

# The Relationship Between the Serum Level of Vitamin D and Hypocalcemia After Total Thyroidectomy

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**Abstract-** Vitamin D plays a crucial role in calcium metabolism through the parathormone-dependent process. The deficiency of this important nutrient may be associated with hypocalcemia after thyroidectomy. To evaluate the role of vitamin D in predicting hypocalcemia following total thyroidectomy. In this study, sixty-two patients who underwent total thyroidectomy for benign or malignant thyroid disease were included in this prospective study. Preoperative vitamin D serum levels and parathormone (PTH) levels were determined. The association between preoperative vitamin D status and the development of hypocalcemia was investigated. In this study, 62 patients were evaluated. The mean age of the subjects was 47 years. Of the 62 patients studied, of which 9 were male patients (14.5%), and 53 were female (85.5%), the results of our study showed. In both groups with and without vitamin D deficiency, calcium levels decreased significantly ( $P=0.01$ ). In our study, it was found that there was no significant relationship between postoperative hypocalcemia and vitamin D deficiency. ( $P=0.441$ ). After reviewing the data and according to Spearman correlation statistical test, no significant relationship was observed between serum parathyroid hormone (PTH) and calcium after thyroidectomy ( $P=0.340$ ). Vitamin D deficiency is a risk factor of hypocalcemia after total thyroidectomy for benign goiter. Although post thyroidectomy hypocalcemia is multifactorial, vitamin D deficiency, particularly severe form, is significantly associated with the development of biochemical and clinical hypocalcemia. Vitamin D supplementation can prevent this unwanted complication in such patients.

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## Introduction

Total thyroidectomy is one of the most performed surgical procedures worldwide (1). Total thyroidectomy (TT) is a routine for the surgical treatment of multinodular goiter, while postoperative hypocalcemia is a frequent complication. The etiology of postoperative hypocalcemia is multifactorial, even though the most important component is surgical trauma to the parathyroid glands (2). It is frequently mild and transitory

(in up to 50% of cases) and infrequently permanent (5%) (3). Nevertheless, it is constantly a concern and challenge for surgeons and patients (4). TT might cause hypoparathyroidism due to the ignored removal of the parathyroid gland or damage to its blood supply (5). It has been experimental that vitamin D deficiency favors the entrance of postoperative hypocalcemia in patients who undergo surgery for multinodular goiter or Graves'–Basedow disease (6). Vitamin D shows a central role in the homeostasis of calcium and the intestinal absorption

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of calcium and phosphate (7). However, the role of vitamin D in the prediction of postoperative hypocalcemia still remains a provocative issue (8).

The synthesis of vitamin D active form in the kidneys (1-25[OH]D<sub>3</sub>) is a process controlled by parathyroid hormone (PTH), and therefore by increasing vitamin D levels, the secretion of PTH is reduced (9). If this connection between preoperative vitamin D deficiency and postoperative hypocalcemia is confirmed, vitamin D levels might be a decent indicator of this risk that could be tranquil to the quantity and correct before surgery (10).

Due to the role of vitamin D in calcium metabolism in the body and the existence of few studies on the relationship between vitamin D levels and calcium levels after thyroidectomy, we decided to conduct a study to determine the level of vitamin D in patients with thyroidectomy and its effect on calcium and hypocalcemia after thyroidectomy. In this study, an attempt was made to closely monitor patients' pre- and post-hospitalization, inpatient and preoperative, during, postoperative, and postoperative interventions to reduce the involvement of confounding factors in the results. Measure vitamin D with a higher level of calcium and possible hypocalcemia with higher accuracy and provide a more conclusive result for practical purposes.

## Materials and Methods

### Study design, area, and period

A retrospective study was conducted on a group of patients who underwent total and subtotal thyroidectomy in 2018-2020 referred to Razi hospital in the north of Iran. The study was performed by the declaration of Helsinki and approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1397.463). Inclusion criteria were indications for thyroidectomy (included any kind of suspicious mass or malignancies that had previously been confirmed by a pathology examination). Exclusion criteria were preoperative hypocalcemia, parathyroid adenoma, any underlying disease that affects parathyroid hormone levels, vitamin D, calcium, and albumin (such as chronic kidney disease, indigestion, and malabsorption), patient dissatisfaction participating in the study included a previous major procedure such as total laryngectomy or parathyroidectomy, receiving prophylactic drug therapy for osteoporosis, including calcium and vitamin D supplementation, and patients with hyperthyroidism and active Grave's.

