Trial Protocol

project name: Prevalence of hyperthyroidism with hypercalcemia and clinical observation after vitamin D3 treatment

Project Leader: meixi

Project Responsible unit: The First Affiliated Hospital of Chengdu Medical College

Project Department: Endocrinology and Metabolism Department

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1.Research background

Graves' disease (GD) is a multifactorial disease caused by a complex interaction of genetic and environmental factors. Autoimmune thyroid disease (AITD). The typical signs and symptoms of hyperthyroidism, such as hyper perspiration, tremor, palpitations, or tachycardia, rarely occur with hypercalcemia as the first symptom. Hypercalcemia caused by hyperthyroidism is caused by bone calcium being mobilized into the blood and increasing blood calcium levels.

Clinical work in patients with hyperthyroidism can cause electrolyte disturbances, and the typical symptoms of hyperthyroidism are usually irritability, hyper sweating, palpitations without heart disease, good appetite but weight loss, and goitre. Hyperthyroidism with electrolyte disturbances is a common clinical manifestation, but GD combined with hypercalcemia is relatively rare, with a clinical incidence of 15% ~ 20%[1]. However, the treatment of hypercalcemia is still quite difficult, and other causes of hypercalcemia caused by hyperthyroidism only need to be excluded. The most important thing is to control hyperthyroidism. However, the control of hyperthyroidism needs a certain time, at this time should be timely symptomatic treatment of hypercalcemia, to prevent the occurrence of hypercalcemia crisis, should cause the attention of clinicians. However, changes in blood calcium or 25-hydroxyvitamin D (25-OHvit D) levels during thyrotoxicosis treatment are unknown. Thyrotoxicosis is one of the causes of hypercalcemia, which is speculated to be due to increased bone turnover caused by excessive thyroid hormone level [2-3]. Recent studies have found established associations between different types of autoimmune diseases and vitamin D has been shown to be a modulator of innate and adaptive immunity [4]. In addition, vitamin D supplementation has been found to prevent the occurrence and/or development of various autoimmune diseases in human and animal models [5].

This study was designed to observe the dynamic changes of serum calcium concentration and thyroid stimulating hormone receptor antibody (TRAb) and 25-ohvit D levels in patients with hyperthyroidism during oral treatment with antithyroid agents plus vitamin D3. However, the effect of vitamin D3 supplementation on GD with hypercalcemia has not been studied. Therefore, this study aimed to analyse the relationship between hyperthyroidism and the incidence of hypercalcemia in Xindu District, Chengdu city, Sichuan Province. To observe the serum calcium and bone metabolism index of vitamin D3 combined with traditional antithyroid drugs. To investigate the incidence of hypercalcemia in hyperthyroidism patients with gastrointestinal symptoms as the first manifestation and the correlation between hypercalcemia and hyperthyroidism treated with vitamin D3.

Reference:

[1] Korytnaya E, Rao N G, Mayrin J V. An Unusual Case of Hypercalcemia Associated with Graves' Disease and Vitamin D Deficiency[J]. Clinical Medicine Insights Endocrinology & Diabetes, 2011, 4:25.

[2]. Baxter J D , Bondy P K . Hyperscalcemia of Thyrotoxicosis[J]. Annals of Internal Medicine, 1966, 65(3):429-442.

[3]. Alikhan Z , Singh A . Hyperthyroidism manifested as hypercalcemia.[J]. Southern Medical Journal, 1996, 89(10):997-998.

[4]. Wei R , Sylvia C . Mechanisms Underlying the Regulation of Innate and Adaptive Immunity by Vitamin D[J]. Nutrients, 2015, 7(10):8251-8260.

[5]. Sheriba N , Elewa A A , Mahdy M , et al. Effect of vitamin D 3 in treating hyperthyroidism in patients with graves' disease[J]. The Egyptian Journal of Internal Medicine, 2017, 29(2):64.

