

Predictive Value of Age and Serum Parathormone and Vitamin D₃ Levels for Postoperative Hypocalcemia After Total Thyroidectomy for Nontoxic Multinodular Goiter

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Hypothesis: Age, postoperative serum parathormone (PTH) level, and preoperative serum 25-hydroxyvitamin D₃ (25-OHD) level predict postoperative hypocalcemia after total thyroidectomy.

Design: Prospective clinical trial.

Setting: Tertiary referral center.

Patients: One hundred thirty patients with nontoxic multinodular goiter. Patients were divided into 2 groups according to the postoperative serum calcium level. Group 1 (n=32) consisted of patients with a postoperative serum calcium level of 8 mg/dL or less, and group 2 (n=98) consisted of patients with a postoperative serum calcium level higher than 8 mg/dL.

Interventions: The preoperative serum 25-OHD level and preoperative and postoperative serum calcium and PTH levels were determined.

Main Outcome Measures: The number of patients developing hypocalcemia and prediction of postopera-

tive hypocalcemia by the serum 25-OHD and PTH levels.

Results: Hypocalcemia developed in 32 patients (24.6%) (group 1). The preoperative serum 25-OHD level and postoperative serum calcium and PTH levels in group 1 were significantly lower than in group 2 ($P = .001$). With logistic regression analysis, factors that were predictive of postoperative hypocalcemia included a preoperative serum 25-OHD level less than 15 ng/mL ($P < .001$; odds ratio, 558.5), a postoperative serum PTH level less than 10 pg/mL ($P = .01$; odds ratio, 16.4), and being older than 50 years ($P = .01$; odds ratio, 4.6).

Conclusions: Age, a low preoperative serum 25-OHD level, and a low postoperative serum PTH level are significantly associated with postoperative hypocalcemia. The low preoperative serum 25-OHD level was more significant than the low postoperative serum PTH level in the prediction of postoperative hypocalcemia.

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THYROIDECTOMY IS ONE OF the most frequent operations performed for patients with nontoxic multinodular goiter. The goals of surgical treatment in thyroid disease should be to eliminate the disease with low complication rates and to minimize reoperation for incidental thyroid carcinoma in multinodular goiter.¹⁻⁵ In recent years, total thyroidectomy (TT) and near-total thyroidectomy have emerged as surgical options in the surgical treatment of patients with nontoxic multinodular goiter, especially in endemic iodine-deficient regions.⁶⁻¹⁰ Transient hypocalcemia is the most frequent complication after TT and continues to challenge even the experienced surgeon.¹¹⁻¹⁵ The etiology of hypoparathyroidism seems to be a multifactorial phenomenon, but the most important factors are the iatrogenic surgical trauma

to parathyroid glands, the extent of surgery, the experience of the surgeon, and the number of functioning glands left behind. Among the potential factors causing this, a decrease of serum calcium in hungry bone syndrome is implicated in patients with hyperthyroidism. The postoperative reversal of osteodystrophy and the deposition of calcium in bones may also contribute to a decreased serum calcium level.¹¹⁻¹⁴

Vitamin D₃ has a critical role in calcium homeostasis. After it is acquired by either sunshine or diet, it is converted to 25-hydroxyvitamin D₃ (25-OHD) in the liver. Serum 25-OHD is supposedly biologically inactive. However, it is the most reliable parameter reflecting the vitamin D₃ status of the body. Serum 25-OHD is hydroxylated in the kidney to 1,25-dihydroxyvitamin D₃ (calcitriol), which is the active metabolite of vitamin D₃ that binds to a nuclear receptor. Interaction

with genomic DNA reveals the biological effects of vitamin D₃, ie, increased intestinal calcium and phosphate absorption, decreased parathormone (PTH) secretion, and increased osteoclastic differentiation. 1 α -Hydroxylation and production of active vitamin D₃ in the kidney are stimulated by increased PTH concentrations.¹⁶⁻¹⁸

Recently, several investigators¹⁹⁻²² have suggested that intraoperative or postoperative serum PTH levels are early predictors of the development of postoperative hypocalcemia after TT. The aims of this prospective clinical study are the following: (1) to evaluate the accuracy of age and postoperative serum PTH levels to predict patients at risk for postoperative hypocalcemia; and (2) to suggest that the preoperative serum vitamin D₃ level might predict the development of hypocalcemia after total thyroidectomy. To our knowledge, this is the first prospective study performed to detect the value of the serum 25-OHD level to predict postoperative hypocalcemia after TT.

