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IS THERE A RELATIONSHIP BETWEEN VITAMIN D STATUS AND HYPOCALCEMIA AFTER TOTAL THYROIDECTOMY?

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Abstract

Context. Vitamin D plays a crucial role in calcium metabolism through parathormone-dependent process. Deficiency of this important nutrient may be associated with hypocalcemia after thyroidectomy.

Objective. To evaluate the role of vitamin D in predicting hypocalcemia following total thyroidectomy.

Subjects and Methods. One hundred and fifty patients who underwent total thyroidectomy for benign or malignant thyroid disease were included in this prospective study. The association between preoperative vitamin D status and the development of hypocalcemia were investigated.

Results. Biochemical and symptomatic hypocalcemia were found in 28 (18.7%) and 22 (14.7%) patients, respectively. Preoperative vit D level was found significantly lower in patients with biochemical ($p = 0.006$) and clinical ($p < 0.001$) hypocalcemia in comparison to normocalcemic patients. The patients who had <10 ng/mL vit D level (severe deficiency) developed significantly more biochemical and clinical hypocalcemia than the patients with serum vit D level higher than 10 ng/mL ($p = 0.030$ and $p < 0.001$, respectively).

Conclusions. Although postthyroidectomy hypocalcemia is multifactorial, vit D deficiency, particularly severe form, is significantly associated with the development of biochemical and clinical hypocalcemia. Vit D supplementation can prevent this unwanted complication in such patients.

Key words: Postoperative hypocalcemia, total thyroidectomy, vitamin D deficiency.

INTRODUCTION

Total thyroidectomy is among the most performed surgical procedures worldwide. However, it is associated with specific morbidities such as hematoma with airway compression, hoarseness and ventilation problems due to recurrent laryngeal nerve injury-and hypocalcemia. Among those, postoperative hypocalcemia is one of the most common complications following total thyroidectomy, with a reported incidence of up to 60% (1).

Although hypocalcemia is often asymptomatic or causes mild symptoms such as perioral or distal acral paresthesia, severe clinical findings including painful cramps, tetany, and convulsion can be also seen, which can limit the routine daily activities of such patients. To date, several clinical studies have focused on identifying a risk factor or modelling system to predict hypocalcemia after thyroid surgery. In those studies, intraoperative parathyroid hormone (PTH) level less than 10 pg/mL, preoperative serum calcium, magnesium and phosphate levels were found to be associated with postoperative hypocalcemia; however, none of those could provide a definitive prediction of this important complication (2-5).

Recently, the role of 25-hydroxyvitamin D (vit D) in the development of hypocalcemia after thyroidectomy has been one of the main interests of researches, due to its important role in calcium homeostasis. However, the role of vit D in prediction of postoperative hypocalcemia still remains a controversial issue (6, 7). Here, we aimed to determine whether vit D can be used as a predictor of hypocalcemia in Turkish patients who underwent total thyroidectomy for benign and/or malignant thyroid diseases.

MATERIAL AND METHODS

Patients and study design

This study was designed to evaluate the possible association between preoperative serum vit D level and the development of postoperative hypocalcemia. Informed consent was obtained from all patients. The study protocol was approved by Local Ethics Committee of Ankara Numune Training and Research Hospital (permit no: 945/2015).

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One hundred and fifty patients who underwent total thyroidectomy for benign and/or malignant thyroid disease by the same surgery team in Ankara Numune Training and Research Hospital between January 2015 and April 2015 were included in this prospective study. Exclusion criteria were previous thyroid surgery or irradiation, coexisting parathyroid disease, using a drug that interfered with calcium (Ca) homeostasis (Ca or vit D supplements, lithium, bisphosphonates, diuretics, etc.), and biochemical findings indicating renal insufficiency (serum creatinine> 2 mg/dL, creatinine clearance <40 ml/min and glomerular filtration rate (GFR) <60 mL/min/1.73 m^2). Patients' age, gender, preoperative serum vit D and Ca levels, postoperative 2th day serum Ca level, type of surgery (total thyroidectomy with or without central neck compartment dissection), presence of hyperthyroidism, and final pathology report were recorded. The preoperative Vit D level was taken within several days before surgery when the patient had been fasting overnight. An electro immunochemiluminescence method was used for the determination of vitamin D concentrations.

