

# Factors Affecting Hypocalcaemia Following Total Thyroidectomy: A Prospective Study

## Total Tiroidektomi Sonrası Hipokalsemiyi Etkileyen Faktörler: Prospektif Bir Çalışma

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### Abstract

**Objective:** After thyroidectomy hypocalcaemia is the most significant complication for clinicians. In this study, we investigated the factors associated with development of hypocalcaemia after thyroidectomy.

**Materials and Methods:** We investigated the patients prospectively for age, gender, preoperative diagnosis, hormonal status, operative time, operating surgeon, existence of parathyroid gland injury at the operation, parathyroid gland auto-transplantation, preoperative use of anti-thyroid drugs and amount of bleeding at the operation. After operation in 1 and 2 days, serum calcium and phosphor, and in the 1 day parathyroid hormone values were evaluated. The chi-square test was applied in the analysis of categorical variables. Logistic regression model was used to determine the risk of hypocalcaemia in the univariate analysis.

**Results:** Hypocalcaemia developed in 47 of 196 patients. Female gender, preoperative diagnosis of thyroid cancer and toxic nodular goitre, <3cm nodule size, parathyroid injury and auto-transplantation and low vitamin D levels were factors found to be associated with hypocalcaemia in the Logistic regression analysis.

**Conclusion:** The factors associated with hypocalcaemia were defined to be "gender, preoperative diagnosis, parathyroid gland injury, nodule size and vitamin D deficiency", it is a multifactorial problem and it would not be proper to define a few etiological factors.

**Key Words:** Thyroidectomy, hypocalcaemia

### Özet

**Amaç:** Tiroidektomi sonrası hipokalsemi tiroid ameliyatlarının en sık karşılaşılan komplikasyonlarından olup günümüzde klinisyenler açısından hala önemini korumaktadır. Biz bu çalışmada tiroidektomi sonrası hipokalsemi gelişmesine etki eden faktörleri araştırdık.

**Gereç ve Yöntem:** Hastaların prospektif olarak yaş, cinsiyet, preoperatif tanı, hormonal durum, ameliyat süresi, ameliyatı yapan doktor, ameliyatta paratiroid hasarı olup olmadığı, paratiroid ototransplantasyonu yapıp yapılmadığı, ameliyat öncesi antitiroid ajan kullanıp kullanmadığı, ameliyattaki kanama miktarları yönünden değerlendirildi. Ameliyattan sonra 1. ve 2. günlerde serum kalsiyum ve fosfor, 1. günde paratiroid hormon düzeylerine bakıldı. Kategorik değişkenlerde ki-kare testi uygulandı. Tek değişkenli analizlerde hipokalsemi riskini belirlemek için lojistik regresyon modeli uygulandı.

**Bulgular:** Hastaların 47'sinde hipokalsemi bulguları geliştiği görüldü. Hipokalsemi bulguları gelişen hastalarda, cinsiyetin kadın olmasının, preoperatif tanının tiroid kanseri ve toksik noduler guatr olmasının, nodül boyutunun 3 cm'den küçük olmasının, paratiroid hasarı ve ototransplantasyon yapılmış olmasının, vitamin D düzeyinin düşük olmasının hipokalsemi gelişmesi ile ilişkili olduğu görüldü.

**Sonuç:** Çalışmamızda hipokalsemi bulguları gelişmesi üzerine etkili faktörler "cinsiyet, preoperatif tanı, paratiroid hasarı, nodül boyutları ve Vitamin D eksikliği" olarak bulunmasına rağmen, hipokalsemi etyolojisinin sadece bu faktörlere bağlamak doğru olmaz, bu daha çok multifaktöriyel bir durumdur.

**Anahtar Kelimeler:** Tiroidektomi, hipokalsemi

### Introduction

Thyroidectomy performed for any cause is among the endocrine operations most commonly performed by surgeons [1]. The mortality after thyroid operations is nearly zero and these operations have no severe morbidity. However, the most common complications are superior and inferior nerve injury and hypocalcaemia.

The rate of transient hypoparathyroidism following thyroid surgery is between 6.9 and 49%, while that of permanent hypoparathyroidism changes between 0.4% and 33%.

Hypocalcaemia-related symptoms are observed 24 and 48 hours after the operation [2]. There are patients and clinical conditions under risk for hypocalcaemia.

Our aim in this study is to investigate the factors affecting the development of hypocalcaemia on patients undergoing thyroid surgery.

### Materials and Methods

The study protocol was approved by the Board of Ethics of Medical Faculty, Ataturk University. One hundred and ninety-

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six patients who had undergone total thyroidectomy at the Ataturk University Medical Faculty, Department of General Surgery, between October 15, 2007 and October 15, 2008 were included in the study. The patients were assessed prospectively for age, gender, preoperative diagnosis (multinodular goitre, toxic goitre, thyroid cancer, Basedow-Graves, thyroiditis, recurrence), hormonal status (hypothyroidism, euthyroidism, hyperthyroidism), operation time, the surgeon performing the operation {less experienced (Assistant Professor- senior resident), experienced (Associate Professor- senior resident), highly experienced (Professor-senior resident)}, presence of parathyroid injury during the operation, parathyroid auto-transplantation, preoperative antithyroid agent use, amount of haemorrhage during operation, and nodule diameter. The relation of all these factors with hypocalcaemia was assessed.

