficiency of vitamin D was more common in GD patients than in control subjects. An independent risk factor for GD patients' RIT failure. In the study's conclusions, patients who failed the RIT of GD had lower serum 25(OH)D levels than those who succeeded. Therefore, serum 25(OH)D levels below 20 may be a risk factor on its own for predicting RIT failure in GD patients [7-10].

A study was conducted to investigate the connection between hypothyroidism and vitamin D insufficiency as well as to define the relationship between serum levels of calcium and the condition. The serum levels of vitamin D (25-OH) in 30 hypothyroid patients and 30 healthy volunteers were assessed using the spectrophotometric technique. A vitamin D deficit was deemed to exist when levels fell below 20 ng/ml. All individuals had their calcium levels and thyroid hormone (TSH, T3, and T4) levels checked. In comparison to controls, serum 25(OH) vitamin D levels were considerably lower in hypothyroid individuals. When compared to male patients, it was not substantially lower in female patients. [11-13] In addition, hypothyroid patients' serum calcium levels significantly dropped in comparison to controls. [14] They concluded hypocalcaemia and

hypovitaminosis D in hypothyroid individuals are substantially correlated with the degree of severity of the condition. This promotes the wisdom of vitamin D therapy and suggests that all hypothyroid patients undergo testing for serum calcium levels and vitamin D deficiency [15].

Conclusion

The study has concluded that the thyroid dysfunction and changes in bone metabolism in individuals with hyperthyroidism, in conjunction with elevated levels of calcium in the blood, can be effectively managed by using adjuvant therapy involving vitamin D3.

The present study highlights the importance of taking into account functional gastrointestinal disorders in the diagnostic process of hyperthyroidism, even in the absence of typical symptoms. The study was limited by the small number of cases and a short duration of observation. Therefore, it is imperative for future studies to include a more comprehensive collection of cases and an extended period of observation. Moreover, further inquiry is necessary to clarify the mechanisms by which thyrotoxicosis induces hypercalcemia and to examine the effects of vitamin D3 supplementation on antibodies associated with thyroid dysfunction.

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