2. Research purpose

Objective To analyze the relationship between hyperthyroidism and hypercalcemia in Xindu district of Chengdu, Sichuan province. To observe the serum calcium and bone metabolism index of vitamin D3 combined with traditional antithyroid drugs. To investigate the incidence of hypercalcemia in hyperthyroidism patients with gastrointestinal symptoms as the first manifestation and the correlation between hypercalcemia and hyperthyroidism treated with vitamin D3.

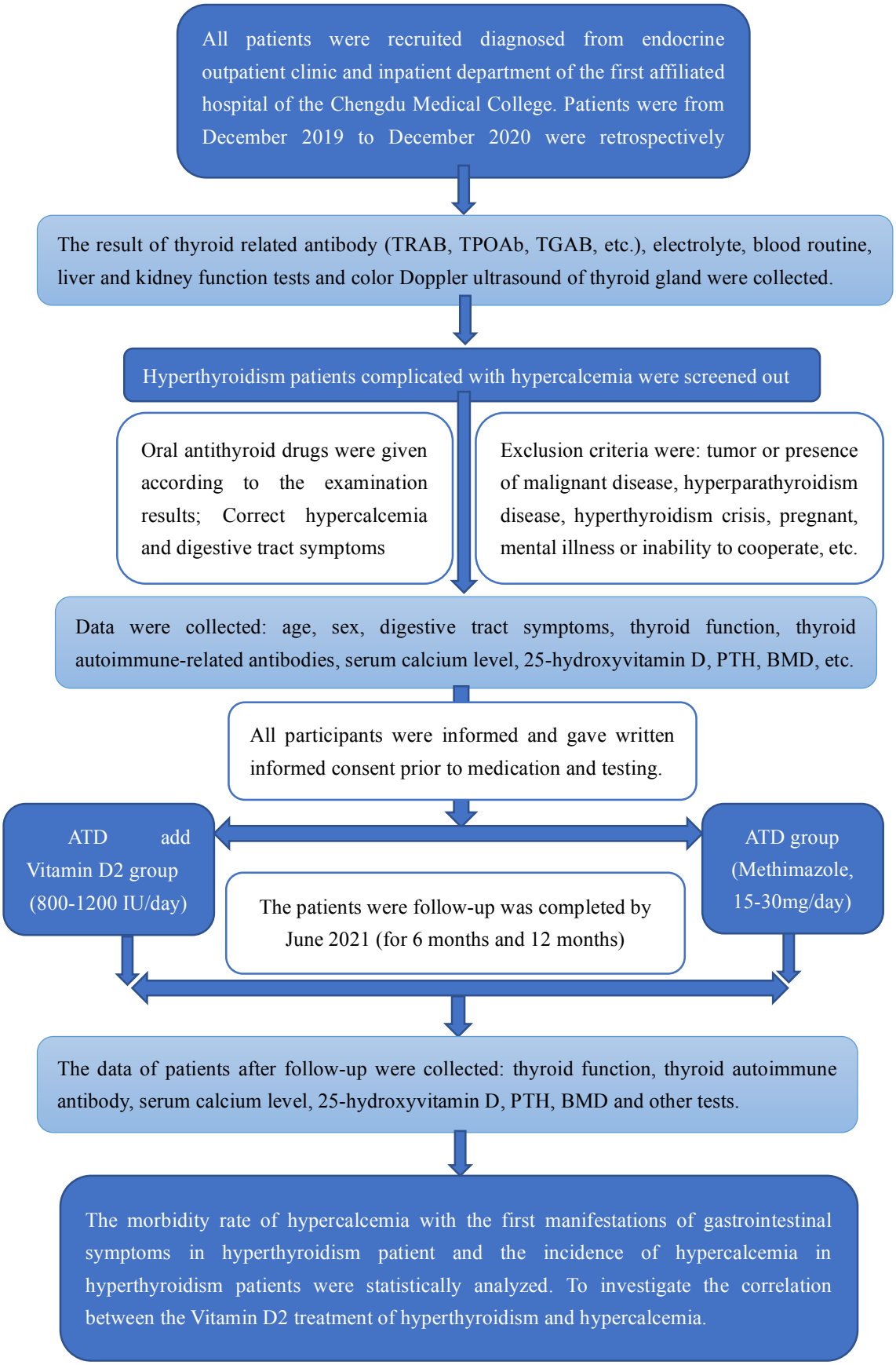
3. Study design types, principles and test procedures

