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Does preoperative vitamin D deficiency delay recovery time from transient hypocalcemia after thyroidectomy?

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ABSTRACT

Aim: To investigate the relationship between preoperative vitamin D deficiency and the recovery/healing time from postoperative hypoparathyroidism or hypocalcemia.

Material and Method: The sample consisted of patients that underwent thyroidectomy and preoperative 25-hydroxy-vitamin D analysis between 2014 and 2018 at the General Surgery Clinic of Health Sciences University Ankara Numune Training and Research Hospital. Of the 1598 patients who underwent total thyroidectomy, 73 were included in the study. These patients were selected from 214 patients who developed postoperative hypocalcemia. The patients' demographic characteristics, surgical indications, operative findings, postoperative pathology results, preoperative and postoperative biochemical parameters and clinical outcomes were retrospectively obtained from the electronic records.

Results: Of the 73 patients included in the study, 10 (13.7%) were male and 63 (86.3%) were female. Preoperative vitamin D level was normal in 16 patients and deficient in 57. The patients were divided into two groups: Group 1 with normal preoperative vitamin-D levels and Group 2 with vitamin D deficiency. There was no statistically significant difference between Groups 1 and 2 in terms of parathormone (months 1, 2 and 3) and calcium levels ($p>0.05$); however, preoperative vitamin D levels statistically significantly differed between the two groups.

Conclusion: Our study suggests that having a normal level of vitamin D or deficiency does not have significant effect on the recovery time from hypocalcemia after thyroidectomy. Therefore, we consider that it is not necessary to measure vitamin D in routine preoperative screening or apply a vitamin D replacement.

Keywords: Preoperative vitamin D level, transient hypocalcemia, postoperative parathormone level

INTRODUCTION

Hypoparathyroidism and hypocalcemia are well-known complications after thyroidectomy (1). However, most studies on the improvement of parathyroid function after thyroidectomy have a limited sample size or report the outcomes over a short observation period after surgery (2). Some researchers found that the recovery time of parathyroid function after thyroidectomy may take more than one year (3). This duration is becoming longer in parallel to the increased incidence of thyroid cancer observed in recent years (4). In the literature, the risk of developing this complication has been determined to vary between 1 and 50% (5).

In Turkey, of the population living in different regions, more than 30% have vitamin D deficiency (6). Low vitamin D induces calcium absorption by increasing calcium reabsorption in the kidney. This may result in increased parathormone (PTH) levels and compensatory hyperparathyroidism, which maintain normal calcium levels (7). Most patients who develop postoperative hypocalcemia recover within a few months, but the course of symptomatic hypocalcemia may be catastrophic since it can lead to prolonged hospitalization or re-hospitalization (8).

Post-thyroidectomy hypocalcemia is the most common complication of thyroidectomy and can cause transient or permanent hypocalcemia(9). Despite many studies investigating postoperative hypocalcemia, conflicting results have been obtained concerning the effect of preoperative vitamin D deficiency on postoperative

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hypocalcemia (10). Some researchers have shown that vitamin D deficiency is correlated with postoperative hypocalcemia, and thus require a longer hospital stay (11). The best indicator of Vitamin D status in tissues is serum 25-hydroxyvitamin D level(12) .Various cut off values for vitamin D deficiency have been accepted by different organizations and authors (13). Vitamin D deficiency, which is a global health problem, is generally defined as serum 25-hydroxyvitamin D levels less than 20 ng/mL (14). In studies undertaken in Turkey, the optimal values for vitamin D have also been accepted as >20 ng/ml (15). In this study, we aimed to investigate the association between vitamin D deficiency and the recovery time from postoperative hypoparathyroidism and hypocalcemia.