METHODS

PATIENTS

In the Department of Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, 130 consecutive patients with nontoxic multinodular goiter treated by bilateral TT from January 1, 2005, to December 1, 2005, were included prospectively in this study. Patients having hyperthyroidism, substernal goiter or a previous thyroid or neck operation, and concomitant parathyroid disease were excluded. No patients underwent bone mineral density measurement. However, no patients had signs or symptoms indicating metabolic bone disease or were receiving medications known to affect serum calcium metabolism such as oral calcium and vitamin D supplementation, antiresorptive agents, hormone replacement therapy for postmenopausal women, anabolic agents, thiazide-type diuretics, and antiepileptic agents. The study plan was reviewed and approved by our institutional ethical committee, and informed consent was obtained from all of the patients.

Serum calcium, PTH, 25-OHD, alkaline phosphatase, creatinine, and albumin levels were determined the day before surgery. Serum PTH and calcium levels were measured 12 hours postoperatively, and measurements of serum calcium levels were repeated 24 hours postoperatively. The lowest postoperative serum calcium level was determined for all of the patients. The serum calcium concentration was adjusted for serum albumin concentration. The main indications for surgery were large goiter with compressive effect to all of the patients. Total thyroidectomy was performed by experienced endocrine surgeons (Y.E., A.B., S.O., and S.T.) and is defined as total bilateral extracapsular thyroidectomy. Recurrent laryngeal nerves were carefully identified and dissected. We attempted to identify all parathyroid glands and preserve them with meticulous dissection for their blood supply. For this reason, all of the vessels were ligated close to the thyroid gland, especially the branches of the inferior thyroid artery. Where we could not identify lower parathyroid glands, we did not dissect the thymus or the thyrothymic ligament to find unexposed glands. No biopsies were taken from parathyroids. There were no patients with damaged parathyroid glands autotransplanted into the sternocleidomastoid muscle. Signs of ischemia of parathyroid glands were not observed during the operations. In the histopathologic examination of the resected thyroid tissue, parathyroid tissue was not identified.

One hundred thirty patients were divided into 2 groups according to the postoperative calcium level. Patients in group 1 (n=32) had a postoperative serum calcium level of 8 mg/dL or

less, whereas patients in group 2 (n=98) had a serum calcium level higher than 8 mg/dL (to convert milligrams per deciliter to millimoles per liter, multiply by 0.25). Hypocalcemia was defined as a serum calcium concentration of 8 mg/dL or less. Asymptomatic hypocalcemia was a laboratory finding, whereas symptomatic hypocalcemia had clinical symptoms besides laboratory findings. The presence of clinical symptoms or signs of hypocalcemia were reported, and they included facial paresthesia, positive Chvostek or Trousseau signs, and muscular spasm. The serum calcium level of patients with hypocalcemia was measured every 12 hours until the serum calcium level stabilized. All of the patients who developed asymptomatic hypocalcemia were treated with oral calcium (3-6 g/d). Symptomatic hypocalcemia was treated with parenteral calcium and an oral calcitriol supplementation of 1.0 to 1.5 μ g/d. Those patients with asymptomatic hypocalcemia were discharged with oral calcium, whereas patients with symptomatic hypocalcemia were discharged with oral calcium and/or calcitriol at doses modified in relation to the serum calcium concentration and were followed up weekly until their serum calcium and PTH levels normalized.