3.1. Research design

This study is a retrospective analysis. The data and data of all patients were collected from the His system of the First Affiliated Hospital of Chengdu Medical College to analyze the effects of the two treatment methods on newly diagnosed GD patients with hypercalcemia, including standard ATD treatment and vitamin D3 supplementation. All patients were from the endocrinology outpatient department and inpatient department of the First Affiliated Hospital of Chengdu Medical College. Patients were enrolled from June 2019 to June 2020, and follow-up was completed in June 2021. All patients with hyperthyroidism were confirmed by thyroid function examination and thyroid stimulating hormone receptor antibody (TRAb) test, and completed the collection of medical history and clinical data. Hyperthyroidism was defined as thyroid stimulating hormone (TSH) levels below the lower limit of the reference range (0.56 -- -5.91 mIU/ L) levels of total or free triiodothyronine (occurrence) and free thyroxine (FT4) levels above the upper limit of the normal range (occurrence 3.53 -- -7.37 pmol/L) L; FT4 7.98-16.02 pmol/L), TRAb level increased (normal range $\leqslant$1.75 IU/L). Hypercalcemia was defined as blood

calcium >2.52mmol/L(normal range 2.11-2.52pmol/L).

3.2. Research Steps:


All patients were recruited diagnosed from endocrine outpatient clinic and inpatient department of the first affiliated hospital of the Chengdu Medical College. Patients were from December 2019 to December 2020 were retrospectively
The result of thyroid related antibody (TRAB, TPOAb, TGAB, etc.), electrolyte, blood routine, liver and kidney function tests and color Doppler ultrasound of thyroid gland were collected.
Hyperthyroidism patients complicated with hypercalcemia were screened out
Oral antithyroid drugs were given according to the examination results; Correct hypercalcemia and digestive tract symptoms
Exclusion criteria were: tumor or presence of malignant disease, hyperparathyroidism disease, hyperthyroidism crisis, pregnant, mental illness or inability to cooperate, etc.
Data were collected: age, sex, digestive tract symptoms, thyroid function, thyroid autoimmune-related antibodies, serum calcium level, 25-hydroxyvitamin D, PTH, BMD, etc.
All participants were informed and gave written informed consent prior to medication and testing.
ATD add Vitamin D2 group (800-1200 IU/day)
ATD group (Methimazole, 15-30mg/day)
The patients were follow-up was completed by June 2021 (for 6 months and 12 months)
The data of patients after follow-up were collected: thyroid function, thyroid autoimmune antibody, serum calcium level, 25-hydroxyvitamin D, PTH, BMD and other tests.
The morbidity rate of hypercalcemia with the first manifestations of gastrointestinal symptoms in hyperthyroidism patient and the incidence of hypercalcemia in hyperthyroidism patients were statistically analyzed. To investigate the correlation between the Vitamin D2 treatment of hyperthyroidism and hypercalcemia.

4.Case selection

4.1. Inclusion criteria

Patients aged between 18 and 70 years, first diagnosed as GD with hypercalcemia, and eligible for ATD treatment.

4.2. Exclusion criteria

(1) No hyperthyroidism or previous hyperthyroidism; (2) serum calcium < 2.52mmol/L and impaired renal function (glomerular filtration rate [eGFR] <45mL/min); (3) Tumor or malignant disease; (4) hyperparathyroidism; (5) Hyperthyroidism crisis; (6) diabetes insipidus; (7) pregnancy; (8) Mental illness or inability to cooperate.

