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A single Center study

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Narin Nasiroglu Imga*, Hakan Atas**, Murat Torgutalp***, Gul Daglar**, Dilek Berker*

**Sağlik Bilimieri University, Ankara Numune Education and Research Hospital Department of Endocrinology and Metabolism, Ankara, Turkey*
***Sağlik Bilimieri University, Ankara Numune Education and Research Hospital Department of Surgery, Ankara, Turkey*
****Ankara University Faculty of Medicine Department of Rheumatology, Ankara, Turkey*

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BACKGROUND: *Post-operative hypoparathyroidism is a complication in patients who undergo thyroid surgery. Our study aimed to evaluate the incidence and causes of post-operative transient and permanent hypoparathyroidism in patients undergoing thyroid surgery.*
MATERIALS AND METHODS: *The data of 933 consecutive patients who underwent total thyroidectomy in a single center were retrospectively evaluated. The rate of post-operative hypoparathyroidism, clinicopathological features, and laboratory parameters during the post-operative first day, first month, and first year of patients with and without hypoparathyroidism were analyzed. Patients with hypoparathyroidism were classified as transient or permanent cases.*
RESULTS: *The incidence of post-operative hypoparathyroidism was 22.7%, including transient (20.6%) and permanent (2.1%). In multivariable analysis, independent predictors of permanent hypoparathyroidism were as follows: surgery due to malignant thyroid disease, tumor multifocality, and pre-operative vitamin-D deficiency (VDD) (p<0.001, 0.047, and 0.002, respectively). During the post-operative first month, the mean serum PTH levels were found to be 7.58 pg/mL, and they remained low on the post-operative first year in patients with permanent hypoparathyroidism.*
CONCLUSION: *Surgery due to thyroid malignancy and VDD should be considered risk factors for permanent hypoparathyroidism in patients who undergo thyroid surgery. The post-operative first month is important in the prediction of permanent hypoparathyroidism.*

KEY WORDS: Hypoparathyroidism, Permanent, Transient

Introduction

Hypoparathyroidism is characterized by deficiency or insufficiency of parathyroid hormone (PTH), leading to hypocalcemia and mild hyperphosphatemia in the circulation, and it may be life threatening. The most frequent cause of acquired acute parathyroid dysfunction is post-surgical hypoparathyroidism, which frequently results from anterior neck surgery due to injury or removal of the parathyroid gland; approximately 20-30% of patients develop transient and 1-7% develop permanent hypoparathyroidism after total thyroidectomy (TT) [1,2]. The initial manifestation of post-operative parathyroid failure is hypocalcemia detected within 24 hours of thyroidectomy, which occurs in 30-60% of patients undergoing TT [3]. Hypocalcemia requires close observation and frequently causes elongation of hospitalization with repeated laboratory assessments, and if not treated, the function of the neurological, cognitive, muscular, and cardiac systems becomes impaired [4]. Thus, it is essential to rapidly identify and treat patients who develop hypoparathyroidism after thyroid surgery. The factors

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Correspondence to: Narin Nasiroglu Imga, MD, Ankara Numune Education and Research Hospital Department of Endocrinology and Metabolism, 06100, Ankara, Turkey (e-mail: xnarinx@yahoo.com)

leading to post-operative hypoparathyroidism are controversial. Young age, female gender, Graves's disease, lymphadenectomy, fewer than three glands left in situ and incidental parathyroidectomy are thought to be risk factors [5,6]. The incidence of transient and permanent hypoparathyroidism after thyroidectomy remains uncertain, varying from 10-60% and 0-3%, respectively [5-8].

The aims of this study were to investigate the anthropometric and laboratory characteristics of patients who underwent thyroid surgery and to determine the incidence of transient and permanent hypoparathyroidism and the role of pre-operative and post-operative calcium, phosphate, PTH, and 25-hydroxyvitamin D [25(OH)D] levels in these patients.

Patients and Methods

Study Population

This retrospective study reviewed the medical records of 1,267 consecutive patients older than 18 years who underwent thyroid surgery between January 2014 and February 2017. The local ethical committee was approved the study. Of these patients, 933 who fulfilled the study criteria were included in the study. Patients who had a history of parathyroid gland dysfunction, chronic renal insufficiency, diseases affecting calcium and phosphate homeostasis, and those receiving calcium and/or vitamin D supplementation before surgery were excluded from the study. The thyroid gland volume and central and bilateral neck lymph nodes (LN) of each patient were examined by ultrasound. Thyroid gland volume was calculated according to the ellipsoid formula: height x width x depth x 0.479 [9]. Fine needle aspiration biopsy (FNAB) was performed for thyroid nodules or lymph nodes to detect malignant thyroid disease metastases.