### Studied population and laboratory tests

Based on vitamin D levels before surgery, patients were divided into two groups with normal vitamin D (between 30-30 ng/ml) and vitamin D deficiency (less than 30 ng/ml). Then, postoperative calcium changes in patients were measured in two forms: normal calcium (8.5-5.5 mg/dl) and hypocalcemia (less than 8.5 mg/dl) based on vitamin D levels before surgery. Calcium, phosphorus, parathormone, and vitamin D levels were measured by the enzyme-linked immunosorbent assay (ELISA). Biotek microplate reader ELX-800, made in 750-400 nm microplates, has four filters, 630, 9090, 405 nm, source Tungsten light, and resolution are 0.001 OD. The status of thyroid tissue cytopathology was also calculated based on a biopsy performed according to the Bethesda standard. Based on this, the patient's pathology will be divided into six categories. Accordingly, to (I) non-diagnostic; (ii) benign; (iii) an atypically insignificant atypia (AUS) or an unexplained follicular lesion (FLUS); (iv) Follicular neoplasm or suspected follicular neoplasm; (V) Suspected of malignancy and (vi) malignant. The information of all patients who entered the study, including age, sex, underlying disease, body mass index, length of hospital stay, type of thyroid pathology, serum calcium levels, phosphorus, parathormone before and immediately after surgery, and vitamin D levels before surgery were measured and It was recorded in the pre-prepared information form. The volume of the sample required to evaluate the serum level of vitamin D before surgery with hypocalcemia after thyroidectomy with 95% confidence (significance level 5%) and 90% test power based on the results of Tripathi *et al.*'s study (11) according to the minimum sampling formula 31 people were estimated in each group.

### Data processing and analysis

The SPSS software version 21.0 was used for data analyses. To describe quantitative variables with normal distribution, mean and standard deviation (about 95% confidence) were used, and for quantitative variables with abnormal distribution, the mean and intermediate-range were used. Qualitative variables were also described based on numbers and percentages. The normal distribution of quantitative study variables was measured using tensile and skew values and the Shapiro-Wilk test. To compare quantitative variables between two groups with and without vitamin D deficiency from the independent t-test; and covariance analysis, ANCOVA was used by modifying the variable effect before surgery. Comparison of quantitative variables before and after

thyroidectomy using paired t-test; paired t-test (equivalent to nonparametric Wilcoxon) was used. To compare hypoxia in two groups, the Chi-Square test and, if not validated, the Fisher's Exact Test. Correlation of variables using Pearson correlation coefficient; Pearson correlation (Spearman correlation) was measured.

## Results

A total of 62 patients with a mean age of 47±18.9 years were included in the study. Of these patients, 53 (85.5%) were female, and 9 (14.5%) were male. There were no significant differences based on age mean and

gender between two groups of patients with normal vitamin D and vitamin D deficiency. Regarding the underlying disease, 43 patients (69.4%) did not have an underlying disease, 19 patients (30.7%) had one to three underlying diseases. Of these, high blood pressure with 7 (11.3%) cases had the highest prevalence. The BMI of patients was 35.6±18.29. After examining the data and using the Mann-Whitney test, there was no significant difference between the BMI status in the two groups ( $P=0.642$ ) (Table 1).

Among the patients assessed, pathology findings were not significantly different in the two groups ( $P=0.980$ ). (Table 2).

**Table 1. Patient characteristics and clinical data of the study population**

Variable	Level	N	%
Sex	Male	9	14.5
	Female	53	85.5
	No	43	69.4
	DM	3	4.8
Underlying Diseases	HTN	7	11.3
	HLP	2	3.2
	DM HTN	3	4.8
	DM HLP	1	1.6
	HTN HLP	2	3.2
	DM HTN HLP	1	1.6
	Body Mass Index (Mean±SD)		29.18 ± 8.1
Age (Mean±SD)		47.01 ± 12.8	

**Table 2. Abundant distribution of pathological status in two groups with and without Vitamin D deficiency**

Pathology	Vit D		Total
	Insufficient	Sufficient	
Benign	31.3%	33.3%	32.3%
AUS/FLUS	15.6%	13.3%	14.5%
Ferrochloric uptake/or suspected follicular neoplasm	6.3%	6.7%	6.5%
Suspicious of malignancy	15.6%	23.3%	19.4%
Malignant	12.5%	13.3%	12.9%
Multi-nodular goiter	15.6%	10.0%	12.9%
sympathetic guitar	3.1%	0.0%	1.6%

The incidence of symptomatic hypocalcemia was (n=32), and asymptomatic hypocalcemia (only the laboratory hypocalcemia; Ca<8 mg/dl) was (n=30). The mean of serum calcium after thyroidectomy decreased in both vitamin D studied groups, but these differences were not statistically significant in any of these groups ( $P>0.05$ ). The incidence of hypocalcemia in two groups with and without vitamin D deficiency was 56.7% (N=17) and 46.3% (N=13); there was not any association between postoperative hypocalcemia and vitamin D deficiency ( $P>0.05$ ).