BIOCHEMICAL ANALYSIS

Serum calcium, alkaline phosphatase, creatinine, and albumin levels were determined by an autoanalyzer (Cobas Integra 800; Roche Diagnostics, Basel, Switzerland). Serum 25-OHD and PTH levels were determined by immunoradiometric assay using commercially available kits—the PTH 120-minute immunoradiometric assay kit and the 25-OHD radioimmunoassay kit, respectively (BioSource Europe SA, Nivelles, Belgium). Reference ranges of biochemical parameters were as follows: 8.5 to 10.5 mg/dL for serum calcium; 90 to 260 U/L for serum alkaline phosphatase (to convert units per liter to microkatal per liter, multiply by 0.0167); 0.6 to 1.5 mg/dL for serum creatinine (to convert milligrams per deciliter to micromoles per liter, multiply by 88.4); 3.5 to 5.0 g/dL for serum albumin (to convert grams per deciliter to grams per liter, multiply by 10); 6 to 46 ng/mL for serum 25-OHD (to convert nanograms per milliliter to nanomoles per liter, multiply by 2.496); and 10 to 65 pg/mL for serum PTH (to convert picograms per milliliter to nanograms per liter, multiply by 0.1053).

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 11.0 statistical software for Windows (SPSS, Inc, Chicago, Illinois). Results were expressed as mean (standard deviation). Comparisons of data were done by Wilcoxon signed rank test, χ^2 test, and logistic regression analysis. Results were considered statistically significant at $P < .05$ (2-tailed).

RESULTS

The mean (SD) age was 48.2 (11.5) years (range, 17-67 years) for 130 patients. The female to male ratio was 7.6:1 (n=115 and 15, respectively). The mean (SD) preoperative levels of serum albumin, creatinine, calcium, PTH, alkaline phosphatase, and 25-OHD were 3.8 (0.6) g/dL, 0.8 (0.2) mg/dL, 8.7 (0.3) mg/dL, 38.3 (8.4) pg/mL, 174.6 (88.7) U/L, and 18.2 (14.3) ng/mL, respectively. The mean (SD) postoperative serum calcium and PTH levels were 8.3 (0.8) mg/dL and 31.4 (15.6) pg/mL, respectively. Postoperative serum calcium and PTH levels were lower than preoperative serum calcium and PTH levels (both $P = .001$) (**Table 1**).

Table 1. Demographic and Biochemical Parameters of the Patients^a

Parameter	Mean (SD)	Range
Age, y	48.2 (11.5)	17-67
Preoperative serum albumin, g/dL	3.8 (0.6)	3.2-4.3
Preoperative serum creatinine, mg/dL	0.8 (0.2)	0.7-1.3
Preoperative serum calcium, mg/dL	8.7 (0.3)	8.0-9.5
Postoperative serum calcium, mg/dL	8.3 (0.8) ^b	6.0-9.5
Preoperative serum PTH, pg/mL	38.3 (8.4)	19.0-56.0
Postoperative serum PTH, pg/mL	31.4 (15.6) ^b	5.0-56.0
Preoperative serum ALP, U/L	174.6 (88.7)	67.0-356.0
Preoperative serum 25-OHD, ng/mL	18.2 (14.3)	5.0-53.0

Abbreviations: ALP, alkaline phosphatase; PTH, parathormone; 25-OHD, 25-hydroxyvitamin D₃.

SI conversion factors: For albumin, to convert grams per deciliter to grams per liter, multiply by 10. For creatinine, to convert milligrams per deciliter to micromoles per liter, multiply by 88.4. For calcium, to convert milligrams per deciliter to millimoles per liter, multiply by 0.25. For PTH, to convert picograms per milliliter to nanograms per liter, multiply by 0.1053. For ALP, to convert units per liter to microkatal per liter, multiply by 0.0167. For 25-OHD, to convert nanograms per milliliter to nanomoles per liter, multiply by 2.496.

^a Among the patients, 115 were female and 15 were male.

^b $P < .01$ compared with preoperative calcium and PTH levels.

There was no operative mortality. The incidence of transient vocal cord paralysis was 5.3% (7 of 130 patients). Persistent vocal cord paralysis and hypoparathyroidism were not encountered in our series. In the histopathologic evaluation, papillary thyroid cancer was detected in 15 patients (11.5%), of whom 13 (86.6%) had papillary microcarcinoma (≤ 1 cm). The mean (SD) size of the tumor was 4.6 (3.3) mm (range, 2-13 mm). Four patients had thyroid capsule invasion and 3 patients had vascular invasion. Papillary thyroid carcinoma was multifocal in 3 patients. Those patients with papillary thyroid carcinoma were classified as a low-risk group.