Permanent hypoparathyroidism was defined as a low PTH concentration (<13 pg/ml) requiring therapy with calcium and or vitamin D replacement 1 year after TT [10,11]. Vitamin D deficiency (VDD) is defined as a 25(OH)D ≤20 ng/ml and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml [12]. Patients with post-operative hypocalcemia were treated with oral or intravenous calcium and/or oral calcitriol supplementation. If the initial dose was not sufficient, the dosage was titrated.

The following parameters were assessed for statistical analysis: patient age, gender, body mass index (BMI), thyroid gland volume, indication for thyroid surgery, type of LN dissection (central or central+lateral), LN metastasis, and post-operative pathology (benign or malign). In malign thyroid diseases (papillary thyroid carcinoma [PTC]), follicular thyroid carcinoma [FTC]), medullary thyroid carcinoma [MTC]) tumor location (right, left, isthmus, bilateral) and tumor characteristics (size, multifocality, extracapsular invasion) were recorded. Removal of more than 1 parathyroid gland during the surgery was defined as incidental parathyroidectomy. Pre-operative and post-operative first day, first month, and first year serum calcium, phosphate, PTH, and 25(OH)D measurements were recorded.

Surgical Procedure

The operations were performed on every patient by an experienced high- volume surgical team that performed thyroid surgery mre than 100 times per year, using the capsular dissection technique. Surgical indication was benign thyroid disease in 839 patients (90%), and 94 patients (10%) showed circumstantial evidence of malignant thyroid tumor histology. If there was pre-operative evidence of metastatic lymph nodes in the lateral compartment, in addition to bilateral central LN dissection (LND), lateral LND was performed. In 117 patients (12.0%), a bilateral central LND (n=51) and a lateral LND (n=27) were performed. Ninety-four patients (10.1%) were operated for malignant thyroid disease, including differentiated thyroid carcinoma (DTC) in 90 and MTC in 4 cases. None of the MTC patients had multifocal tumors. Identification and preservation of the recurrent laryngeal nerves and parathyroid glands were conducted. In patients who had an incidental parathyroidectomy, removal of 1 or 2 parathyroid glands was performed; none of the patients underwent resection of 3 or 4 parathyroid glands. Operation mortality did not occur in any patient.

Laboratory Analyses

Pre-operative and post-operative first day, first month, and first year serum-corrected calcium, phosphate, 25(OH)D, and intact PTH levels were evaluated. Serum albumin (reference range: 3.5-5 g/dl), calcium (reference range: 8.5-10.2 mg/dl), and phosphate (reference range: 2.5-4.5 mg/dl) levels were measured by photometric methods (AU5800 Autoanalyzer, Beckman Coulter Inc., Brea, CA, USA). Serum total calcium levels were corrected according to albumin concentration using the following formula: [(4-serum albumin) x 0.8]+ total serum calcium [13]. Serum PTH (normal range: 12–88 pg/ml) levels were determined via the chemiluminescent immunoassay (AU5800 Autoanalyzer, Beckman Coulter Inc., Brea, CA, USA) method. Serum 25(OH)D concentration was measured using an electroluminescence method on the Cobas E-411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The intraassay and interassay coefficients of variations (CV) were 3.2% and 7.8%, respectively. The minimum detection limit of the 25(OH)D kit was 3 ng/mL. Serum thyroid stimulating hormone (TSH) (normal range: 0.34-5.6 mg/dl) level was measured with a chemiluminescent immunoassay

(CLIA) using a DXI 800 Unicel (Beckman Coulter Inc., Brea, CA, USA) immunoassay device.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows 20 (SPSS, Inc., Chicago, IL, USA). Variables were expressed as the mean ± standard deviation, median (min-max), absolute numbers, or percentages. Statistical differences between 2 groups with normal distribution were analyzed using Student's t-test, whereas non-normal distributions were assessed with the Mann–Whitney U-test. Categorical variable comparisons between groups were performed using the chi-square test. The relationships between continuous variables were measured using Spearman's rho correlation coefficient test. Multivariate stepwise logistic regression modeling was performed to identify independent predictors of permanent hypoparathyroidism. The statistical significance level was set at a p-value less than 0.05.