All patients were classified into three groups according to postoperative serum Ca levels: no hypocalcemia, biochemical hypocalcemia (without any hypocalcemia-related symptom or sign), and clinically or symptomatic hypocalcemia. Hypocalcemia was defined as serum corrected Ca level less than 8.0 mg/dL. Corrected Ca was calculated according to the following formula: corrected Ca = measured Ca + 0.02 × (40 – serum albumin). Patients were considered to have clinically or symptomatic hypocalcemia in case of hypocalcemia-related symptoms such as perioral or fingertip paresthesias or numbness, positive Chvostek's or Trousseau's sign, and cramping.

All patients were also divided into four groups according to the preoperative serum vit D levels, as described previously (8): (I) severely deficient (<10 ng/mL), (II) deficient (10-19ng/mL), (III) insufficient (20-29ng/mL), (IV) sufficient (≥30ng/mL).

Diagnostic work-up, surgical treatment and postoperative follow-up

Diagnostic work-up included preoperative ultrasonography and fine-needle aspiration cytology (FNAC) in all patients. All hyperthyroid patients were made euthyroid before surgery. Total thyroidectomy was the surgical treatment of choice; however, dissection of central compartment was only performed in patients who had a diagnosis of papillary thyroid cancer on FNAC preoperatively. Selective lateral neck dissection was not indicated in the study population due to the lack of metastatic finding both clinically and radiologically.

The patients who had serum corrected Ca<8.0 mg/dL and developed signs or symptoms related to hypocalcemia throughout the hospitalization were treated with intravenous calcium gluconate replacement. These patients were also maintained on oral therapy of calcium citrate 1,200 mg with vitamin D 500 IU until at least initial outpatient follow-up (about 15th day of discharge). The patients with persistent hypocalcemia and/or clinical symptoms were also given calcitriol 0.25-0.5 mcg. All patients were followed-up at regular intervals, and hypocalcemia requiring calcium/vit D supplementation throughout 6 months after thyroidectomy was considered as permanent hypocalcemia.

Statistical analysis

The Statistical package for social science (SPSS 21.0 software, IL-Chicago- USA) standard version was used for data analyses. The results of descriptive analysis were presented as mean ± SD/percentages for continuous variables and number/percentage for categorical variables. Mann Whitney U test, Fisher's exact test and Chi-squre test were used to investigate the differences between the groups and subgroups. Binary logistic regression was used to determine the association of independent factors with postoperative hypocalcemia. Significance level was accepted as $p < 0.05$.

RESULTS

A total of 150 patients with a mean age of 47.6 y were included in the study. Of these patients, 128 (85.3%) were female and 22 (14.7%) were male. While 24 (16%) patients received an anti-thyroid medication due to hyperthyroidism at least one year prior to surgery, the remaining 126 (84%) patients had euthyroid disease. All patients underwent total thyroidectomy with (n= 15, 10%) or without (n= 135, 90%) central neck dissection. Benign lesions were identified in 94 patients (62.7%). All malignant lesions were papillary carcinoma, and identified in 56 (37.3%) patients.

Most of the patients (96%) were normocalcemic in the preoperative period. However, five patients had a Ca level higher than 10.5 mg/dL and one patient had a Ca level less than 8.0 mg/dL. These six patients had normal PTH levels. The mean preoperative vit D level was 13.1ng/mL in the entire cohort, and only 7

(4.7%) patients had a sufficient (>= 30 ng/dL) serum vit D level. No patient was hypocalcemic before surgery. While postoperative laboratory hypocalcemia (according to the corrected Ca level) was found in 28 (18.7%) cases, 22 (14.7%) patients developed symptomatic hypocalcemia. All patient characteristics and clinicopathological findings were presented in Table 1.