MATERIAL AND METHOD

Patient Data

In this study, the data obtained from the electronic records of all patients who underwent thyroidectomy between 2014 and 2018 at the General Surgery Clinic of Ankara Numune Training and Research Hospital were retrospectively utilized. This retrospective study was approved by Health Sciences University, Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (Date: 28.03.2019, Decission No: E.Kurul-E-19-2631/2631). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Of the 1598 patients who underwent total thyroidectomy, 73 were included in the study. These patients were selected from 214 patients who developed postoperative hypocalcemia. The demographic features, surgical indications, operative findings, postoperative pathology results, preoperative and postoperative biochemical parameters, and clinical outcomes of the patients were noted. Only patients for whom a preoperative 25-hydroxy-vitamin D analysis was undertaken and who developed hypocalcemia after thyroidectomy were included in the study. Vitamin D deficiency was defined as vitamin D levels of <20 ng/mL. In addition, the postoperative thresholds were accepted as <8 mg/dl for serum calcium levels and <14 pg/ml for PTH (PTH reference values of our hospital: 15-65 pg/ml) (16). Normal parathyroid function was defined as a normal PTH value in asymptomatic patients who did not require replacement therapy. Excluded from the study were patients with chronic kidney disease or history of parathyroidectomy, those supplemented with calcium or vitamin D, and those who underwent surgery due to a recurrent benign or malignant disease and patients who underwent thyroidectomy for primary hyperparathyroidism. There were no patients with permanent hypoparathyroidism that matched the specified criteria.

Statistical Analysis

All data were analyzed using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). The data of continuous variables were given as mean±standard deviation (SD). Categorical data were obtained as frequency with percentages. The Mann-Whitney U test was used to compare the continuous variables depending on data distribution, and the chi-square test or Fisher's exact test was employed for categorical variables. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 73 patients included in the study, 10 (13.7%) were male and 63 (86.3%) were female. The median (IQR) age was 49 (38-55) years. The preoperative vitamin D level was normal in 16 patients and deficient in 57. The patients were divided into Group 1 with normal preoperative vitamin D levels and Group 2 with vitamin D deficiency. The indications for thyroidectomy were as follows: nodular goiter in 47 patients (64.4%), differentiated thyroid cancer+undifferentiated thyroid cancer in 21 patients (28.8%), Graves' disease in one patient (1.4%), and toxic multi-nodular goiter in four patients (5.5%). The types of operation performed were thyroidectomy (n=50; 68.5%), thyroidectomy+central lymph node dissection (CLND) (n=15; 20.5%), completion thyroidectomy (n=1; 1.4%), and thyroidectomy+CLND+lateral neck dissection (n=7; 9.6%) (**Table 1**). The median (IQR) value of incidental parathyroid excision was 0.0 (0-1). The mean duration of hospitalization was 3.95 (1-14) days.

Table 1. Features of the patients

Feature	n (%)
Sex	
Male	10 (13.7)
Female	63 (86.3)
Age- Median (IQR)	49 (38-55)
Indication	
Nodular Goiter	47 (64.4)
DTC and UDTC	21 (28.8)
Graves' Disease	1 (1.4)
Toxic MNG	4 (5.5)
Operation type	
Thyroidectomy	50 (68.5)
Thyroidectomy +CLND	15 (20.5)
Completion Thyroidectomy	1 (1.4)
Thyroidectomy +CLND +LND	7 (9.6)
Excised Parathyroid count- Median (IQR)	0.0 (0-1)
Hospital stay (day)- Mean (Min-Max)	3.95 (1-14)

IQR: Interquartile range, DTC: Differentiated thyroid cancer, UDTC: Undifferentiated thyroid cancer, MNG: Multi-nodular goiter, CLND: Central lymph node dissection, LND: Lateral neck dissection.

Table 2 presents the demographic distribution of the patients in Group 1 (n=16) and Group 2 (n=57). The PTH values at postoperative months 1, 2 and 3 were 16.50 (10.80-33.60), 22.45 (12.30-43.60) and 25.75 (13.05-38.30), respectively for Group 1 and 19 (10.55-30.25), 23.20 (13.20-32.20) and 25.95 (19.80-35.40), respectively for Group 2. The calcium values at postoperative months 1, 2 and 3 were measured as 9.16 (8.73-9.57), 8.90 (8.21-9.26) and 8.7 (8.12-9.25), respectively for Group 1 and 8.81 (8.25-9.48), 8.54 (8.14-9.14) and 8.76 (8.18-9.09), respectively for Group 2. There was no statistically significant difference between Groups 1 and 2 in terms of PTH (months 1, 2 and 3) and calcium levels in the postoperative period (p>0.05). However, the preoperative vitamin D level statistically significantly differed between the two groups (**Table 3**).

