Original Article

Prevalence of hyperthyroidism with hypercalcemia in Xindu district and the efficacy of vitamin D3 treatment in these patients: a randomized trial

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Background: This trial aimed to analyze the relationship between hyperthyroidism and the morbidity rate of hypercalcemia in the Xindu district, Chengdu, Sichuan province. We observed the level of serum calcium, the bone metabolic and thyroid autoimmune-related antibodies index during vitamin D3 treatment combined with traditional antithyroid drugs (ATD).

Methods: Our research included hyperthyroid patients with a first-time diagnosis of Graves diseases (GD) combined with hypercalcemia on the basis of conventional anti-hyperthyroidism therapy, which were randomized into a vitamin D3 group (vitamin D3, 800–1,200 IU/day) and an ATD group (methimazole, 15–30 mg/day). All hyperthyroidism patients with hypercalcemia were analyzed, and changes in serum calcium (Ca^{2+}), parathyroid hormone (PTH), thyroid function, thyroid autoimmune-related antibodies, and 25-dihydroxyvitamin D (25-OHVit D) levels during treatment of thyrotoxicosis with added vitamin D3 were explored.

Results: In total, 184 patients with hyperthyroidism were observed, including 36 (19.57%) patients associated with hypercalcemia, with an age of onset of (56.39±5.80) years old. Twelve (6.52%) of these 36 cases reported digestive symptoms as the first manifestation, and four (2.17%) patients presented with a hypercalcemia crisis as the first manifestation. Serum Ca^{2+}, free triiodothyronine (FT_3), free thyroxine (FT_4), and thyrotropin hormone receptor antibody (TRAb) levels increased in patients with hypercalcemia. Following the addition of vitamin D3 treatment, serum Ca^{2+}, FT_3, FT_4, and TRAb levels were significantly decreased relative to the ATD group, while the thyroid-stimulating hormone (TSH), PTH, and 25-OHVit D levels were normalized.

Conclusions: Our study highlighted the importance of taking functional digestive disturbance into consideration in hyperthyroidism diagnosis, even in the absence of the typical symptoms. The level of thyroid related antibodies, thyroid function, and bone metabolism in hyperthyroidism patients combined with hypercalcemia could be improved by vitamin D3 adjuvant therapy.

Trial Registration: Chinese Clinical Trial Registry: ChiCTR2100047870.

Keywords: Hyperthyroidism; hypercalcemia; morbidity; vitamin D3; thyroid related antibodies

Submitted Jul 01, 2021. Accepted for publication Aug 27, 2021. This article was updated on November 21, 2021.
The original version is available at: https://dx.doi.org/10.21037/apm-21-1947.
doi: 10.21037/apm-21-1947

Introduction

Hyperthyroidism is typically characterized by symptoms such as irritability, sweating, palpitations without heart disease, weight loss despite good appetite, and goiter. Hyperthyroidism with electrolyte disturbance is the common clinical manifestation; however, Graves diseases (GD) accompanied by hypercalcemia is rarely observed, with a clinical incidence of 15–20% (1). However, changes in the levels of blood calcium or 25-hydroxyvitamin D (25-OHVit D) during the management of thyrotoxicosis remain unclear. Also, it is difficult to provide an adequate diagnosis and treatment of hypercalcemia patients due to the problem of excluding other causes. One reason is that hypercalcemia is caused by thyrotoxicosis, presumably due to the high levels of thyroid hormone leading to an increase in bone turnover (2,3).

In this study, we observed the dynamic changes in serum calcium (Ca^{2+}) concentration relative to thyrotropin hormone receptor antibody (TRAb) and 25-OHVit D levels in hyperthyroidism patients during the course of conventional antithyroid oral medication therapy with the addition of vitamin D3. The effect of supplemental vitamin D3 on hypercalcemia in GD has not previously been investigated. Thus, we aimed to investigate whether vitamin D3 supplementation improves the recovery of serum Ca^{2+} and digestive disturbance symptoms in GD, and also describe the changes in these outcomes in response to antithyroid drugs (ATD).

GD is a multifactorial autoimmune thyroid disease (AITD) that is caused by the complex interaction of environmental and genetic factors. Typical signs and symptoms of hyperthyroidism include hyperhidrosis, tremor, palpitations, or tachycardia; however, symptoms of hypercalcemia rarely occur as the initial manifestations in hyperthyroidism. Hyperthyroidism leads to hypercalcemia due to bone calcium mobilization into the blood and increased levels of blood calcium.