Postoperative serum Ca levels were found to be significantly lower than preoperative serum Ca levels ($p<0.001$). The mean preoperative vit D levels were 14.8, 10.6, and 8.5 ng/dL in patients with normocalcemia, biochemical hypocalcemia, and clinical hypocalcemia, respectively. There was no significant difference between normocalcemic patients and patients who had biochemical/clinical hypocalcemia in terms of age, gender, hyperthyroidism, central lymph node dissection, final histopathology ($p>0.05$). Preoperative serum Ca level and preoperative vit D level were found significantly different in patients with biochemical/clinical hypocalcemia in comparison to patients with normocalcemia ($p<0.05$). All the statistical analyses of demographic, laboratory and clinicopathological findings between the patients with normocalcemia and the patients with biochemical/symptomatic hypocalcemia were presented in Table 2.

The incidence of biochemical and symptomatic hypocalcemia was also statistically evaluated according

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

Data	n (%)
Age (y*)	47.6±13.29 (18-81)
Gender	
Male	22 (14.6%)
Female	128 (85.4%)
Thyroid function status	
Euthyroid	126 (84%)
Hyperthyroid	24 (16%)
Preoperative Ca (ng/mL)	9.3±0.47 (7.9-11.3)
Preoperative vit D (ng/mL)	13.1±9.9 (3-76.3)
Type of surgery	
Total thyroidectomy alone	135 (90%)
Total thyroidectomy+central dissection	15 (10%)
Final histopathology	
benign	94 (62.7%)
malign	56 (37.3%)
Incidental parathyroidectomy	6 (4%)
Postoperative Ca (ng/mL)	8.2±0.65 (6.7-9.8)
Biochemical hypocalcemia	50 (33,3%)
Symptomatic hypocalcemia	22 (14.6%)

Data are presented as mean ± SD for age, preoperative Ca, preoperative vit D, and postoperative Ca; n (%) for other variables. y: year

Table 2. Comparison of demographic, laboratory and clinicopathological findings between the patients with normocalcemia and the patients with biochemical/simptomatic hypocalcemia

	Normocalcemia (n= 100)	Bio. Hypocalcemia (n= 28)	p	Symp. Hypocalcemia (n= 22)	p
Age	47.8±13.6	44.1±12.02	0.194	50.7±12.52	0.363
Gender					
Male	16 (16%)	3 (10.7%)	0.764	3 (13.6%)	1.000
Female	84 (84%)	25 (89.3%)		19 (86.4%)	
Hyperthyroidism	14 (14%)	4 (14.3%)	1.000	6 (27.3%)	0.198
Preoperative Ca (mg/dL)	9.4±0.47	9.1±0.34	**0.002**	9.08±0.42	**0.001**
Preoperative vit D (ng/mL)	14.8±11.25	10.6±5.04	**0.006**	8.5±5.02	**0.000**
central dissection	10 (10%)	3 (10.7%)	1.000	2 (9.1%)	1.000
Final pathology			0.388		0.311
benign	66 (66%)	16 (57.1%)		12 (54.5%)	
malign	34 (34%)	12 (42.9%)		10 (45.5%)	
Inc. parathy*	6 (6%)	0	0.338	0	0.590
Postoperative Ca(mg/dL)	8.6±0.44	7.6±0.27	**0.000**	7.3±0.32	**0.000**

Abbrevations: Inc. parathy: Incidental parathyroidectomy, Bio: Biochemical, Symp: Symptomatic

Table 3. The incidence of biochemical and symptomatic hypocalcemia according to the four vit D categories

	Sufficient (≥30 ng/mL)	Insufficient (20-29 ng/mL)	Deficiency (10-19 ng/mL)	S*. deficiency (<10 ng/mL)
Number of patients	7 (4.7%)	15 (10%)	59 (39.3%)	69 (46%)
Normocalcemia	7 (100%)	12 (80%)	44 (74.6%)	37 (53.6%)
Biochemical hypocalcemia	0	2 (13.3%)	12 (20.3%)	14 (20.3%)
Symptomatic hypocalcemia	0	1 (6.7%)	3 (5.1%)	18 (26.1%)

*S: Severe

to the four vit D categories (Table 3).There was a significant difference between these groups in terms of laboratory (p=0.009) and symtomatic hypocalcemia (p=0.004).