POSTOPERATIVE HYPOCALCEMIA

In 32 of 130 patients (24.6%) (ie, group 1), the serum calcium level was found to be less than 8 mg/dL at 12 and 24 hours postoperatively. These patients were noted to have a serum PTH level less than 15 pg/mL (mean [SD], 6.5 [1.6] pg/mL) at 12 hours postoperatively.

Age and the serum alkaline phosphatase level were significantly higher in group 1 when compared with group 2 ($P = .001$). There were no significant differences between the preoperative serum albumin, creatinine, calcium, and PTH levels of groups 1 and 2 ($P > .05$). The preoperative serum 25-OHD level and postoperative serum calcium and PTH levels were significantly lower in group 1 than in group 2 ($P = .001$) (**Table 2**).

Of 32 patients, 22 (68.8%) developed symptomatic hypocalcemia and 10 (31.2%) developed asymptomatic hypocalcemia. The preoperative serum 25-OHD level of the patients with symptomatic hypocalcemia (mean [SD], 5.6 [1.2] ng/mL) was significantly lower than that of patients with asymptomatic hypocalcemia (mean [SD], 16.2 [6.3] ng/mL) ($P = .005$). Hospital stay was significantly longer in group 1 (mean [SD], 3.6 [1.1] days; range, 2-6 days) compared with group 2 (mean [SD], 1.3 [0.4] days; range,

Table 2. A Comparison of Laboratory Features in Patients With Hypocalcemia and Patients With Normocalcemia

Parameter	Patients With Hypocalcemia (n=32)	Patients With Normocalcemia (n=98)	P Value
Age, mean (SD), y	56.8 (7.6)	38.7 (10.1)	.001
Female/male, No.	28/4	80/18	.44
Preoperative serum calcium, mean (SD), mg/dL	8.9 (0.3)	8.7 (0.3)	.33
Postoperative serum calcium, mean (SD), mg/dL	7.2 (0.2)	8.6 (0.2)	.001
Preoperative serum PTH, mean (SD), pg/mL	37.5 (7.5)	38.4 (7.4)	.47
Postoperative serum PTH, mean (SD), pg/mL	6.5 (1.6)	39.4 (7.3)	.001
Preoperative serum ALP, mean (SD), U/L	267.6 (78.5)	118.7 (33.2)	.001
Preoperative serum 25-OHD, mean (SD), ng/mL	9.7 (3.6)	32.5 (11.2)	.001

Abbreviations: ALP, alkaline phosphatase; PTH, parathormone; 25-OHD, 25-hydroxyvitamin D₃.

SI conversion factors: For calcium, to convert milligrams per deciliter to millimoles per liter, multiply by 0.25. For PTH, to convert picograms per milliliter to nanograms per liter, multiply by 0.1053. For ALP, to convert units per liter to microkatal per liter, multiply by 0.0167. For 25-OHD, to convert nanograms per milliliter to nanomoles per liter, multiply by 2.496.

1-2 days) ($P = .001$). In addition, hospital stay was significantly longer in the patients with symptomatic hypocalcemia (mean [SD], 4.1 [1.2] days; range, 3-6 days) compared with the patients with asymptomatic hypocalcemia (mean [SD], 2.6 [0.5] days; range, 2-3 days) ($P = .004$).

The results of the logistic regression analysis for postoperative hypocalcemia are shown in **Table 3**. Age, postoperative serum PTH level, and preoperative serum 25-OHD level were independent significant variables of the development of hypocalcemia after TT. Patients older than 50 years had a 4.6-fold increased risk of postoperative hypocalcemia (odds ratio, 4.6; 95% confidence interval, 1.3-15.8), patients with a postoperative serum PTH level less than 10 pg/mL had a 16.4-fold increased risk for postoperative hypocalcemia (odds ratio, 16.4; 95% confidence interval, 1.8-143.8), and patients with a preoperative serum 25-OHD level less than 15 ng/mL had a 558.5-fold increased risk for postoperative hypocalcemia (odds ratio, 558.5; 95% confidence interval, 27.6-11 291.9).