Recent studies have found that vitamin D has an established association with different kinds of autoimmune diseases, and has been demonstrated to be a modulator of innate and adaptive immunity (4). Furthermore, it has been observed that supplementation with vitamin D can prevent the onset and/or development of various autoimmune disorders in human beings and animal models (5).

Thus, our study aimed to analyze the relationship between hyperthyroidism and the morbidity rate of hypercalcemia in the Xindu district, Chengdu, Sichuan province. We observed the level of serum calcium and the bone metabolic index during treatment with vitamin D3 combined with traditional ATDs. Furthermore, we also investigated the morbidity rate of hypercalcemia with the first manifestations of gastrointestinal symptoms in hyperthyroidism patients, as well as the correlation between vitamin D3 treatment of hyperthyroidism and hypercalcemia. Project research design scheme as shown in *Figure 1*.

We present the following article in accordance with the CONSORT reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1947).

Methods

Research subjects

All participants were informed and provided written informed consent. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the committee on Chengdu Medical College Ethics (No.: 2021CYFYIRB-BA-21-01). This study was a randomized, single-blinded (All the patients were blinded during the trial), parallel group trial on the effects of 12 months of vitamin D3 versus non-added vitamin D3 given as a supplement to ATD treatment to newly diagnosed GD patients combined with hypercalcemia. Patients diagnosed at the Endocrine Outpatient Clinic and Inpatient Department of the First Affiliated Hospital, Chengdu Medical College from December 2019 to December 2020 were recruited, and follow-up was completed by June 2021. All hyperthyroidism patients were diagnosed via thyroid function and thyrotropin hormone receptor antibody (TRAb) tests, and had complete medical history and clinical data. The primary endpoints were to observe the prevalence of hypercalcemia in patients with hyperthyroidism and the changes of thyroid autoimmune-related antibody indexes after intervention therapy with vitamin D3 supplementation. Secondary endpoints were changes in blood calcium, bone markers and bone mineral density. Hyperthyroidism was defined as thyroid-stimulating hormone (TSH) levels below the lower limit of the reference range (0.56–5.91 mIU/L) and total or free levels of free triiodothyronine (FT_3) and free thyroxine (FT_4) above the upper limit of the normal range (FT_3 3.53–7.37 pmol/L; FT4 7.98–16.02 pmol/L), as well as elevated levels of TRAb (normal range ≤1.75 IU/L). Hypercalcemia was defined as serum Ca^{2+} >2.52 mmol/L (normal range 2.11–2.52 pmol/L).