In the present study, between calcium and parathyroid

hormone after surgery in two groups with and without vitamin D deficiency, no significant correlation was obtained. ( $P=0.340$ ). There was no significant association between postoperative phosphorus and postoperative parathyroid hormone in the deficiency of the vitamin D group. ( $P>0.05$ ) The association between postoperative phosphorus and postoperative parathyroid hormone was not significantly associated with vitamin D deficiency ( $P>0.05$ ). A significant difference was observed in the vitamin D deficiency group in the comparison between postoperative parathyroid hormone and preoperative parathyroid hormone ( $P=0.045$ ). Comparison of

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postoperative parathyroid hormone and preoperative parathyroid hormone in the group without vitamin D deficiency there was a significant difference ( $P=0.006$ ).

Also, no significant difference was observed in the group without vitamin D deficiency compared to postoperative phosphorus and preoperative phosphorus ( $P=0.125$ ). There was no significant difference in vitamin D deficiency between preoperative and postoperative phosphorus deficiency ( $P=0.0784$ ).

## Discussion

Vitamin D deficiency has emerged as a significant public health problem throughout the world (12). Although hypocalcemia is a common complication following thyroidectomy, it is usually temporary, and only 1-3% of the patients develop enduring hypocalcemia, which is distinct as ongoing hypocalcemia within six months after surgery (13). Vitamin D is the principal factor that maintains calcium homeostasis (14). The results of our study showed that factors such as age, sex, BMI, length of hospital stay, and underlying thyroid pathology did not significantly differ between the two groups, so these underlying factors did not lead to bias in our patients. Studies are showing that transient hypocalcemia is associated with aging (15). A systematic study by Edafe *et al.*, showed that the mean age of patients with transient hypocalcemia and those who did not have significant differences were observed. Also, some studies have reported more postmenopausal hypocalcemia in women (16). As mentioned, there was no significant difference between age and sex in our study groups, so these two factors were not a factor in the study of hypocalcemia in the two groups under study. Some studies, such as a study by Kirkby-B *et al.*, Of hypocalcemia in patients, were associated with an increased length of hospital stay (17). In our study, because radiation therapy was similar in our patients after thyroidectomy, the effect of hospital stay time as a possible cause of calcium change was removed from the disruptive factors. Our patients were divided into two groups with vitamin D deficiency and adequate vitamin D levels. Calcium, phosphorus, and PTH were assessed before and after surgery in these patients. The results of our study showed that there was no significant association between postoperative hypocalcemia and postoperative vitamin D deficiency, and both groups studied in our study (vitamin D deficiency and adequate vitamin D) showed moderate to moderate calcium deviation. Vitamin D plays an important role in calcium metabolism by increasing calcium absorption for the gastrointestinal

tract (18). The results of our study were similar to those of Chia *et al.*, (19). According to the results of our study, serum levels of vitamin D before complete thyroidectomy do not play a role in postoperative hypocalcemia, which is one of the most important and approximately common complications of this surgery. In the last two decades, total thyroidectomy has become one of the treatment options for malignant and benign thyroid diseases, leading to post-thyroid hypocalcemia (12). In our study, there was no significant association between serum PTH and calcium levels in the two groups, but PTH before and after surgery showed significant differences between the two groups but between phosphorus before and after surgery in the two groups. You haven't seen it. Some studies have suggested that measuring PTH on the first day after surgery may be a useful method for predicting hypocalcemia after a thyroidectomy, thus preventing long-term hospitalization. In addition, the PTH dose on the first day after surgery is more reliable and cheaper than the rapid PTH procedure during surgery (15). The strengths of this study include the use of a forward-looking database to extract large amounts of data, including the symptoms of hypocalcemia, calcium replacement, and long-term hypoparathyroidism. The uniformity of surgery and the performance of a surgeon are other strengths of our study. This hypothesis requires further research to determine effective parameters in the future.

Vitamin D deficiency was common in our population of patients undergoing thyroidectomy; however, it was not associated with an increased risk of postoperative hypocalcemia. According to the results of our study, serum levels of vitamin D before thyroidectomy do not play a role in postoperative hypocalcemia, which is one of the most important and approximately common complications of this surgery. Careful and prolonged follow-up of calcium, vitamin D, and parathyroid hormone levels should be suggested for these patients.

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