When patients were divided into two subgroups according to the 20 ng/mL cut-off value of vit D, there was a significant difference in the incidence of biochemical hypocalcemia (p= 0.048) while no significant difference was found in terms of incidence of clinical hypocalcemia (p= 0.200).

On the other hand, when vit D level of 10 ng/mL was accepted as cut-off value, patients who had <10 ng/mL vit D level(severe deficiency of vit D) developed significantly more biochemical and clinical hypocalcemia than the patients with serum vit D level higher than 10 ng/mL (p= 0.030 and p<0.001, respectively).

The incidence of biochemical and symptomatic hypocalcemia was also statistically compared between the patients who had <10 ng/mL vit D level and those with 10-19 ng/mL vit D level. Both the incidence of laboratory hypocalcemia and of clinical hypocalcemia were significantly higher in the patients with severely deficient serum vit D than in the patients with 10-19 ng/mL levels of vit D (p= 0.017 and p= 0.002, respectively).

Finally, multiple logistic regression analysis was performed to assess whether preoperative serum vit D level (using the cutoff value of 10ng/mL) was an independent predictor of postoperative biochemical and clinical hypocalcemia. However, analyses showed that <10 ng/mL vit D level was not an independent predictor of both biochemical and clinical hypocalcemia after total thyroidectomy(p>0.05).

DISCUSSION

Although hypocalcemia is a common complication following thyroidectomy, it is usually temporary, and only 1-3% of the patients develop permanent hypocalcemia which is defined as ongoing hypocalcemia within 6 months after surgery (9). Similarly, 47.9% of the patients developed postoperative hypocalcemia (both biochemical and symptomatic) in our study consistent with the previous reports, and only one patient was diagnosed as permanent hypocalcemia due to the need of Ca supplementation 6 months after surgery. The etiology of postoperative hypocalcemia is often multifactorial, but hypoparathyroidism as a result of the accidental removal, injury or devascularization of the parathyroid glands during surgery is responsible for the majority of cases (10). Whatever the reason, hypocalcemia, particularly severe or permanent form of negatively affecting the quality of life, is an extremely annoying condition for both surgeons and patients. In addition, hypocalcemia leads to a longer hospital stay, extra medication, laboratory tests and outpatient visits, which are associated with increase in health costs. Several risk factors including old age, female sex, experience of the surgeon, identification of a greater numbers of parathyroid glands, presence of thyroiditis, surgery for intrathoracic or large goiter, hyperthyroidism (Graves' disease), cancer, central lymphadenectomy, reinterventions have been documented for the development of postoperative hypocalcemia (11-14). In our study, age, gender, hyperthyroidism, malignancy and central compartment dissection were not found to be statistically associated with the development of postoperative hypocalcemia.

It is well known that hypocalcaemia typically occurs at 24-48 h after thyroidectomy, and may be delayed until the fourth postoperative day in a small number of patients (10). Although most of the patients undergoing thyroid surgery can be uneventfully discharged one day after the operation, a concern regarding hypocalcemia leads to prolongation of hospitalization. This approach which is unnecessary most of the time causes increased health costs and decreased patient satistification. Therefore, a single and easy-to-use indicator of postoperative hypocalcemia can be very useful in routine practice.