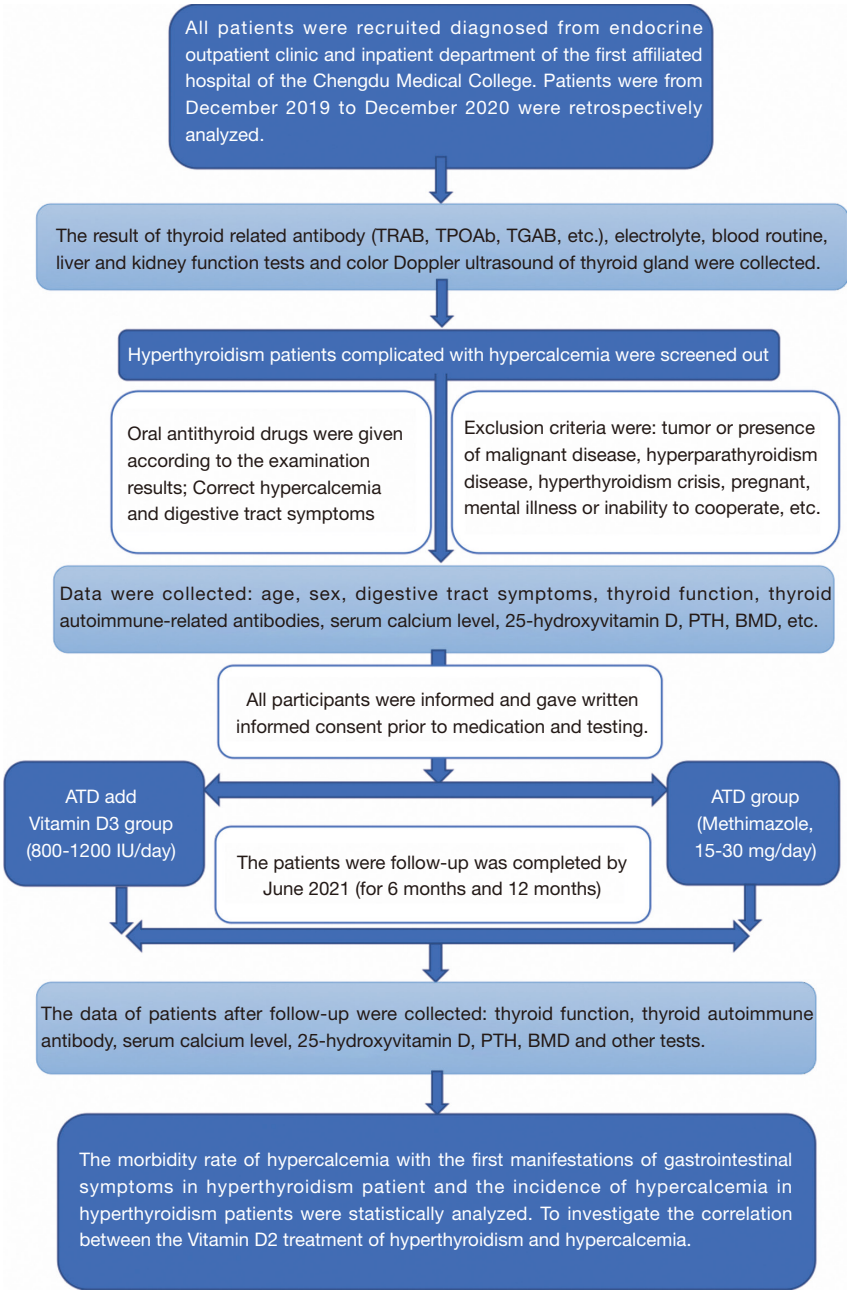

Figure 1 The project research design scheme.

The inclusion criteria were as follows: (I) patients aged between 18 and 70 years; (II) first-time diagnosis of GD; (III) hyperthyroidism combined with hypercalcemia at the first visit; and (IV) initiated or planned ATD as the treatment of choice. The exclusion criteria were as follows: (I) patients with non-hyperthyroidism disease or previous hyperthyroidism; (II) patients with serum Ca^{2+} <2.52 mmol/L or impaired kidney function [estimated glomerular filtration rate (eGFR) <45 mL/min] (III) patients with tumor or presence of malignant disease; (IV) patients with hyperparathyroidism disease; (V) patients with hyperthyroidism crisis; (VI) patients with diabetes insipidus; (VII) those who were pregnant; and (VIII) patients with mental illness or an inability to cooperate.

Table 1 Basic information of the two groups of patients

Groups	Age	Sex	
		Male	Female
Vitamin D group	56.00±6.02	7	11
ATD group	56.78±5.91	8	10
P value	0.786		

There were no significant differences in the basic information of the two groups (P>0.05). ATD, antithyroid drug.

During the study period, based on the description of exclusions and dropouts described above, 184 newly diagnosed GD patients were screened. In summary, 36 participants were included in the study and randomized (allocation ratio in this trial is 1:1) into a vitamin D3 group (Vitamin D3 800–1,200 IU/day, n=18) and an ATD group (methimazole 15–30 mg/day, n=18). The basic information of the two groups of patients is shown in *Table 1*. All hyperthyroidism patients with hypercalcemia were analyzed, and changes in the levels of serum Ca^{2+}, parathyroid hormone (PTH), thyroid function, thyroid autoimmune-related antibodies [including TRAb, thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb)], and 25-OHVit D during treatment of thyrotoxicosis with added vitamin D3 were investigated.