Results

Among all patients (n=933), the incidence of post-operative hypoparathyroidism was found to be 22.7% (n=212), including transient hypoparathyroidism in 20.6% (n=192) of patients and permanent hypoparathyroidism in 2.1% (n=20) of patients (Fig. 1). Table I shows the characteristics of patients without (n=721) and with (n=212) post-operative hypoparathyroidism. The percentage of female patients (82.5%) was found to be greater in patients without post-operative hypoparathyroidism (p=0.001). Elderly patients and patients who had excessive thyroid gland volume experienced post-operative hypoparathyroidism more often (p<0.001). In patients with post-operative hypoparathyroidism, the indication for TT was more frequently found in the malignant group than in the benign group (31.9% versus 21.7%; p=0.025), but no differences were found in terms of type of LND (28% versus 31%; p=0.736) or presence of LN metastasis (21.2% versus 22.8%; p=0.781). Tumor location and tumor characteristics did not differ between the groups, but the frequency of incidental parathyroidectomy was higher in patients with post-operative hypoparathyroidism (p=0.016). The distributions of the surgical indications of all patients, including patients with and without post-operative hypoparathyroidism, are given in Table II. Among all patients, 71.9% had euthyroid multinodular goiter (MNG), 3.9% had Graves's disease, 13.3% had toxic diffuse MNG, 0.9% had toxic NG, and 10.1% had thyroid carcinoma. Post-operative hypoparathyroidism tends to occur more frequently in patients whose thyroid surgery indication was due to carcinoma.

Factors affecting transient (n=192) and permanent (n=20) hypoparathyroidism are given in Table III. Female patients were more than male patients in each group, but the gender-based difference was not statistically significant (70.3% versus 90.0%; p=0.062). No difference was found in terms of gender, age, or BMI between the 2 groups (p>0.05). In patients who had excess thyroid volume, the risk of permanent hypoparathyroidism was higher (20.56 ± 13.61 versus 52.62 ± 49.34; p<0.001). The indication of thyroid surgery for malignant diseases and the number of patients undergoing LND was higher in the permanent hypoparathyroidism group (p<0.001; for both). Patients whose post-operative thyroid pathology revealed DTC with multifocal tumor had higher risk

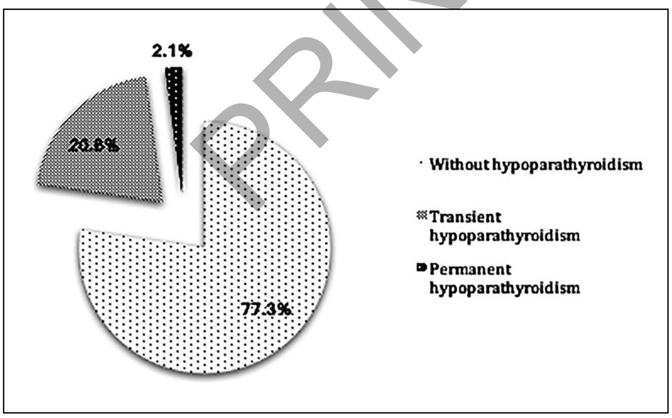

Fig. 1: The distribution of all patients underwent thyroid surgery including transient and permanent hypoparathyroidism.

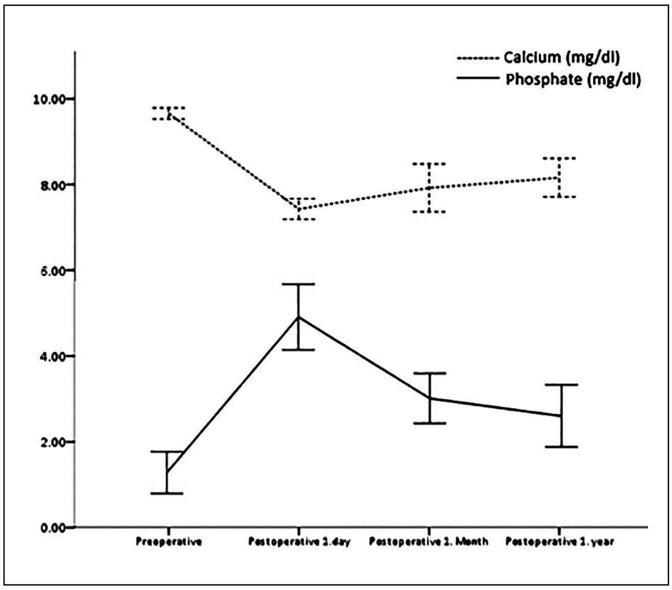

Fig. 2: The course of mean serum calcium and phosphate levels in patients with permanent hypoparathyroidism.

