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Factors Affecting Incidence of Hypocalcemia Post Thyroid Surgery

Tiroid Ameliyatı Sonrası Hipokalsemi İnsidansını Etkileyen Faktörler

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Abstract

Objective: Thyroid surgery is a common surgical procedure. Hypocalcemia after thyroid surgery continues to be a significant medical complication. The present study evaluates the rate of transient hypocalcemia (TH) and permanent hypocalcemia (PH) post thyroid surgery and investigates the predictive factors behind its development. **Material and Methods:** In this study, we retrospectively evaluated 2,381 cases who underwent thyroidectomy between the years 2009 and 2019. TH and PH were assessed based on clinicopathological features. **Results:** The mean age of patients included in this study was 45 (14-87) years; 35.8% were under the age of 40 83.6% were females. The rate of incidental parathyroidectomy (confirmed by pathology reports) was 9.7% (n=199). TH and PH developed in 16.1% (n=316) and 5.1% (n=105) of the cases, respectively. Incidental parathyroidectomy and total thyroidectomy [odds ratio (OR) 95% confidence interval (CI); 1.767, 3.017] can be considered independent risk factors for the development of TH. Age, gender, absence of preoperative hyperthyroidism, total thyroidectomy, Hashimoto thyroiditis, thyroid gland volume, and incidental parathyroidectomy are the risk factors for the development of PH [OR (95% CI); 0.981, 3.695, 2.65, 4.270, 1.741 1.002, 2.235]. **Conclusion:** The incidence of permanent hypocalcemia development in patients with preoperative hyperthyroidism is low.

Keywords: Hypocalcemia; thyroidectomy; parathyroid gland; hyperthyroidism

Özet

Amaç: Tiroid cerrahisi yaygın bir cerrahi girişimdir. Tiroid cerrahisi sonrası hipokalsemi önemli bir tıbbi komplikasyon olmaya devam etmektedir. Bu çalışma, tiroid cerrahisi sonrası geçici ve kalıcı hipokalsemi oranlarını değerlendirmekte ve gelişiminin arkasındaki öngörücü faktörleri araştırmaktadır. **Gereç ve Yöntemler:** Bu çalışmada, 2009-2019 yılları arasında tiroidektomi yapılan 2.381 olgu retrospektif olarak değerlendirildi. Geçici ve kalıcı hipokalsemi, klinik ve patolojik özelliklere göre değerlendirildi. **Bulgular:** Bu çalışmaya dâhil edilen hastaların ortalama yaşı 45 (14-87), %35,8'i 40 yaşın altında ve %83,6'sı kadındı. İnsidental paratiroidektomi oranı (patoloji raporları ile doğrulanan) %9,7 (n=199) idi. Olguların sırasıyla %16,1'inde (n=316) ve %5,1'inde (n=105) geçici ve kalıcı hipokalsemi gelişti. İnsidental paratiroidektomi ve total tiroidektomi [göreceli olasılıklar oranı [odds ratio (OR)] %95 güven aralığı (GA); 1,767, 3,017] geçici hipokalsemi gelişimi için bağımsız risk faktörleri olarak saptandı. Yaş, cinsiyet, preoperatif hipertiroidi olmaması, total tiroidektomi, Hashimoto tiroiditi, tiroid bezi hacmi ve insidental paratiroidektomi kalıcı hipokalsemi gelişimi için risk faktörleri olarak saptandı [OR (%95 GA); 0,981, 3,695, 2,65, 4,270, 1,741 1,002, 2,235]. **Sonuç:** Preoperatif hipertiroidili hastalarda kalıcı hipokalsemi gelişme insidansı düşüktür.

Anahtar kelimeler: Hipokalsemi; tiroidektomi; paratiroid bezi; hipertiroidizm

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Introduction

Thyroid surgery is among the most common surgical procedures (1). Post-surgical complications are seen in more than half the cases, including postoperative bleeding, hoarseness, and hypocalcemia [transient hypocalcemia (TH) or permanent hypocalcemia (PH)], among which hypocalcemia is the most common (2). Although some existing underlying conditions and preoperative risk factors have been addressed, hypocalcemia prevention and treatment remains a challenge (3). The present study evaluated the rates of TH and PH developed post-surgery and investigated the predictive factors behind its occurrence. The information provided in this study will assist clinicians in predicting the risk of hypocalcemia post-surgery and plan treatment strategies accordingly.