Drugs and clinical test kit

Vitamin D3 Soft Capsules (400 μg/pill) were purchased from Sinopharm Holding Star Shark Pharmaceutical (Xiamen) Co. Ltd, China, and thiamazole tablets (10 mg/tablet) were obtained from Merck KGaA, Germany. Assays for thyroid function (including TSH, FT_3, and FT_4) and all other biochemical measurements were performed at the clinical laboratory of the First Affiliated Hospital of the Chengdu Medical College (Beckman Coulter, Inc., USA). Bone mineral density (BMD) was measured using GE Dual X-ray Bone Density Tester (LUANR iDXA, GE Corporation of USA). The plasma levels of PTH (Abnova, Walnut, CA, USA; normal range, 10–65 pg/mL) and 25-OHVit D [including D_2 and D_3; Guangzhou Jinqirui Biological Technology Co. Ltd, China; normal range, adults (>14 years old): <50 nmol/L (equivalent to <20 ng/mL): vitamin D deficiency, 50.0–75.0 nmol/L (equivalent to 20–30 ng/mL): vitamin D deficiency, 75–250 nmol/L (equivalent to 30–100 ng/mL): normal vitamin D, >250 nmol/L (equivalent to >100 ng/mL): vitamin D overdose] were measured by electrochemiluminescence immunoassay using the Cobas 6000 analyzer (Roche, USA).

Statistical analyses

All collected data were included in the statistical analysis. P values <0.05 were considered significant. Data were analyzed using SPASS 23.0 software (SPSS; Chicago, IL, USA).

Results

The incidence of hypercalcemia and calciotropic hormones

Of the 184 patients with hyperthyroidism, from December 2019 to December 2020 were recruited, and follow-up was completed by June 2021, as shown in *Figure 1* and *Table 1*, 36 patients were associated with hypercalcemia (accounting for 19.57%). Twelve (6.52%) of these 36 cases reported digestive symptoms as the first manifestation, while four (2.17%) presented with hypercalcemia crisis as the first manifestation. The serum Ca^{2+} of these four patients returned to normal after treatment with double rounds of phosphate and fluid. Following addition of vitamin D3 to the conventional anti-thyroidism drug therapy, the serum Ca^{2+} and PTH levels in the vitamin D3 group were significantly decreased compared to those in the ATD group (P<0.05), while the 25-OHVit D concentrations in the vitamin D3 group increased to the normal range compared to those in the ATD group (P<0.05, *Table 2*).

The index of thyroid function and thyroid autoantibodies

The FT_3 and FT_4 levels in the vitamin D3 group were significantly decreased compared with those in the ATD group (P<0.05), while the TSH and TRAb levels in the vitamin D3 group increased to the normal range compared to those in the ATD group (P<0.05, *Tables 3* and *4*). Furthermore, the 25-OHVit D and FT4 levels decreased in parallel (*Figure 2*); the serum 25-OHVit D levels of two groups were lower than the normal range, while the serum PTH levels were in the low-normal range but were not suppressed before anti-thyroid treatment (*Figure 3*).

Compared with ATD group, the level of PTH and 25-hydroxyvitamin D values increased to the high-normal range following addition of vitamin D3 to conventional oral anti-thyroid treatment, and the hypercalcemia was completely relieved (*Figure 4*). Also, compared to the ATD group, the serum Ca^{2+} and FT_4 levels were decreased

Table 2 Index of calciotropic hormones

Serum electrolytes	Ca^{2+} (mmol/L)	PTH (pg/mL)	25-OHVit D (D2+D3) (ng/mL)
Normal range	2.11–2.52	12–88	Deficiency <50
Vitamin D3 group			
Baseline	3.15±0.49	31.89±7.15	27.78±9.96
6 months	2.39±0.15	52.00±8.65	64.44±10.43
12 months	2.30±0.13	48.00±8.77	86.11±5.67
ATD group			
Baseline	2.89±0.22	41.56±8.32	36.11±9.03
6 months	2.59±0.13	45.56±9.18	39.67±9.27
12 months	2.51±0.07	46.11±9.71	27.22±5.49
F values			
Vitamin D3 group	47.97	60.27	246.83
ATD group	36.89	7.34	2.97
P values			
Vitamin D3 group	<0.001	<0.001	<0.001
ATD group	<0.001	0.002	0.061

P values were compared between the vitamin D3 and ATD groups at baseline, 6 months, and 12 months. 25-OHVit D, 25-hydroxyvitamin D; PTH, parathyroid hormone; ATD, antithyroid drug.

in parallel with the treatment of vitamin D3 added to oral anti-thyroid therapy, while the PTH, TRAb, and 25-hydroxyvitamin D concentrations were normalized.

Bone mineral density (BMD)

BMD was measured in the 36 GD patients with hypercalcemia. We found that the BMD index in vitamin D3 group were normalized with the addition vitamin D3 ($P<0.05$, *Table 5*).