Preoperatively, the serum 25-OHD level was 15 ng/mL or less in 77 patients and higher than 15 ng/mL in 53 patients. Postoperative serum calcium and PTH levels in patients with a serum 25-OHD level of 15 ng/mL or less (mean [SD], 8.2 [0.9] mg/dL and 28.3 [16.2] pg/dL, respectively) were significantly lower than in patients with a serum 25-OHD level higher than 15 ng/mL (mean [SD], 8.5 [0.5] mg/dL and 34.6 [13.2] pg/dL, respectively) ($P < .01$). Of the 77 patients with a serum 25-OHD level of 15 ng/mL or less, 24 (31.2%) developed postoperative hypocalcemia; of the 53 patients with a serum 25-OHD level higher than 15 ng/mL, 8 (15.1%) developed postoperative hypocalcemia. The ratio of postoperative hypocalcemia was significantly higher in the patients with a serum 25-OHD level of 15 ng/mL or less than in the patients with a serum 25-OHD level higher than 15 ng/mL

Table 3. Logistic Linear Regression Analysis Between Dependent and Independent Parameters

Dependent Variable	Independent Variable ^a	OR (95% CI)	P Value
Postoperative serum calcium level	Age	4.6 (1.3-15.8)	.01
	Postoperative serum PTH level	16.4 (1.8-143.8)	.01
	Preoperative serum 25-OHD level	558.5 (27.6-11 291.9)	< .001

Abbreviations: CI, confidence interval; OR, odds ratio; PTH, parathormone; 25-OHD, 25-hydroxyvitamin D₃.

^aRisk for developing postoperative hypocalcemia at an age older than 50 years, when the serum PTH level was less than 10 pg/mL (to convert to nanograms per liter, multiply by 0.1053), and when the serum 25-OHD level was less than 15 ng/mL (to convert to nanomoles per liter, multiply by 2.496).

($P < .03$). The ratio of symptomatic hypocalcemia was significantly higher in the patients with a serum 25-OHD level of 15 ng/mL or less than in the patients with a serum 25-OHD level higher than 15 ng/mL (83.0% vs 25.0%, respectively; $P < .03$).

Preoperatively, the serum 25-OHD level was 25 ng/mL or less in 97 patients and higher than 25 ng/mL in 33 patients. Of the 97 patients with a serum 25-OHD level of 25 ng/mL or less, 31 (32.0%) developed postoperative hypocalcemia; of the 33 patients with a serum 25-OHD level higher than 25 ng/mL, 1 (3.0%) developed postoperative hypocalcemia. The ratio of postoperative hypocalcemia was significantly higher in the patients with a serum 25-OHD level of 25 ng/mL or less than in the patients with a serum 25-OHD level higher than 25 ng/mL ($P < .001$).

According to the cutoff of 25 ng/mL for the preoperative serum 25-OHD level, logistic regression analysis for postoperative hypocalcemia was performed. The preoperative serum 25-OHD level was the only independent significant variable of postoperative hypocalcemia ($P = .001$), whereas age and the postoperative serum PTH level were not significant variables of postoperative hypocalcemia ($P = .63$ and $P = .12$, respectively). Patients with a preoperative serum 25-OHD level of 25 ng/mL or less had a 15-fold increased risk for postoperative hypocalcemia (odds ratio, 15.4; 95% confidence interval, 2.0-115.9; $P = .009$).

FOLLOW-UP

Ten of 32 patients with asymptomatic hypocalcemia were treated only with oral calcium supplementation. Twenty-two patients with symptomatic hypocalcemia were treated with parenteral calcium as well as oral vitamin D₃ and calcium supplementation until they were discharged. Symptomatic patients ($n = 22$) were treated with parenteral calcium and calcitriol supplementation. Treatment was discontinued at the first week in 10 patients with asymptomatic hypocalcemia. In patients with symptomatic hypocalcemia, treatment was discontinued at the second week in 4 patients, at the third week in 6 patients, at the fourth week in 8 patients, and at the fifth week in 4 patients. Treatment in all of the patients with symptomatic hypocalcemia could not be stopped in the first week. However, treatment was discontinued at the first week in all of the patients with asymptomatic hypocalcemia.