TABLE 1 - *Characteristics of patient without and with postoperative hypoparathyroidism.*

Variable	Patients without postoperative hypoparathyroidism (n=721)	Patients with postoperative hypoparathyroidism (n=212)	P
Gender, Female, n (%)	595 (82.5)	153 (72.2)	0.001
Age	47.4 ± 12.1	52 ± 12.3	<0.001
BMI	28.2 ± 4.5	28.3±4.1	0.923
Thyroid gland volume, ml	19.91 ± 19.24	49.87 ± 48.18	<0.001
Indication of thyroidectomy			0.025
Benign, n (%)	657 (78.3)	182 (21.7)	
Malign, n (%)	64 (68.1)	30 (31.9)	
LN dissection			0.080
Yes, n (%)	83 (70.9)	34 (29.1)	
No, n (%)	638 (78.2)	178 (21.8)	
Type of LN dissection, n=117			0.736
Central, n (%)	54 (72)	21 (28)	
Central+Lateral, n (%)	29 (69)	13 (31)	
LN metastasis			0.781
Yes, n (%)	41 (78.8)	11 (21.2)	
No, n (%)	680 (77.2)	201 (22.8)	
Postoperative pathology			0.289
Benign, n (%)	392 (76)	124 (24)	
Malign, n (%)	329 (78.9)	88 (21.1)	
PTC	321	80	
FTC	6	8	
MTC	2	2	
Tumor location (n=417)			0.266
Right, n (%)	118 (35.9)	30 (34.1)	
Left, n (%)	94 (28.6)	31 (35.2)	
Isthmus, n (%)	18 (5.5)	1 (1.1)	
Bilateral, n (%)	99 (30.1)	26 (29.5)	
Tumor Characteristics (n=417)			
Size, mm	14.6 ± 13.9	17 ± 19	0.271
Multifocal, yes (%)	125 (38)	41 (46.6)	0.143
Extracapsular invasion, yes (%)	49 (14.9)	12 (13.6)	0.767
Incidental parathyroidectomy			0.016
Yes, n (%)	149 (71.3)	60 (28.7)	
No, n (%)	572 (79.2)	150 (20.8)	
Preoperative			
TSH, mg/dl	1.46 ± 1.22	1.33 ± 1.16	0.171
Serum calcium, mg/dl	9.4 ± 0.4	9.4 ± 0.4	0.904
Serum phosphate, mg/dl	3.3 ± 0.5	3.3 ± 0.5	0.328
PTH, pg/ml	60.4 ± 22.4	58.5 ± 18.9	0.639
25(OH)D, ng/ml	17.9 ± 10.9	16.7 ± 9.1	0.369

BMI: Body mass index; LN: Lymph node; PTC: Papillary thyroid carcinoma; FTC: Follicular thyroid carcinoma; MTC: Medullary thyroid carcinoma; TSH: Thyroid stimulant hormone; PTH: Parathormone

of permanent hypoparathyroidism (p=0.034). The frequency of incidental parathyroidectomy was higher in patients with permanent hypoparathyroidism (p=0.001). Pre-operative low calcium levels and VDD were associated with permanent hypoparathyroidism (p=0.002 and p <0.001; respectively). On the first post-operative day, serum calcium and PTH levels were starting to decrease, whereas phosphate levels were increased but not significantly different between the 2 groups. At the first post-operative month after surgery, serum PTH levels were lower in the permanent group than in the transient group (7.58 ± 3.09 versus 28.96 ± 15.79; p<0.001). Consistent with this result, at the post-operative first year, serum PTH levels remained lower in the permanent group (8.56 ± 4.46 versus 36.99 ± 13.26; p<0.001). Changes in mean serum calcium and phosphate levels in patients with permanent hypoparathyroidism are shown in Fig. 2. On the post-operative first day, serum calcium levels began to

TABLE II - *The distribution of 933 patients in terms of indication for total thyroidectomy.*

Variable	Total (n = 933)	Patients without postoperative hypoparathyroidism (n=721)	Patients with postoperative hypoparathyroidism (n=212)
Euthyroid MNG	671 (71.9%)	530, 79%	141, 21%
Graves	36 (3.9%)	32, 88.9%	4, 11.1%
Toxic diffuse MNG	124 (13.3%)	87, 70.2%	37, 29.8%
TNG	8 (0.9%)	8, 100%	0
Carcinoma	94 (10.1%)	64, 68.1%	30, 31.9%