Discussion

In 1891, Von Recklinghausen first reported that hyperthyroidism initiated disorders in bone and mineral metabolism (6). However, in these cases, blood calcium rarely increases beyond 2.7 mmol/L (7). Although hypercalcemia is known to be one of the complications of thyrotoxicosis, its morbidity rate and pathogenesis remain unclear. Therefore, typical hypercalcemia symptoms rare occur. The reasons for hypercalcemia vary, and it could be divided into PTH dependency and non-PTH dependency (8). However, in our study, these results did not support hyperparathyroidism. Thus, we considered that the low level of PTH was induced by the significant increase of serum Ca^{2+}, which gave negative feedback to PTH inhibition. Typically, the reason for non-PTH dependent hypercalcemia is malignant tumor, whose incidence rate ranks the second after hyperparathyroidism. Other reasons include multiple myeloma, vitamin A or D poisoning, glucocorticoids, renal disease, hyperthyroidism, and so on. In all cases in our study, the results did not support these diseases.

Previous studies have reported that the prevalence of hypercalcemia in patients with hyperthyroidism is 17–50% (9,10). However, the truth of its prevalence may be difficult to evaluate. On one hand, many case reports have demonstrated that hypercalcemia may not be a common clinical manifestation that occurs in acute conditions of thyrotoxicosis (2), and thus might cause us to ignore testing for serum Ca^{2+} concentrations. On the other hand, many case reports also have described hyperthyroidism combined with other illnesses, such as tumor, renal insufficiency, or hyperparathyroidism (11-13). In our study, we observed a total of 184 patients with hyperthyroidism, 36 of whom were associated with hypercalcemia (accounting for 19.57%).

Table 3 Thyroid function results

Thyroid function	FT_3 (pmol/L)	FT_4 (pmol/L)	TSH (IU/L)
Normal range	3.53–7.37	7.98–16.02	0.56–5.91
Vitamin D3 group			
Baseline	18.13±2.38	54.89±8.24	0.038±0.031
6 months	6.70±0.47	13.07±1.59	0.91±0.61
12 months	4.55±0.71	10.98±2.27	1.47±0.78
ATD group			
Baseline	16.52±2.96	47.61±8.08	0.039±0.032
6 months	6.89±0.19	13.79±1.32	0.65±0.42
12 months	5.10±1.01	10.44±2.09	1.49±1.12
F values			
Vitamin D3 group	508.39	431.22	55.28
ATD group	304.48	268.09	38.42
P values			
Vitamin D3 group	<0.001	<0.001	<0.001
ATD group	<0.001	<0.001	<0.001

P values were compared between the vitamin D3 and ATD groups at baseline, 6 months, and 12 months. FT_3, free triiodothyronine; FT_4, free thyroxine; TSH, thyroid-stimulating hormone; ATD, antithyroid drug.

Table 4 Data of thyroid autoantibodies

Anti-thyroid antibody	Anti-TPO (IU/mL)	Anti-Tg (IU/mL)	TRAb (IU/L)
Normal range	0–34.0	0–115	0–1.75
Vitamin D3 group			
Baseline	66.04±23.38	131.00±16.08	5.94±1.57
6 months	41.28±11.18	66.72±7.76	2.07±078
12 months	8.49±3.36	17.08±9.51	1.09±0.15
ATD group			
Baseline	65.10±18.73	126.76±21.20	5.92±1.20
6 months	45.19±15.29	88.77±9.85	3.03±0.99
12 months	35.92±8.79	24.51±11.59	1.79±0.31
F values			
Vitamin D3 group	32.94	215.29	57.26
ATD group	9.07	105.98	47.99
P values			
Vitamin D3 group	<0.001	<0.001	<0.001
ATD group	0.001	<0.001	<0.001

P values were compared between the vitamin D3 and ATD groups at baseline, 6 months, and 12 months. TRAb, thyrotropin hormone receptor antibody; ATD, antithyroid drug.

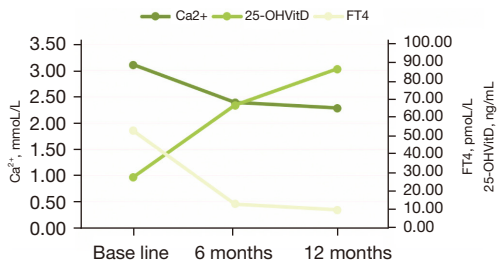

Figure 2 Relationship between 25-OHVit D and FT_4 in the two groups. 25-OHVit D, 25-hydroxyvitamin D; FT_4, free thyroxine.