Material and Methods

Study Design

This study lists 2,381 cases of thyroidectomy performed in our center between 2009 and 2019. Weretrospectively evaluated the data with the information availed from the hospital records. We excluded 327 cases because of missing data; history of anterior neck surgery; preoperative abnormal levels of calcium, parathyroid hormone, albumin, and alkaline phosphatase (n=304); parathyroid autotransplantation (n=23).

Ethical Statement

The permission to conduct this study was obtained from the Clinical Research Ethics Committee of İnönü University (Date: 08.01.2020, Approval No: 2019/215) and have followed the Principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" amended in October 2013, www.wma.net). Informed consent was obtained from the patients included in the study.

Laboratory Reports and Their Interpretations

Calcium levels were measured before and after surgery (within 24-48 h, the following month, and then 6th months later). Post-surgery, 8.5-10.5 mg/dL calcium were considered acceptable values. Calcium levels below 8.5 mg/dL along with clinical symptoms including postoperative numbness in the perioral area or hands, Chvostek sign, Trousseau sign, or the presence of tetany were defined as TH. Patients without clinical signs but with calcium levels below 8.0 mg/dL were also included in the TH group. PH was considered if calcium level was less than 8.0 mg/dL, or parathormone level was below 13 pg/mL, or clinical symptoms persisted even with prescribed calcium supplement 6 months post-operation. Incidental parathyroidectomy is the presence of parathyroid tissue in a thyroidectomy specimen.

TH and PH were evaluated based on certain factors, such as age and gender of the patient, the experience of the surgeon, American Society of Anesthesiologists (ASA) score, the surgical procedure involved, existing hyperthyroidism or Hashimoto thyroiditis, presence of malignancy, tumor dimensions (mm), presence of multifocal tumors, thyroid volume (cm^3), and the number of incidental parathyroidectomies. Hyperthyroidism was diagnosed as per the result of thyroid function tests (T3, T4, and thyroid-stimulating hormone) conducted before surgery, and Hashimoto thyroiditis diagnosis was based on postoperative histopathological evaluation. Thyroid gland volume was measured macroscopically by pathologists after thyroidectomy. The experience of the physician was based on the mean number of thyroid surgeries performed annually by 26 general surgeons and surgical oncologists who worked at our center during the stated period (less experienced: 1-10 operations/year; medium experienced: 11-24 operations/year; highly experienced: ≥25 operations/year).

Statistical Analysis

The Number Cruncher Statistical System 2007 program (Kaysville, Utah, USA) was used for the statistical analysis. Descriptive statistical values (mean, median, frequency, percentage, standard deviation, minimum, and maximum values) were used for the estimation of the data. The normality of the distribution of the numerical values was tested with the Shapiro-Wilk test and graphs. The student's t-test and

Mann-Whitney U test were used for the comparison of quantitative variables between the 2 groups with and without normal distribution, respectively. Pearson's chi-square test, Fisher-Freeman-Halton test, and Fisher's exact test were used for comparing qualitative variables. The level of statistical significance was accepted as $p<0.05$. An receiver operating characteristics (ROC) curve analysis was used to assess the sensitivity, specificity, and cut-off values of the parametric data with statistical significance. The differentiation rate of the cut-off value was considered high when the area under the curve (AUC) was above 0.5 and close to 1.

All variables with a p value <0.10 in the univariate analyses were considered eligible for inclusion in the multivariate analysis and were tested for collinearity. A stepwise univariate and multivariate logistic regression analysis was performed. Variables that remained significant ($p<0.05$) in the multivariate model were considered independent predictors of TH and PH. Hosmer-Lemeshow goodness of fit statistics was used to assess the model fit. Odds ratio and 95% confidence intervals were calculated for each predictor.

Results

The median age of patients included in the study was 45 (14-87) years, 736 (35.8%) were under the age of 40, and 83.6% were females. Hyperthyroidism and Hashimoto thyroiditis was diagnosed in 281 (13.7%) and 507 (24.7%) patients, respectively. The median thyroid volume, measured postoperatively, was found to be 145 cm^3 (4.5-1,700).

Malignancy was detected in 15.8% (n=325) of the patients. The median tumor dimension was 7 mm (range: 1-75 mm), and multifocal tumors were present in 23.1% (n=75) cases. The number of operations performed annually by the surgeons was between 2 and 68 (average=26). Out of total thyroidectomy cases of 87.4% (n=1,795), 71.3% (n=1,454) were performed by experienced surgeons. The incidental parathyroidectomy was reported in 9.7% (n=199); at least one parathyroid gland was detected in 86.4% of cases. TH and PH were found in 16.1% (n=316) and 5.1% (n=105) of the cases, respectively.