MNG: Multinodular goiter; TNG: Toxic nodular goiter

decrease, whereas phosphate levels increased. During the first month and first year with treatment support for hypoparathyroidism, they returned to near normal levels. In patients with post-operative hypoparathyroidism, pre-operatively no correlation was found between PTH and serum calcium and phosphate levels (P=0.521, p=0.289) (Table IV). However, during the post-operative first day, first month, and first year, positive correlations were detected between calcium and PTH levels (r=0.440, P<0.001; r=0.325, P=0.002; r=0.316, P=0.002; respectively) and negative correlations were detected between PTH and phosphate levels (r=-0.469, P=0.01; r=-0.363, P=0.006; r=-0.210, P=0.071; respectively). The correlation was found to be stronger on the post-operative first day. The logistic regression modeling analysis (Table V) determined that thyroid surgery indication for malignant thyroid disease, multifocal tumors, and pre-operative low 25(OH)D levels were found to be independent risk factors for permanent hypoparathyroidism by univariate and multivariate analyses. If the indication of TT was due to malignant thyroid disease, the risk of permanent hypoparathyroidism increased 10.567-fold (p<0.001). Tumor multifocality increased the risk of permanent hypoparathyroidism 3.839-fold (p=0.047). Incidental parathyroidectomy increased the risk of permanent hypoparathyroidism 3.228-fold, but this increase is not statistically significant (p=0.058). In pre-operative VDD, every 1 ng/ml of 25(OH)D deficiency increased the risk of permanent hypoparathyroidism 0.766-fold (p=0.002).

Discussion

Postsurgical hypoparathyroidism may be transient or permanent, with hypoparathyroidism defined by most studies as PTH levels that are insufficient to maintain normocalcemia. Different periods have been used to define post-operative permanent hypoparathyroidism. Some authors describe post-operative parathyroid gland injury to be permanent if recovery of function has not occurred within 6 months [14,15], whereas others define permanence as lack of recovery 1 year after surgery [16,17]. Therefore, we determined that the 1-year period is a reasonable period on which to base the definition of permanent hypoparathyroidism; hence we re-evaluated our patient's 1 year after operation. In another study, the frequency of transient hypoparathyroidism was 23.7%, and the frequency of permanent hypoparathyroidism was 4.3% after thyroid surgery [18]. In our study, in 20.6% of patients with post-operative hypoparathyroidism, PTH and calcium levels had returned to normal 1 year after the surgery, but in 2.1%, post-operative hypoparathyroidism persisted. These results are consistent with those of previous studies.

In the literature, various cut-off levels for PTH for the definition of post-operative hypoparathyroidism are available. A prospective study with 170 patients who underwent TT for various diagnoses of thyroid diseases found that post-operative PTH level ≤15 pg/mL or serum calcium level ≤7.6 mg/dL on the post-operative second day increased the risk of post-operative hypoparathyroidism [8]. In addition, recovery of the parathyroid gland was defined as PTH ≥10 pg/mL without the use of any medication with calcium or calcitriol [11]. Soon et al. researched the effectiveness of early post-operative serum PTH measurement for predicting hypoparathyroidism and revealed that 1 hour after TT, a serum PTH level < 9 pg/mL predicts the development of hypocalcemia symptoms with 92.3% sensitivity and 78.8% specificity [19]. Others found that on the post-operative first day, PTH level <15 pg/mL combined with serum calcium level <7.6 mg/dL on the second post-operative day predicted post-operative hypoparathyroidism with 96.3% sensitivity and 96.1% specificity [8]. In our study, although on the post-operative first day PTH levels did not differ between the transient and permanent groups, at the post-operative first month, mean PTH levels were significantly lower (7.58 pg/mL) in the permanent hypoparathyroidism group than in the transient hypoparathyroidism (28.96 pg/mL) group. Furthermore, 1 year after surgery, this difference remained. Thus, we decided that a follow-up visit during the post-operative first month is important in predicting permanent hypoparathyroidism.