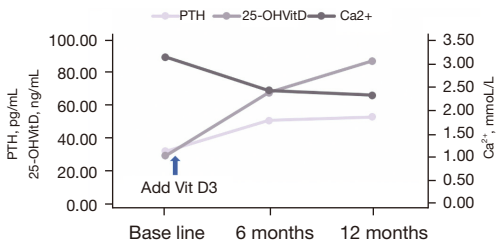

Figure 3 Relationship between 25-OHVit D, PTH, and serum Ca^{2+} in the two groups. 25-OHVit D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

Three (2.23%) of these 18 cases reported digestive symptoms as the first manifestation, and two (1.49%) of them presented with hypercalcemia crisis as the first manifestation. We also found that the majority (77%) of these 18 patients were aged 50–65 years or older, and these patients had varying degrees of low bone mass or osteoporosis.

Thyroid hormones have an important influence on bone turnover, and thus, we analyzed the BMD results of the 18 hyperthyroidism patients. Our study found that the average age of these 18 patients ranged from 56–65, including 12 females and six males, and the T-value of BMD detected was −3.0±−0.7, with 72% of the patients being diagnosed with osteoporosis and 28% with bone loss. The reason for elevated blood calcium is that excessive thyroid hormones accelerate bone absorption, and bone calcium is mobilized to release into the bloodstream. We speculate that the reason why elderly patients with hyperthyroidism are prone to hypercalcemia may be that they have low bone mass or

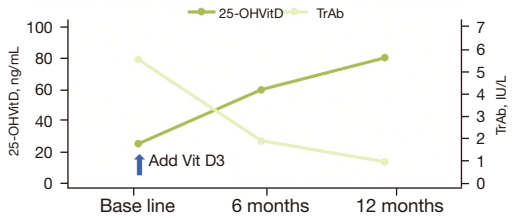

Figure 4 Relationship between 25-OHVit D and TRAb in the two groups. 25-OHVit D, 25-hydroxyvitamin D; TRAb, thyrotropin hormone receptor antibody.

osteoporosis, which accelerates calcium transfer from bone to blood.

Vitamin D drops are different from calcitriol in that each tablet contains vitamin D3 (400 IU/tablet). The use of common vitamin D3 increased the levels of 25-OHVit D and 25-$(OH)_2VitD_3$ in the blood, and the latter had sufficient levels to promote intestinal calcium transport, which could effectively mobilize blood calcium, promote bone formation, and increase bone mineralization. In addition, ordinary vitamin D3 was transformed into 1,25-$(OH)_2VitD_3$, with the highest activity after lightening of the liver and kidney, which stimulated osteoblasts to proliferate, differentiate, and promote bone formation (14). Recent research has indicated that the 1,25-OHVitD3 levels, like PTH, are not inhibited in all hyperthyroidism patients with hypercalcemia (15). In this study, we examined the relationship between hyperthyroidism, PTH, serum Ca^{2+} and 25-OHVit D levels. We observed that the changes in 25-OHVit D concentration were likely mediated by hypercalcemia and increased FT_4 levels. Our study showed that the serum 25-OHVit D levels of both groups were lower than the normal range, while the serum PTH level was in the low-normal range, but was not suppressed before anti-thyroid treatment; this observation is consistent with the findings of other studies (16). We speculated that the low-normal PTH value may have been the result of attenuated adipose reserves of cholecalciferol after extensive weight loss caused by thyrotoxicosis, which could have led to decreased suppression of PTH. However, our results also showed that, compared with the ATD group, the level of PTH and 25-OHVit D values were increased to the high-normal range following addition of vitamin D to traditional oral anti-thyroid treatment, and the hypercalcemia were completely returned to normal levels.

Previous studies have indicated that the concomitant changes of bone resorption and bone formation may reflect the coupling nature of bone turnover, and the increase of bone turnover markers has been observed in patients with hyperthyroidism (17), and that this change may be directly correlated with serum FT_4 levels (18). Our study showed that the serum Ca^{2+} and FT_4 levels were decreased in parallel with the treatment of vitamin D3 added to oral anti-thyroid therapy, while the concentrations of PTH, TRAb, and 25-OHVit D were normalized. We hypothesized that the normalization of TPOAb, TGAb, and TRAb level may be related to the treatment of vitamin D3 supplementation in addition to traditional oral ATD. However, the specific mechanism of its influence is still unclear and requires further research.