Transient Hypocalcemia

No statistically significant association was found between age, gender, ASA score, presence of hyperthyroidism, presence of Hashimoto thyroiditis, malignancy, tumor dimension or the presence of multifocal tumors, the experience of the surgeons, the number of incidental parathyroidectomies, and the development of TH ($p>0.05$) (Table 1).

A statistically significant association was found between thyroid volume and the development of TH ($p=0.025$); the thyroid volume, removed from patients that developed TH, was found to be higher than in those without hypocalcemia. Thyroid volume (post thyroidectomy) of 185 cm^3 was regarded as the cut-off level for the development of TH in a ROC analysis (AUC: 0.540; $p=0.024$). The incidence of TH inpatients who underwent a bilateral total thyroidectomy (total thyroidectomy and completion total thyroidectomy for cancer) was found to be higher than in those with subtotal thyroidectomy (unilateral total, one side total/other subtotals, and bilateral subtotal thyroidectomies, $p<0.01$). The rate of TH was higher in the group with incidental parathyroidectomy ($p=0.001$). The Enter method used for logistic regression analysis identified the presence of incidental parathyroidectomy and total thyroidectomy as independent risk factors for the development of TH (Table 1, Table 2).

Permanent Hypocalcemia

The median age of patients that developed PH was found to be lower than those without hypocalcemia, that is, the rate of development of PH decreased with increased age ($p=0.014$). Thus, young age was an independent risk factor for the development of PH according to logistic regression analysis. An ROC analysis revealed that the risk of development of PH was significantly higher in patients aged 46 years and younger ($p=0.008$, AUC: 0.571) (Table 1, Table 2, Figure 1).

PH prevalence was higher in women than in men ($p<0.01$), and the logistic regression analysis revealed gender to be an independent risk factor for the development of PH ($p=0.038$).

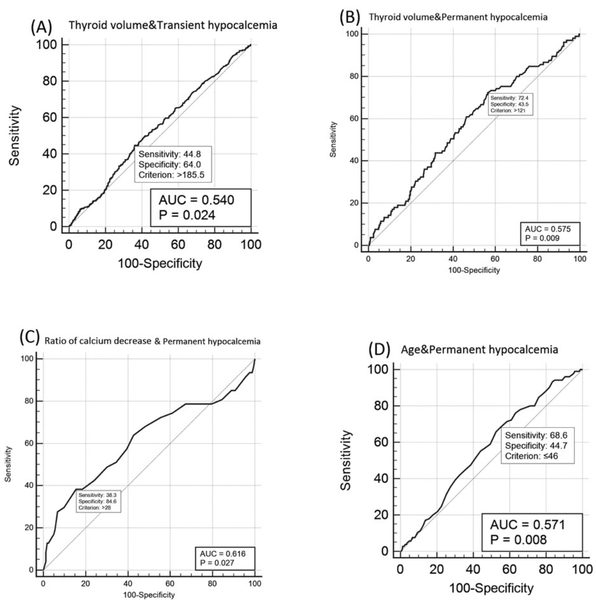
Table 1. The relationship between demographics, pre&postoperative features, and hypocalcemia.