In this perspective, the potential role of preoperative serum vit D level in predicting hypocalcemia after thyroid surgery has been examined

with a great interest in the recent studies (6, 7, 13, 15). The background of this idea depended on the crucial role of vit D in Ca metabolism. Vit D is a fat-soluble vitamin, and derived from cholesterol. Exposure to sunlight and intake of foods containing vit D are essential to obtain sufficient serum levels of this nutrient. Its active form syntesized in kidney by a PTH-dependent process is responsible for increase in gastrointestinal absorption of Ca and renal resorption of Ca and phosphate (16). Serum level less than 20 ng/mL is generally accepted as deficiency of vit D, which is a common condition in Turkey as well as in the other parts of the world (8, 17). As previously reported, vit D deficiency has been associated with various pathological conditions such as bone disease, obesity, cancer, lipid metabolism disorders, diabetes mellitus, and cardiovascular diseases (18, 19). Besides, vit D deficiency leads to secondary hyperparathyroidism that is characterized with hypocalcemia and hyperphosphatemia. Therefore, it can be suggested that patients who have deficiency of vit D may prone to develop hypocalcemia after thyroid surgery.

The clinical studies which examined the association of preoperative vit D status with postoperative hypocalcemia reported diverse results. In a study with 152 patients undergoing near-total thyroidectomy, vit D was not found as a predictor of postoperative hypocalcemia. However, Ca and vit D supplementation were routinely given to those patients postoperatively (15). Chia *et al.* also reported that there was no association between the preoperative vit D level and postoperative hypocalcemia, but their study population mainly consisted of patients undergoing parathyroidectomy (20). Similarly, Griffin *et al*. found no correlation between vitamin D and risk of postoperative hypocalcemia (21). However, they included both patients with total thyroidectomy and patients who had completion thyroidectomy in their work. In a recent study from Iran, vit D deficiency was not found to have a significant effect on hypocalcemia after thyroidectomy. However, vit D deficiency was defined as serum Vit D level less than 10 ng/mL in that study, and the patients was divided into two groups by using cut-off value of 10 ng/mL (22). Although definition of vit D deficiency can vary among the different parts of the world, a cut-off value of 10 ng/mL seems to be very low for the classification of patients in terms of vit D status. In fact, 20 ng/mL is generally accepted as a cut-off value of vit D deficiency by the majority of medical centers in the world (8, 23).

Contrary to the reports mentioned above, there are also a small number of clinical studies indicating an association between preoperative vit D status and postoperative hypocalcemia. In one of those, a significant difference in the incidence of hypocalcemia after total thyroidectomy was shown between the patients with vit D >20ng/ml and the patients with vit D<10ng/ml. The authors also reported that lower levels of vit D were associated with delay in patient's discharge because of hypocalcemia treatment (6). Similarly, Erbil *et al.* showed that a preoperative serum vit D level less than 15 ng/mL, a postoperative serum PTH level less than 10 pg/mL, and age above 50 were the predictive factors of postoperative hypocalcemia after total thyroidectomy for nontoxic multinodular goiter (24). In another study by Díez *et al.*, vit D<30 ng/mL and PTH<13 pg/mL were found to have independent prognostic values on the risk of hypocalcemia after total thyroidectomy for benign goiter (25). It should be stated here that the present study was only designed on the association between preoperative vit D status and the incidence of postoperative hypocalcemia. Preoperative or postoperative PTH value was not a routine biochemical parameter in all patients included in the study. Therefore, PTH was excluded from the statistical analysis due to irregular medical records. On the other hand, our results clearly showed that there is a significant association between vit D status and hypocalcemia after total thyroidectomy. Different cut-off values of vit D have reported in the studies investigated the relationship of vit D status and the incidence of hypocalcemia following thyroid surgery (6, 24, 25). In our work, we found that serum vit D level less than 20ng/mL was only associated with biochemical hypocalcemia, but vit D level less than 10ng/mL was an independent risk factor for the development of postoperative hypocalcemia, consistent with the study by Kirkby (6).

In conclusion, our study suggested that vit D status had a significant effect on the incidence of hypocalcemia after total thyroidectomy. Although postthyroidectomy hypocalcemia is multifactorial, vit D deficiency, particularly severe form, is significantly associated with the development of biochemical and clinical hypocalcemia. Vit D supplementation can prevent this unwanted complication in such patients.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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