In addition, it is worth noting that our study also identified three cases of hyperthyroidism patients with hypercalcemia crisis as the first manifestation, such as repeated abdominal discomfort, nausea, and vomiting. After rehydration, diuresis, calcium reduction therapy, and the addition of vitamin D3 to hyperthyroidism treatment, the serum Ca^{2+} level could rapidly decrease or revert back to normal. It is known that hyperthyroidism can cause the osteoporosis: bone calcium is mobilized into the blood, thereby increasing blood calcium. Increased blood calcium may significantly increase the secretion of gastric acid. A possible mechanism is the calcium in advanced acetylcholine is released by synapse, which provokes gastric acid secretion by stomach cells via vagus nerve stimulation (19). Another possible mechanism is vagus nerve stimulating gastrin release, which leads to increased gastric acid secretion (20). However, hyperthyroidism control requires a certain period of time, which demands immediate treatment on hypercalcemia to prevent a hypercalcemia crisis (21,22).

Conclusions

Our study highlights the importance of taking functional digestive disturbance into consideration in the diagnosis of hyperthyroidism, even in the absence of the typical symptoms. The level of thyroid function and bone metabolism in hyperthyroidism patients combined with hypercalcemia can be improved by vitamin D3 adjuvant therapy. However, our study was limited by the fact that the number of cases collected was small, and the observation time was short. Thus, collection and observation of more cases for further research is needed. Also, further investigation is required to determine the mechanisms by which thyrotoxicosis induces hypercalcemia and the effect of vitamin D3 supplementation on thyroid-associated

Table 5 The result of BMD

Variable	L2–4	Femoral neck	Trochanter major	Total hip
T value				
Normal range		Low bone mass: –2.5 to –1.0, Osteoporosis: <–2.5		
Vitamin D3 group				
Base line	–2.90±0.10	–2.80±0.22	–2.62±0.21	–2.90±0.23
12 months	–1.79±0.28	–1.59±0.44	–1.77±0.53	–2.16±0.13
ATD group				
Base line	–2.91±0.37	–2.66±0.27	–2.79±0.20	–2.93±0.25
12 months	–2.55±0.27	–2.23±0.48	–2.37±0.33	–2.44±0.23
F value				
Vitamin D3 group	123.46	54.42	20.02	70.64
ATD group	5.68	5.48	10.65	18.67
P value				
Vitamin D3 group	<0.001	<0.001	0.001	<0.001
ATD group	0.030	0.033	0.005	0.001
Z value				
Normal range	≤–2.0			
Vitamin D3 group				
Base line	–2.37±0.18	–2.33±0.44	–2.62±0.33	–2.41±0.13
12 months	–1.89±0.01	–1.53±0.16	–1.61±0.05	–1.75±0.17
ATD group				
Base line	–2.30±0.03	–2.75±0.09	–2.08±0.06	–2.33±0.27
12 months	–2.02±0.08	–2.09±0.05	–1.71±0.40	–1.84±0.25
F value				
Vitamin D3 group	11.99	5.92	18.07	18.32
ATD group	23.72	79.927	1.70	3.51
P value				
Vitamin D3 group	0.179	0.207	0.139	0.055
ATD group	0.091	0.012	0.411	0.202

P values were compared between the vitamin D3 and ATD groups at baseline and 12 months. ATD, antithyroid drug; BMD, bone mineral density.

antibodies.

Acknowledgments

Funding: This study received the support from the Key Discipline Construction Project of Sichuan Province (2017, No. 62).

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1947

Trial Protocol: Available at https://dx.doi.org/10.21037/apm-21-1947

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-1947

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1947). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the committee on Chengdu Medical College Ethics (No.: 2021CYFYIRB-BA-21-01). All participants were informed and provided written informed consent.

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(English Language Editor: A. Kassem)

Cite this article as: Mei X, Zeng J, Dai WX, Yang HL, Li Y, Tang MW, Qiu P. Prevalence of hyperthyroidism with hypercalcemia in Xindu district and the efficacy of vitamin D3 treatment in these patients: a randomized trial. Ann Palliat Med 2021;10(9):9640-9649. doi: 10.21037/apm-21-1947