		Transient hypocalcemia			Permanent hypocalcemia		
		Yes (n=316)	No (n=1,633)	p value	Yes (n=105)	No (n=1,949)	p value
Age	Minimum-maximum (median)	16-84 (44.5)	14-87 (45)	[a]0.513	17-74 (41)	14-87 (45)	**[a]0.014***
Gender, (%)	Male	45 (13.8)	280 (86.2)	[b]0.172	5 (1.4)	331 (98.6)	**[b]0.001****
	Female	271 (16.7)	1,353 (83.5)		100 (5.8)	1,618 (94.2)	
Hyperthyroidism, n (%)	Yes	51 (19.1)	216 (81.5)	[b]0.212	6 (2.1)	275 (97.9)	**[b]0.015***
	No	265 (15.7)	1,417 (84.3)		99 (5.6)	1,674 (94.4)	
Hashimoto thyroiditis, n (%)	Yes	85 (18)	387 (82)	[b]0.196	39 (7.7)	468 (92.3)	**[b]0.002****
	No	231 (15.7)	1,261 (84.5)		66 (4.3)	1,481 (95.7)	
Thyroid volume cm^3	Minimum-maximum (median)	12.8-1,105 (160)	4.5-1,700 (140)	**[d]0.025***	13.5-1,020 (180)	4.5-1,700 (142.9)	**[a]0.010***
Malignancy, n (%)	Malign	49 (16.3)	250 (83.7)	[b]0.908	21 (6.5)	304 (93.5)	[b]0.229
	Benign	267 (16.2)	1,383 (83.8)		84 (4.8)	1,645 (95.2)	
Tumor size (n=325)	Minimum-maximum (median)	1-65 (6)	1-75 (7)	[d]0.495	1-45 (12)	1-75 (7)	[a]0.127
Multifocality; n (%) (n=325)	Yes	15 (21.4)	55 (78.6)	[b]0.159	5 (6.6)	70 (93.4)	[d]1.000
	No	34 (14.4)	202 (85.6)		16 (6.4)	234 (93.6)	
Surgeon's experience (n=2,040)	Low	24 (18,9)	103 (81.1)	[a]0.121	7 (5.3)	125 (94.7)	[a]0.624
	Medium	75 (17.2)	362 (82.8)		19 (4.2)	435 (95.8)	
	High	216 (15.6)	1,168 (84.4)		77 (5.3)	1,377 (94.7)	
Type of surgery, n (%)	Total	301 (17.4)	1,420 (82.6)	[c]0.001**	102 (5.6)	1,717 (94.4)	**[c]0.005**
	Subtotal	15 (6.8)	213 (93.2)		3 (1.3)	232 (98.7)	
IPT; n (%)	Yes	45 (25)	135 (75)	**[b]0.001****	19 (9.5)	180 (91.5)	[b]0.003**
	No	271 (15.3)	1,498 (84.7)		86 (4.4)	1,769 (95.6)	
Number of IPT; n (%) (n=199)	1	38 (23.7)	122 (76.3)	[b]0.565	14 (8.1)	158 (91.9)	[d]0.148
	≥2	7 (29.2)	17 (70.8)		5 (18.5)	22 (81.5)	
BCD, % (n=209)	Mean±SD	21.80±6.05	16.00±3.0		24.43±8.09	21.77±6.05	[e]0.041*

*$p<0.05$; **$p<0.01$ [a]Mann-Whitney U test; [b]Pearson's chi-square test; [c]Fisher-Freeman-Halton test; [d]Fisher's exact test; [e]Student's t-test; SD: Standard deviation; IPT: Incidental parathyroidectomy; BCD: Blood calcium drop.

Table 2. Logistic regression analysis related to transient and permanent hypocalcemia.		
-Independent predictors of transient hypocalcemia		
Risk factors	**OR (95% CI)**	**p value**
Incidental parathyroidectomy	1.767 (1.230-2.538)	**0.002**
Total thyroidectomy	3.017 (1.761-5.169)	**<0.001**
The p value of the Hosmer-Lemeshow test was 0.845; the following factors were entered into the multivariate logistic regression analysis: The presence of incidental parathyroidectomy, thyroid volume, and total thyroidectomy.		
-Independent predictors of permanent hypocalcemia		
Risk factors	**OR (95% CI)**	**p value**
Age	0.981 (0.965-0.996)	**0.017**
Gender, female	3.695 (1.472-9.271)	**0.005**
Hyperthyroidism		
Presence	0.377 (0.163-0.874)	**0.023**
Absence	2.65 (1.14-6.13)	
Total thyroidectomy	4.270 (1.334-13.672)	**0.014**
Hashimoto thyroiditis	1.741 (1.146-2.643)	**0.009**
Thyroid volume	1.002 (1.001-1.003)	**0.003**
Incidental parathyroidectomy	2.235 (1.311-3.808)	**0.003**

The p value of the Hosmer-Lemeshow test was 0.957; the following factors were entered into the multivariate logistic regression analysis: Age, gender, hyperthyroidism, total thyroidectomy, Hashimoto thyroiditis, presence of incidental parathyroidectomy, thyroid volume; OR: Odds ratio; CI: Confidence interval.



Results of ROC analyzes.

	Cut-off value	AUC	Sensitivity (%)*	Specificity (%)*	Positive predictive value*	Negative predictive value*	*p value*
Thyroid vol. vs. TH (A)	>185.5 (cm^3)	0.540	44.8	64	19.2	85.8	***0.024***
Thyroid vol. vs. PH (B)	>121 (cm^3)	0.575	72.4	43.5	6.5	96.7	***0.009***
Calcium drop (%) vs. PH (C)	>28	0.616	38.3	84.6	41.9	82.5	***0.027***
Age vs. PH (D)	≤46	0.571	68.6	44.7	6.3	96.3	***0.008***

**95% Confidence Interval, AUC: Area Under Curve, TH: Transient hypocalcemia, PH:Permanent hypocalcemia*

Figure 1. Graphics and results of receiver operating characteristics analyzes.
AUC: Area under the curve.