Table 2. Patient characteristics according to groups

	Normal Vitamin D Levels Group 1 n (%)	Vitamin D Deficiency Group 2 n (%)
Sex		
Male	1 (6.3)	9 (15.8)
Female	15 (93.8)	48 (84.2)
Age- Mean (IQR)	46 (32.5-59)	49
Indication		
Nodular Goiter	12 (75)	35 (61.4)
DTC and UDTC	4 (25)	17 (29.8)
Graves' Disease	0 (0)	1 (1.8)
Toxic MNG	0 (0)	4 (7)
Operation Type		
Thyroidectomy	11 (68.8)	39 (68.4)
Thyroidectomy +CLND	2 (12.5)	13 (22.8)
Completion Thyroidectomy	0 (0)	1 (1.8)
Thyroidectomy +CLND +LND	3 (18.8)	4 (7)
Excised Parathyroid Count-Median (IQR)	0.50 (0-1.50)	0 (0-1)
Hospital Stay (day)-Mean (Min-Max)	3 (2-4)	4 (2-5)

IQR: Interquartile range, DTC: Differentiated thyroid cancer, UDTC: Undifferentiated thyroid cancer, MNG: Multi nodular goiter, CLND: Central lymph node dissection, LND: Lateral neck dissection.

DISCUSSION

Recently, many studies have been conducted to determine the preoperative factors predicting the development of hypocalcemia after thyroidectomy. The causes of hypocalcemia after thyroidectomy are multifactorial, including injury, devascularization, inadvertent excision of parathyroid glands, number of remaining functional glands, scope of surgery, experience of the surgeon, hyperthyroidism, retrosternal goiter, concurrent neck dissection, and thyroid carcinoma (17). During thyroidectomy, incidental parathyroidectomy is not uncommon. Almost half of the parathyroid glands are intrathyroidal, and therefore iatrogenic parathyroidectomy is inevitable (18). The question of how many parathyroid glands should be preserved to maintain normal serum calcium levels remains controversial. Several studies claimed that a single functional gland is sufficient for normal parathyroid activity, but other researchers recommended preserving at least three glands (19, 20).

In the literature, there is also no consensus on how to best define the recovery of parathyroid gland function. Some studies consider a euparathyroid state even in the absence of hypocalcemia symptoms if the serum PTH levels rise to at least 10 pg/mL (2). At the same time, it can be stated that the function of the parathyroid gland is improved when therapeutic calcium or calcitriol supplements are no longer required to prevent hypocalcemia symptoms. Another way of defining the improvement of parathyroid gland function is based on the serum PTH level being within the normal range.

Vitamin D, PTH and calcitonin have a critical role in calcium homeostasis. Therefore, the serum vitamin D level after thyroidectomy is expected to be associated with hypocalcemia; however, this assumption remains controversial (21). For example, some authors reported that preoperative vitamin D deficiency was responsible

Table 3. Laboratory parameters of patients according to groups

	Normal Vitamin D Levels Group 1- Median (IQR)	Vitamin D Deficiency Group 2- Median (IQR)	p value
Postoperative PTH (ng/mL)	5.30 (3.5-6.6)	4.55 (1.8-7.2)	0.382
PTH month 1	16.5 (10.8-33.6)	19 (10.55-30.25)	0.970
PTH month 3	22.45 (12.3-43.6)	23.20 (13.2-32.2)	0.860
PTH month 6	25.75 (13.05-38.3)	25.95 (19.8-35.4)	0.789
Preoperative Ca (mg/dl)	9.49 (9.02-9.64)	9.35 (9.12-9.6)	0.989
Postoperative Ca (mg/dl)	7.57 (7.33-7.82)	7.66 (7.26-7.89)	0.714
Ca month 1	9.16 (8.73-9.57)	8.81 (8.25-9.48)	0.244
Ca month 3	8.9 (8.21-9.26)	8.54 (8.14-9.14)	0.340
Ca month 6	8.7 (8.12-9.25)	8.76 (8.18-9.09)	0.849
Preoperative vitamin D (pg/mL)	27.34 (24.3-40.97)	10.23 (8.38-13.52)	0.000*
Postoperative dose of Ca replacement (g)	1 (1-1)	1 (1-1)	
Postoperative dose of Calcitriol treatment (mcg)	1 (0.5-1)	0.5 (0-0.5)	