5.Research methods and technical routes

5.1. Name and specification of the drug used in the study

Vitamin D3 soft capsule (400ug/ tablet, Sinophin holding Star Shark Pharmaceutical (Xiamen) Co., LTD.); Timazole tablets (10mg/ tablet, Merck KGaA). Thyroid function (including TSH, FT3, FT4) and other biochemical indicators were performed through the clinical laboratory of the First Affiliated Hospital of Chengdu Medical College (Beckman Coulter, Inc, USA). Bone mineral density (BMD) was measured by GE Dual energy X-ray (GE LUANR, USA). Plasma PTH (Abnova, Walnut, CA, normal range, 10-65 pg/mL) and 25-OHvit D(including D2 and D3). Guangzhou Jinchery Biotechnology Co., LTD.; Normal range, Adults (> 14 years):< 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 > 250 nmol/L(equivalent to > 100 ng/mL): Vitamin D overdose was measured by electrochemical luminescence immunoassay using a Cobas 6000 analyzer (Roche, USA).

5.2. Treatment plan

Routine ATD treatment group was given Methimazole tablets 10-30mg/d orally, once a day. In addition to ATD treatment, vitamin D3 was added orally once daily (800-1200IU /day). The patients were treated for 1-1.5 years and followed up for 1 year.

6. Observation items and detection time points

Age, sex, digestive tract symptoms, thyroid function, thyroid autoimmune-related antibodies, serum calcium level, 25-hydroxyvitamin D, parathyroid hormone (PTH), bone mineral density of the patients were collected and observed. The patients were followed up for 1 year to observe thyroid function, thyroid autoimmune-related antibodies, serum calcium level, 25-hydroxyvitamin D, parathyroid hormone (PTH), bone mineral density and so on.

7.Observation of adverse events

This study was a retrospective study with no direct contact with humans, so there were no adverse events.

8.Research quality control and quality assurance

(1) The department of Endocrinology and Laboratory laboratory of our hospital is a provincial key discipline, with sufficient number of visits and relevant testing methods to meet the experimental requirements for the collection of sufficient case samples;

(2) The members of the project team have a reasonable structure. The members of the project team are endocrinologists, and they have the experience and ability of designing, applying, organizing and carrying out scientific research, publishing results and managing the project team.

(3) Provincial medical key disciplines have been established in our department, which provides part of scientific research funds to support the smooth development of scientific research.

9. Data security inspection

The clinical study will develop a data safety monitoring plan based on the risk. All adverse events shall be recorded in detail, properly handled and tracked until they are properly resolved or stabilized, and serious adverse events and unexpected events shall be reported to the ethics committee, competent authorities, sponsors and drug regulatory authorities in a timely manner according to regulations; A cumulative review of all adverse events was conducted periodically by the principal investigator and, if necessary, investigator meetings were held to assess the risks and benefits of the study; Studies with greater than minimum risk will be monitored by independent data monitors, and high-risk studies will establish independent data safety monitoring committees to monitor the accumulated safety data and validity data to make recommendations on whether to proceed with the study.

10. Statistical processing

All data collected were included in the analysis. A p value <0.05 is considered significant. Data were statistically analyzed by SPASS 23.0 software.

11. Ethics of clinical research

Clinical research will follow the world Medical Congress "Declaration of Helsinki" and other relevant provisions. Clinical studies are conducted after the protocol has been approved by the ethics committee prior to the start of the study. Subjects' privacy and data confidentiality will be protected during the study.

12. Research Progress

June 2021 - July 2021: Collect patient case data and data, complete data processing, statistics, analysis and chart sorting.

August 2021 -- September 2021: Sorted out statistical analysis results, wrote and revised treatise, and published it.

13. Participants

Name	Technical position	professional	division	sub-unit
LiYao	Chief physician	Endocrinology	Research Design Guidance	First Affiliated Hospital of Chengdu Medical College
QiuPing	Associate Chief physician	Endocrinology	Research technical guidance	First Affiliated Hospital of Chengdu Medical College
ZengJun	Associate Chief physician	Experimentalist	Research technical advisor	Chengdu Medical College
Tang ming-wei	Attending physician	endocrinology,	collecting patient data	First Affiliated Hospital of Chengdu Medical College
Yang hui-lan	Attending physician	Endocrine	data collation and statistical analysis	First Affiliated Hospital of Chengdu Medical College

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