COMMENT

We investigated the prediction of developing postoperative hypocalcemia by age, preoperative serum 25-OHD

level, and postoperative serum PTH level after TT and found that age, a low preoperative serum 25-OHD level, and a low postoperative serum PTH level were significantly associated with postoperative hypocalcemia. The predictive value of a low preoperative serum 25-OHD level was significantly higher than that of a low postoperative serum PTH level ($P < .001$). Preoperative serum 25-OHD and postoperative serum PTH levels in the patients with hypocalcemia were significantly lower than in the patients with normocalcemia. Age and the serum alkaline phosphatase level in the patients with hypocalcemia were significantly higher than in the patients with normocalcemia ($P < .001$). According to logistic regression analysis, a preoperative serum 25-OHD level less than 15 ng/mL, a postoperative serum PTH level less than 10 pg/mL, and being older than 50 years were significantly predictive factors for postoperative hypocalcemia.

Although the morbidity of thyroid surgery has decreased during the past century, hypoparathyroidism continues to occur. Postoperative hypocalcemia is one of the most frequent complications after TT. In several studies,^{13,23-29} the incidence of hypoparathyroidism varied from 1.6% to higher than 50%. Even when experienced surgeons believe that the parathyroid glands were preserved and reliable during the operation, hypocalcemia may occur.^{13,23,24} The causes of hypocalcemia after TT are multifactorial, and some of the factors involve iatrogenic surgical trauma to parathyroid glands, inadvertent removal of parathyroid glands, the number of functioning glands left behind, the extent of surgery, the experience of the surgeon, hyperthyroidism, retrosternal goiter, concomitant neck dissection, and thyroid carcinoma.^{11-15,29-34} The risk of hypoparathyroidism after thyroid operation for Graves disease is 20 times higher than in nontoxic multinodular goiter.^{35,36} In patients with substernal goiter, parathyroid glands might be removed inadvertently.^{37,38} During thyroid reoperation, fibrosis causes difficult visualization of parathyroid glands and is associated with a higher risk of postoperative hypocalcemia.^{31,32} Therefore, patients having hyperthyroidism, substernal goiter or a previous thyroid or neck operation, and concomitant parathyroid disease were excluded in our study. The symptoms of hypocalcemia usually manifest 24 to 48 hours after the thyroid operations. Monitoring of the postoperative serum calcium concentration is necessary to detect patients who develop hypocalcemia and need supplementation therapy. Some investigators^{14,39,40} follow a strict protocol including frequent measurement of serum calcium levels for several days. There is no consensus about the optimal postoperative time to determine the serum calcium level.^{39,40}

Recently, there has been a great deal of interest in identifying perioperative factors that could predict the development of hypocalcemia after thyroidectomy. Intraoperative or postoperative serum PTH measurements have been demonstrated to be useful in the identification of patients who are at risk for hypocalcemia.¹⁶⁻¹⁹ In addition to its clinical usefulness in the identification of patients who should be treated, a serum PTH assay may also be cost-effective by reducing the postoperative length of hospital stay and the need for expensive postoperative serum calcium monitoring.⁴¹⁻⁴³ The accuracy of a low intraoperative serum PTH level to predict biochemical and symptomatic postoperative hypocalcemia was effective.¹⁶⁻¹⁹ The sensitivity of the intraoperative serum PTH level to predict postoperative hypocalcemia is 70% to 80%.^{16,41-43} In recent studies,^{16,19} low serum PTH levels 8 and 12 hours after operation were the most accurate (98%) predictors of postoperative hypocalcemia. Patients treated by TT and having a serum PTH level greater than 15 pg/mL at 8 hours postoperatively were at extremely low risk for developing postoperative hypocalcemia.^{41,42} In our study, serum calcium and PTH levels were determined the day before operation and serum PTH and calcium levels were measured 12 hours after TT. All of the patients who developed hypocalcemia were noted to have a serum PTH level less than 15 pg/mL at 12 hours postoperatively.