The type of surgery is also a factor in the development

TABLE III - *Patient characteristics of groups with transient hypoparathyroidism compared to permanent hypoparathyroidism.*

Variable	Transient hypoparathyroidism (n=192)	Permanent hypoparathyroidism (n=20)	P
Gender, Female, n (%)	135 (70.3)	18 (90)	0.062
Age	52.3 ± 12.1	49 ± 14.2	0.251
BMI	28.4 ± 4.1	27 ± 4	0.201
Thyroid gland volume, ml	20.56 ± 13.61	52.62 ± 49.34	< 0.001
Indication of thyroidectomy			< 0.001
Benign, n (%)	174 (95.6)	8 (4.4)	
Malign, n (%)	18 (60)	12 (40)	
LN dissection			<0.001
Yes, n (%)	24 (70.6)	10 (29.4)	
No, n (%)	168 (94.4)	10 (5.6)	
Type of LN dissection, n=34			0.604
Central, n (%)	17 (81)	4 (19)	
Central+Lateral, n (%)	7 (53.8)	6 (46.2)	
LN metastasis			0.130
Yes, n (%)	8 (72.7)	3 (27.3)	
No, n (%)	7 (77.8)	2 (22.3)	
Postoperative pathology			0.078
Benign, n (%)	116 (93.5)	8 (6.5)	
Malign, n (%)	76 (86.4)	12 (13.6)	
PTC	70	8	
FTC	5	3	
MTC	1	1	
Tumor location			0.411
Right, n (%)	27 (35.5)	3 (25)	
Left, n (%)	28 (36.8)	3 (25)	
Bilateral, n (%)	21 (27.7)	6 (50)	
Tumor characteristics			
Size, mm	16.31 ± 18.2	21.3 ± 23.9	0.406
Multifocal, yes (%)	32 (42.1)	9 (75)	0.034
Extracapsular invasion, yes (%)	9 (11.8)	3 (25)	0.359
Incidental parathyroidectomy			0.001
Yes, n (%)	49 (81.7)	11 (17.3)	
No, n (%)	143 (95.3)	7 (4.7)	
Preoperative			
TSH, mg/dl	1.29 ± 1.08	1.68 ± 1.78	0.170
Serum calcium, mg/dl	9.66 ± 0.28	9.38 ± 0.39	0.002
Serum phosphate, mg/dl	3.37 ± 0.47	3.15 ± 0.49	0.117
PTH, pg/ml	56.77 ± 18.91	76.27 ± 1.85	0.088
25(OH)D, ng/ml	18.95 ± 9.02	9.07 ± 3.74	<0.001
Postoperative first-day			
Serum calcium, mg/dl	7.62 ± 0.55	7.43 ± 0.51	0.146
Serum phosphate, mg/dl	5.91 ± 1.19	6.27 ± 0.73	0.163
PTH, pg/ml	9.18 ± 8.45	9.0 ± 7.94	0.968
Postoperative first-month			
Serum calcium, mg/dl	8.86 ± 0.92	7.92 ± 1.19	<0.001
Serum phosphate, mg/dl	3.76 ± 0.81	4.27 ± 0.53	0.022
PTH, pg/ml	28.96 ± 15.79	7.58 ± 3.09	<0.001
25(OH)D, ng/ml	20.03 ± 10.79	17.93 ± 4.64	0.592
Postoperative first-year			
Serum calcium, mg/dl	8.81 ± 0.75	8.16 ± 0.97	0.001
Serum phosphate, mg/dl	3.62 ± 0.58	3.96± 0.65	0.041
PTH, pg/ml	36.99 ± 13.26	8.56 ± 4.46	<0.001
25(OH)D, ng/ml	21.33 ± 11.52	25.14 ± 13.16	0.264

BMI: Body mass index LN: Lymph node; PTC: Papillary thyroid carcinoma; FTC: Follicular thyroid carcinoma; MTC: Medullary thyroid carcinoma; TSH: Thyroid stimulant hormone; PTH: Parathormone.

TABLE IV - *Correlations between preoperative and postoperative first day, first month and first year serum PTH and calcium and phosphate levels in patients with postoperative hypoparathyroidism*

Time	Preoperative	Postoperative first-day	Postoperative first-month	Postoperative first-year
Variable		Correlation between PTH and Calcium		
Calcium				
rho	0.114	0.440	0.325	0.316
P values	0.521	<0.001	0.002	0.002
Variable		Correlation between PTH and Phosphate		
Phosphate				
rho	-0.196	-0.469	-0.363	-0.210
P values	0.289	0.01	0.006	0.071

* Spearman's rho test

TABLE V - *Logistic regression analysis of parameters associated with permanent hypoparathyroidism*