A statistically significant inverse association was found between hyperthyroidism and the development of PH; the rate of development of PH in patients with hyperthyroidism was low (p=0.015). A logistic regression analysis revealed that the presence of hyperthyroidism decreased the risk of PH development to 0.377. A statistically significant association was found between the presence of Hashimoto thyroiditis and PH (p=0.002);

the risk of development of PH was high in patients with
Hashimoto thyroiditis. Furthermore, logistic regression analysis found the rate of development of PH to be statistically higher in patients with Hashimoto thyroiditis (p=0.030). The thyroid volume (post thyroidectomy) was higher in patients who developed PH than in those who did not (p=0.010; p<0.05) -indicating thyroid volume to be an independent risk factor for the development of PH according to logistic regression analysis (a higher risk by 1,002-fold). A ROC analysis revealed that a thyroid volume of 121 cm^3 was a risk factor for the development of PH (p=0.009, AUC: 0.575). The rate of PH in the group detected with incidental parathyroidectomy was higher than in the group with no detection of incidental parathyroidectomy (p=0.003); the cases of incidental parathyroidectomy, as per logistic regression analysis, was an independent risk factor for the development of PH, increasing the risk by 2,235-fold. Serum calcium levels at pre and postoperative stages in patients that developed PH, was found to be significantly higher (p=0.041). An ROC analysis revealed a 28% or greater decrease in the serum calcium value estimated before and after (24-48 h) surgery could be considered a risk factor for the development of PH (p=0.027, AUC: 0.616) (Table 1, Table 2, Figure 1).

No significant statistical association was found between the ASA score, the presence of malignancy, tumor dimension, the status of multifocal tumors, experience of the surgeon, surgical method, the number of incidental parathyroidectomies, and the development of PH (p>0.05) (Table 1).

Discussion

Surgical hypoparathyroidism (with a reported incidence varying between 0.33% and 68%) is the most common complication in thyroid surgery. TH and PH occur in up to two-thirds and one-tenth (≥10%) of thyroidectomy cases, respectively (4). Extensive surgery, bilateral thyroid surgery, reoperation, Graves' and Hashimoto diseases are the risk factors involved (2,5). The *in situ* preservation of the parathyroid glands and their blood supply plays a key role in the prevention of surgical hypoparathyroidism. Operations performed by highly experienced surgeons, preoperative localization of aberrant parathyroid glands, preoperative replacement treatment in high-risk patients, immediate implantation of parathyroid glands or delayed implantation of frozen parathyroid glands that are inadvertently excised or have impaired blood supply, and postoperative vitamin D and calcium supplements are recommended to reduce the risk of surgical hypoparathyroidism (5-7). Although the definition of surgical hypoparathyroidism is debatable, TH is defined as low levels of blood calcium post thyroid surgery. PH is characterized by parathyroid function abnormality, even after 6 months of thyroidectomy (5,6).

Hypocalcemia is generally seen in young patients after thyroidectomy (8,9), although it is also reported in aged patients (10,11). Interestingly, meta-analyses have revealed no association between hypocalcemia and age (12). In our study, we found PH developing in many young patients (aged 46 years or younger). Sands et al. reported that compared to men, females showed a 2-fold higher probability of developing TH (13). This result corroborates with other reports (12,14) and also with our findings, where we show a 2.7-fold greater risk of hypocalcemia in females.

Adam et al. reported that patients operated by surgeons performing >25 thyroid surgeries per year had a low risk of morbidity (15). The development of hypocalcemia after thyroidectomy is associated with surgical techniques, surgeon's experience (16-18), and postoperative management (18). However, we did not find any statistical correlation between the surgeon's experience and the occurrence of either TH or PH. Our center employs a few inexperienced surgeons, but intraoperative consultations and close cooperation between them explain our result.