Symptomatic hypocalcemia usually contributes to the length of hospital stay. Some investigators⁴¹⁻⁴⁴ empirically propose routine oral calcium and/or calcitriol administration in patients undergoing TT to increase early hospital discharge. In our study, the hospitalization period was longer for patients with hypocalcemia than for patients with normocalcemia. In previous studies,^{16-19,41-43} only intraoperative and postoperative serum PTH levels were used to predict postoperative hypocalcemia. To our knowledge, ours is the first prospective study performed to detect the strong value of the serum 25-OHD level in predicting postoperative hypocalcemia after TT. Chia et al⁴⁵ demonstrated that preoperative levels of serum 25-OHD did not correlate with postoperative serum calcium levels and were not a useful predictor of postoperative hypocalcemia. However, their patient population included those with thyroid disorders, parathyroid adenoma, and parathyroid hyperplasia and they performed different surgical procedures. We believe that the nonpredictive result associated with the serum 25-OHD level might be related to these factors in their study.

Previous studies⁴⁶⁻⁴⁸ indicated that vitamin D deficiency increased in elderly people, even among healthy, ambulatory elderly people. Advanced age is reported to be a major risk factor for vitamin D deficiency.¹⁶ Aging is associated with alterations in vitamin D metabolism: age-related decline in cutaneous accumulation of 7-dehydrocholesterol (which is converted into previtamin D₃ by solar UV radiation),¹⁷ a decrease in renal 1 α -hydroxylase activity,⁴⁹ and decreased intestinal calcium absorption.⁵⁰ These factors and poorer nutritional intake may be responsible for the increased risk of vitamin D deficiency during aging. Therefore, aging is associated with a decrease in defense mechanisms against hypocalcemia. Being older than 50 years was associated with an increased risk of postoperative hypocalcemia in

our patients who underwent TT. Insufficiency in calcium absorption due to low vitamin D concentration leads to an increase in PTH secretion. An increased PTH concentration stimulates the synthesis of calcitriol, thereby improving calcium absorption efficiency. In our patients recovering from TT, a compensatory increase in PTH may not be achieved transiently; therefore, hypocalcemia develops in these patients more readily. A deficiency in normal homeostatic mechanisms against hypocalcemia during aging may further exaggerate the decrease in serum calcium concentrations.

Vitamin D deficiency has been frequently documented in medically ill and free-living populations.¹⁶ In Turkey, more than 30% of different groups of subjects have vitamin D deficiency.^{48,51} There is currently no consensus on which level of serum 25-OHD is the optimal concentration. While a 25-OHD concentration less than 30 nmol/L has been suggested by some⁵² to represent vitamin D deficiency, others have suggested that concentrations of less than 37.5 nmol/L,⁵³ 40 nmol/L,⁵⁴ 62 nmol/L,⁵⁵ or even 120 nmol/L⁵⁶ are deleterious to bone. In our study, serum 25-OHD levels less than 15 ng/mL (37.5 nmol/L) were accepted to indicate vitamin D deficiency.

Logistic regression analysis for postoperative hypocalcemia was performed according to the cutoff value of 25 ng/mL for the preoperative serum 25-OHD level. The preoperative serum 25-OHD level was the only independent significant variable for postoperative hypocalcemia. A preoperative serum 25-OHD level less than 25 ng/mL indicated a 15-fold increased risk of postoperative hypocalcemia. We believe that patients with a preoperative serum vitamin D level less than 25 ng/mL can compensate for postoperative hypocalcemia due to parathyroid injury without clinical and laboratory findings of hypocalcemia.

A high frequency of vitamin D deficiency could be responsible for the relatively high frequency of temporary postoperative hypocalcemia in our study. In populations with a higher incidence of vitamin D deficiency, the preoperative serum 25-OHD level plays a major role in predicting postoperative symptomatic and/or biochemical transient hypocalcemia in patients who have undergone thyroidectomy for benign conditions. The effects of preoperative supplemental doses of vitamin D on the frequency of post-thyroidectomy transient hypocalcemia should be clarified by further prospective studies.

In conclusion, age, the serum PTH level, and the serum 25-OHD level are predictive factors for hypocalcemia after TT. The preoperative serum 25-OHD level is strongly useful to predict hypocalcemia after thyroidectomy. Patients with a preoperative serum 25-OHD level less than 15 ng/mL should receive calcium or vitamin D supplementation after TT to avoid symptomatic hypocalcemia and to decrease the length of hospital stay.

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