	Univariate			Multivariate				
	p	OR	95% CI	B	S.E.	p	OR	95% CI
Age	0.834	1.004	0.968-1.041					
Gender, Female	0.278	0.443	0.102-1.927					
BMI	0.264	0.934	0.828-1.053					
Thyroid gland volume	0.393	0.999	0.998-1.001					
Postoperative malign pathology	0.171	1.881	0.762-4.647					
Preoperative PTH	0.204	1.029	0.984-1.076					
Postoperative first-day PTH	0.343	0.951	0.858-1.055					
Indication of thyroidectomy, Malign	<0.001	15.201	6.040-38.256	2.358	0.661	<0.001	10.567	2.895 - 38.575
Multifocal malign tumors	0.003	3.940	1.606-9.667	1.345	0.676	0.047	3.839	1.020 - 14.441
Incidental parathyroidectomy	<0.001	5.675	2.171-14.829	1.172	0.619	0.058	3.228	0.960 - 10.857
Preoperative 25(OH)D	<0.001	0.787	0.691-0.897	-0.266	0.086	0.002	0.766	0.648 - 0.906

BMI: Body mass index; PTH: Parathormone; OR: Odds ratio; CI: confidence interval

of hypoparathyroidism. It is well known that post-operative hypoparathyroidism likely occurs in patients who undergo extensive or recurrent thyroid surgery. Moreover, certain types of thyroid conditions–such as toxic nodular goiter, Graves's disease, thyroid carcinoma, substernal goiter, and recurrent thyroid operation–have been associated with increased risk of post-operative hypoparathyroidism [20]. We found that large thyroid gland volume and indication of thyroid surgery for thyroid carcinoma were related to post-operative hypoparathyroidism, particularly permanent hypoparathyroidism. Among all patients, if the indication of thyroidectomy was due to malignant thyroid disease, the risk of permanent hypoparathyroidism increased 10.567-fold. In addition, in DTC patients, tumor multifocality increased the risk of permanent hypoparathyroidism by 3.839-fold. Patients who had toxic diffuse MNG had higher rates of post-operative hypoparathyroidism than those with euthyroid MNG.

Previous studies report rates of permanent hypoparathyroidism ranging from 1.4%–14.3% in those who underwent central LND compared to 0-0.5% in those who did not [21]. In thyroid cancer patients that underwent TT with central or lateral LND performed, permanent hypoparathyroidism developed in 2-10% [10]. In PTC patients, post-operative serum PTH levels remained low for several weeks, and a higher incidence of hypocalcemia was found in the TT with LND group than in the TT without LND group [22]. In our study, no difference was found in terms of performing LND, type of LND, or LN between transient and permanent hypoparathyroidism patients. We believe that routine central LND should be performed after evaluation of the potential risks and benefits because a greater incidence of post-operative hypoparathyroidism has been observed. The expertise and experience of the surgeon are also significant factors in the risk of post-operative hypoparathyroidism; high-volume surgeons had lower complication rates [23,24]. It is reported that in centers with experienced high-volume endocrine surgeons, the frequency of post-operative permanent hypoparathyroidism ranges from 0.9%-1.6%, and the frequency of transient hypoparathyroidism ranges from 6.9%-46% [25]. A previous study indicates that high-volume surgeons have a higher overall post-operative complication frequency when performing TT than when performing lobectomy [26]. In this study, the only type of thyroid surgery performed was TT, so the risks of lobectomy and recurrent thyroid surgeries were not evaluated. The relative risk of post-operative hypocalcemia was found to be greater in patients who underwent TT than in those who underwent hemithyroidectomy (10.67 for transient and 3.17 for permanent) [27]. Thus, it is important to have an experienced surgeon perform thyroid surgery; in addition, our center has high-volume experienced surgeons.

In the current study, we found that if the parathyroid glands were preserved during the thyroid surgery, the incidence of post-operative hypoparathyroidism decreased. In one study for determining the frequency of hypoparathyroidism according to the number of parathyroid glands preserved in patients who underwent TT for papillary thyroid carcinoma, the researchers found that preservation of all parathyroid glands decreased the incidence of transient hypoparathyroidism compared with when 3 or fewer glands were preserved, but it did not affect permanent hypoparathyroidism [28]. The risk of hypoparathyroidism is related to the number of parathyroid glands remaining in situ; the risk was 16% for patients with 1 to 2 preserved glands, 6% for patients with 3 glands, and 2.5% for patients with 4 glands [29]. In our study, when all parathyroid glands remained in situ during the surgery, the incidence of post-operative hypoparathyroidism and permanent hypoparathyroidism decreased. On the other hand, incidental parathyroidectomy increases the risk of permanent hypoparathyroidism 3.228-fold. Chew et al. found no association between the incidental excision of parathyroid glands and post-operative hypocalcemia in patients who underwent TT [30].