The effect of hyperthyroidism and Graves' disease on hypocalcemia is controversial. Even with opposing views (12), many studies and meta-analyses published to date have found Graves' disease to be a risk factor for the occurrence of hypocalcemia post total thyroidectomy (1,19,20). Ríos Zambudio et al. found that patients were at a higher risk of developing PH post multinodular goiter surgeries (21). Conversely, Edafe reported hyperthyroidism and hypocalcemia as unrelated conditions (20). In contrast, we found hyperthyroidism decreased the risk of PH occurrence. In other words, the absence of preoperative hyperthyroidism increases the risk (2.65 times) of PH, a finding not reported earlier. Hypocalcemia seems to be less common in patients suspected to have cancer, as surgeons are meticulous in such cases (22), and the same may be true for hyperthyroidism cases, where the risk of post-surgery bleeding is high (12). The increase in parathormone after hyperthyroidism treatment results in a significant decrease in serum sclerostin and bone marker concentrations (23). Surgical procedures for thyroid cancer and multinodular goiter may contribute more to the development of hypocalcemia than the treatment of hyperthyroidism.

As emphasized frequently in the literature, a higher rate of hypocalcemia (in the case of total thyroidectomy) was also seen in our study. The risk of TH and PH development post total thyroidectomy was increased by 3-and 4.2-fold, respectively.

Ebrahimi et al. reported that the risk of TH and PH was increased in patients with Hashimoto's disease undergoing total thyroidectomy (24). As per the American Association of Clinical Endocrinologists and the American College of Endocrinology, autoimmune thyroid diseases (including Hashimoto disease) can lead to hypocalcemia (6), a report in conflict with other studies (3,13,25). Based on our data, Hashimoto's thyroiditis (which is an independent risk factor for PH) increases the risk of hypocalcemia by 1.7-fold.

In a study by Zheng et al. malignancy was shown to be associated with PH, while tumor localization and its multifocality were unrelated (26). Some studies, however, claimed that malignancy does not facilitate the development of hypocalcemia (13,22,25). In the present study, the presence of malignancy, tumor diameter, and multifocality were unassociated factors for TH and PH development.

The weight of the thyroid (post thyroidectomy) material is associated with PH- the more the weight, the more are the chances of post-surgical complications (1,26). In this study, we preferred to estimate the thyroid volume. As a cut-off value, a volume of 185 cm^3 and 121 cm^3 were found to be risk factors for the development of TH and PH, respectively. We found thyroid volume as an independent risk factor for the development of PH. A sharp fall in calcium levels following total thyroidectomy is associated with TH and PH (27,28). Our result showed that a decrease in preoperative serum calcium levels in the first 24 h was associated with PH in univariate analysis; however, no statistical association was found in a multivariate analysis.

The rate of incidental parathyroidectomy is around 2.3-21.6% and is directly associated with the experience of the surgeon (22,26,29). Ozoğul et al. reported that hypocalcemia development was common after incidental parathyroidectomy (29). Baloch et al. stated that hypocalcemia could be prevented with meticulous surgical techniques and the proper preservation of parathyroid glands (27). Some studies have reported that the identification of a small number of parathyroid glands during surgery increases the risk of TH (30). Most researchers suggest that a single intact parathyroid gland is sufficient for its normal function (31), even though some studies do not link incidental parathyroidectomy with hypocalcemia (22). Incidental parathyroidectomy was found to be an independent risk factor for both TH and PH in our study. That said, no difference was found between one or more incidental parathyroidectomy.

Study Limitations

Retrospective analysis and a few missing data are the limitations of this study. Also, we were unable to diagnose hungry bone syndrome or analyze vitamin D levels in patients with TH.

Conclusion

Based on our data, incidental parathyroidectomy and total thyroidectomy should be considered independent risk factors for the development of TH. Age, gender, absence of preoperative hyperthyroidism, total thyroidectomy, presence of Hashimoto thyroiditis, high volume of the thyroid gland, and the presence of incidental parathyroidectomy are independent risk factors for the development of PH. The low incidence of PH in patients with existing hyperthyroidism is the significant finding of this study. Whether hyperthyroidism reduces PH remains to be seen in future studies.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Nidal İflazoğlu, Ecem Memişoğlu; Design: Nidal İflazoğlu, Ecem Memişoğlu, Mehmet Onur Gül; Control/Supervision: Mehmet Onur Gül, Coşkun Onak; Data Collection and/or Processing: Nidal İflazoğlu, Ecem Memişoğlu, Mehmet Onur Gül, Coşkun Onak; Analysis and/or Interpretation: Nidal İflazoğlu, Mehmet Onur Gül, Coşkun Onak; Literature Review: Ecem Memişoğlu, Coşkun Onak; Writing the Article: Nidal İflazoğlu; Critical Review: Mehmet Onur Gül, Coşkun Onak; References and Fundings: Ecem Memişoğlu; Materials: Nidal İflazoğlu, Mehmet Onur Gül, Coşkun Onak, Ecem Memişoğlu.

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