IQR: Interquartile range, PTH: Parathyroid hormone, Ca: Calcium

for the development of postoperative hypocalcemia (22), in contrast to others suggesting that preoperative vitamin D levels did not predict postoperative hypocalcemia, and therefore it was not necessary include this analysis in routine preoperative screening (16). In Turkey, more than 30% of different sample groups are reported to have vitamin D deficiency (6). Inadequate calcium absorption due to low concentrations of vitamin D results in an increase in PTH secretion, which, in turn, induces calcitriol synthesis and increases calcium absorption (23). This was also confirmed by another study reporting that vitamin D deficiency decreased intestinal calcium absorption and stimulated PTH synthesis and secretion to maintain normal calcium levels (24). Parathyroid glands need to be preserved in patients undergoing thyroidectomy or different surgery to increase PTH synthesis and secretion due to vitamin D deficiency. All these findings support the hypothesis that a normal or deficient level of vitamin D cannot prevent the development of postoperative hypocalcemia in the absence of healthy, functioning parathyroid glands.

There are many studies in the literature exploring the factors affecting transient hypocalcemia following thyroidectomy. For example, in their follow-up of 1,054 cases, Ritter et al. (21) showed that 18% of the patients developed transient hypoparathyroidism, of whom 70% recovered in two months and 5% in 12 months, but progression to permanent hypoparathyroidism was observed in 1.9%. A meta-analysis by Edafe et al. reported that the incidence of transient and permanent hypocalcemia was 27% (19%–38%) and 1% (0%–3%), respectively (9). However, only limited amount of research has been undertaken to investigate the effect of preoperative vitamin D deficiency or the normal level of this vitamin on the recovery process of this condition. Most patients with parathyroid dysfunction return to normal function within a few weeks or one month after surgery (25). We considered that the delayed recovery of parathyroid function might be due to a slow but steady increase in blood flow through neovascularization that occurs on the small surface area of the remaining parathyroid. Our study showed that preoperative vitamin D deficiency or normal level had no significant relationship with recovery time from postoperative hypocalcemia and PTH and calcium levels at postoperative months 1, 2 and 3 ($p>0.05$).

In the literature, many factors have been implicated as etiologic causes of postoperative hypocalcemia. One of the most important factors involved in postoperative calcium hemostasis is the continuation of PTH secretion, and therefore parathyroid glands should be intraoperatively preserved for the secretion of this hormone. For this reason, it is crucial for hemostasis to well define the location of parathyroid glands and preserve them during surgery. Considering that in the literature, approximately half of the glands are reported to be located in the thyroid tissue, hypocalcemia is frequently observed among thyroidectomy cases. In a meta-analysis of four studies and 1,482 patients, it was shown that parathyroid excision was significantly associated with transient hypocalcemia (26). In the current study, thyroidectomy or completion thyroidectomy was performed on many patients, and some cases required additional lymph node dissections. The risk of postoperative hypocalcemia varies depending on the type or difficulty of surgery. Recent studies have shown no significant relationship between preoperative vitamin D levels and postoperative hypocalcemia (10,21,27). In contrast, in their study with 30 patients (12 with vitamin D deficiency and 18 with normal vitamin D levels), Alkhalili et al. (22) reported that preoperative vitamin D deficiency was associated with postoperative hypocalcemia. In a systematic review and meta-analysis of observational study, Konstantina et al. reported that patients with preoperative vitamin D deficiency had an increased risk of transient hypoparathyroidism following thyroidectomy, while those with severe vitamin D deficiency had an increased risk of permanent hypoparathyroidism (28).

Most studies concerning the improvement of parathyroid function after thyroidectomy are limited in terms of sample size or duration of the postoperative follow-up period (29). The process of improvement of the parathyroid function and the variables affecting this process are still poorly understood, and therefore requires further research. More studies are necessary to clarify this multifaceted physiological mystery.

One limitation of this study is that it has a relatively small sample size. Our clinic serves a geographical area containing a significant immigrant population. Therefore, there may be problems in the effective follow-up of patients.

CONCLUSION

This study suggests that neither a normal nor a deficient level of vitamin D has a significant effect on the recovery time from hypocalcemia after thyroidectomy. Therefore, we consider that it is not necessary to measure vitamin D in routine preoperative screening or apply vitamin D replacement.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University, Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (Date: 28.03.2019, Decision No: E.Kurul-E-19-2631/2631).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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