VDD has been recognized as a risk factor for post-operative hypocalcemia following TT in patients with benign thyroid diseases [31,32]. In a recent study, VDD was not found to be a significant risk factor for post-operative hypocalcemia in patients who underwent TT and central compartment LND, but in this study, the sample size was not large enough to determine the risk (n=186) [33]. Pre-operative serum 25(OH)D level <15 ng/mL is found to be a powerful predictive factor for hypocalcemia after TT [34]. We found that VDD was a risk factor for post-operative hypoparathyroidism, including permanent hypoparathyroidism. The mechanism is not clearly known, but in elderly people, VDD is reported to be a risk factor [35]. Aging causes a decline in the cutaneous accumulation of provitamin D3 and leads decreased capacity of the human skin to produce vitamin D3. In addition, in elderly people, inadequate nutrition may be responsible for the increased risk of VDD. Our patients with post-operative hypoparathyroidism are older than patients without post-operative hypoparathyroidism, but no age-based difference was found between patients with transient and permanent hypoparathyroidism. In our study, serum 25(OH)D < 20 ng/mL is accepted as VDD; however, different results can be obtained when vitamin D deficient and insufficient patients are compared. We found that in patients with permanent hypoparathyroidism with VDD, every 1 ng/mL of deficiency in 25(OH)D levels increased the risk of permanent hypoparathyroidism 0.766-fold.

There are some limitations of our study. The first is that the study was retrospective. Prospective studies may enable better understanding of the causes of hypoparathyroidism. The second limitation is that our data were collected from a large study population (933 patients) but in a single center hospital; therefore, a few institutional databases with larger populations may reflect more accurate results. Our patients received calcitriol and calcium supplements based on their serum calcium and PTH measurements after surgery. Because this study is retrospective, the analysis of symptomatic transient hypoparathyroidism has not been clearly investigated. In addition, because this study is not prospective, a cut-off value for PTH for permanent hypoparathyroidism and recovery time of patients with transient hypoparathyroidism could not be given because the data for repeated laboratory tests were not complete for the post-operative first days and weeks; however, in the first month, there was a significant difference between patients with transient and permanent hypoparathyroidism. Nevertheless, mean PTH levels can shed light on this concern.

Conclusion

Post-operative hypoparathyroidism is a common risk for patients who undergo TT due to the long hospitalization period, repetitive laboratory tests, and the administration of various medications. Permanent hypoparathyroidism developed in 2.1% of our patients who underwent TT, and in these patients during the post-operative first month, mean serum PTH levels were 7.58 pg/mL and remained low during the post-operative first year. Indication of thyroid surgery due to malignant thyroid diseases, tumor multifocality, incidental parathyroidectomy, and pre-operative VDD were found to be risk factors for permanent hypoparathyroidism. Therefore, pre-operative VDD should be treated with vitamin D supplementation, and low PTH levels during the post-operative first month is important in the predictivity of permanent hypoparathyroidism.

Riassunto

L'ipoparatiroidismo postoperatorio è una complicanza possibile della chirurgia della tiroide, e ci siamo proposti di studiarne incidenza transitoria o permanente, e cau-

se, in 933 pazienti della nostra casistica di operati alla tiroide controllati retrospettivamente.
Si tratta della casistica dei un singolo unico centro, e di una valutazione retrospettiva riguardante l'incidenza dell'ipoparatiroidismo postoperatorio, le caratteristiche clinico-patologiche del pazienti, ed i parametri di laboratorio del primo giorno postoperatorio, del primo mese e del primo anno di questi pazienti, senza o con ipoparatiroidismo, distinguendo in quest'ultimo gruppo l'ipoparatiroidismo transitorio o permanente.
Come risultato abbiamo riscontrato un'incidenza di ipoparatiroidismo postoperatorio del 22,7% - rispettivamente 20,6% transitorio e 2,1% permanente.
Con l'analisi multivariata i fattori indipendenti di previsione dell'ipoparatiroidismo sono risultati: interventi per patologia maligna, multifocalità del tumore, carenza preoperatoria di vitamina D (VDD) – rispettivamente p<0,001; 0.047; 0.002).
Durante il primo mese postoperatorio i livelli medi del PTH nel siero sono stati trovati essere 7,58 pg/ml, rimanendo bassi per tutto il primo anno postopertorio in caso di iperparatiroidismo permanente.
In conclusione la chirurgia per patologia maligna e la carenza preoperatoria di vit D dovrebbero essere considerato fattori di rischio di ipoparatiroidismo postoperatorio nel pazienti candidati ad intervento chirurgico. Il primo mese postoperatorio è importante per la previsione dell'ipoparatiroidismo permanente.

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