Preoperative thyroid function tests, parathyroid hormone (PTH) levels, serum calcium (Ca), phosphorus (P), and vitamin D (Vit-D) levels were tested before the operation. The thyroid gland was evaluated by ultrasound. After the operation, the serum Ca and P were analyzed on the first and second days and the PTH levels were assessed on the first day. In patients with hypocalcaemia symptoms, Ca and P levels were followed-up daily until the time of discharge. At the end of the first postoperative year, it was accepted as transient hypocalcaemia when hypocalcaemia did not continue after the treatment had ended; it was accepted as permanent hypocalcaemia when it persisted and the patients were followed up for one year.

The inclusion criteria of this study were as follows: elective surgery, no history of previous head and neck related radiotherapy and chemotherapy, total thyroidectomy, no laboratory or clinical findings related with hypocalcaemia before the operation, Ca levels under 8.8 mg/dL or under (8.8-10mg/dL) and hypocalcaemia findings in the postoperative period. Replacement treatment was started for patients with hypocalcaemia findings in the postoperative period. In patients with severe hypocalcaemia findings, intravenous Ca was started at the early period and oral Ca was continued in the maintenance treatment.

The data was given as numbers and percentages. The chi-square test was applied in the analysis of categorical

variables. Logistic regression model was used to determine the risk of hypocalcaemia in parameters when  $p < 0.2$  (gender, parathyroid injury, nodule size, D vitamin and preoperative diagnosis) in the univariate analysis. The estimated relative risk was calculated in the 95% confidence interval (CI). SPSS for windows version 19 package software was used in statistical analysis of the data. P value of  $< 0.05$  was accepted as statistically significant.

## Results

One hundred and ninety six patients were included in the study. One hundred and fifty three patients were female (78.1%) and 43 were male (21.9%). The female/male ratio was 3.55/1 and the mean age was  $49.11 \pm 13.7$ . The distribution of patients according to age and gender is presented in Table 1.

For 76% of the patients, the diagnosis was multinodular goitre and 77% was euthyroid. The mean operation time was 165 minutes and 58.6% of patients had a mean operation time between 120 and 179 minutes. Parathyroid injury was observed in seven patients. The mean amount of haemorrhage in these patients was 127.60 cc. The demographic characteristics of the patients are displayed in Table 2.

The mean calcium levels of patients in the preoperative period included in the study was 9.27 mg/dL. The mean postoperative calcium level was 7.84 mg/dL in the first day and 8.19 (4.7-9.8) in the second day. The preoperative and postoperative laboratory findings of the patients are presented in Table 3.

Among 196 patients included in the study, 47 had (24%) transient hypocalcaemia. In the analysis evaluating the factors effective on hypocalcaemia, gender, preoperative diagnosis, preoperative low Vit-D level, preoperative parathyroid injury and low size of the nodule were found to be effective factors that were statistically significant (Table 4). None of the 196 patients had permanent hypocalcaemia.

These parameters were analyzed using the logistic regression model to determine the risk of hypocalcaemia and the estimated relative risk was calculated. The highest estimated relative risk was 6.840 related to "damage to parathyroid" (Table 5).

**Table 1. The distribution of patients according to age and gender**

	Male		Female		Total	
	n	%	n	%	n	%
<19	1	0.5	4	2	5	2.5
between 20-49	15	7.7	82	41.8	97	49.5
>50	26	13.2	68	34.8	94	48
Total	42	21.4	154	78.6	196	100

**Table 2. The demographic data of the patients**

<b>Diagnosis</b>	<b>n</b>	<b>%</b>
Multinodular goitre	149	76
Basedow-graves	6	3.1
Toxic nodular goitre	14	7.1
Thyroid cancer	9	4.6
Recurrent goitre	18	9.2
<b>Hormonal status</b>		
Hypothyroid	6	3.1
Euthyroid	151	77
Hyperthyroid	39	19.9
<b>Operative time (mean: 165 minutes)</b>		
<119 minutes	26	13.3
120-179 minutes	115	58.6
>180 minutes	55	28.1
<b>Experience of the surgeon</b>		
Less experienced	21	10.8
Experienced	15	7.6
Very experienced	160	81.6
<b>Damage to the parathyroid</b>		
Yes	7	3.6
No	189	96.4
<b>Preoperative drug use</b>		
Yes	79	40.3
No	117	59.7
<b>The amount of bleeding (mean: 127.60 cc)</b>		
<99 cc	48	24.5
between 100-199 cc	97	49.5
between 200-299 cc	46	23.4
>300 cc	5	2.6
<b>nodule diameter</b>		
<3 cm	61	31.1
>3 cm	135	68.9

**Table 3. The preoperative and postoperative laboratory findings of the patients**

<b>Preoperative</b>	<b>range</b>	<b>average</b>
Calcium (mg/dL)	7.4-11.6	(9.27)
Phosphorus (mg/dL)	1.6-5.7	(3.3)
PTH (pg/mL)	11-449	(60.24)
Vit-D (ng/mL)	4-110	(12.97)
<b>Postoperative</b>	<b>range</b>	<b>average</b>
First day of calcium	5.6-9.6	(7.84)
Second day of calcium	4.7-9.8	(8.19)
PTH (pg/mL)	1.2-101	(35.2)

PTH: Parathyroid hormone

Table 4. Factors affecting the development of hypocalcaemia

		Hypocalcaemia			
		No		Yes	
		n	%	n	%
<b>Gender (p=0.032)</b>	Male	38	88.4	5	11.6
	Female	111	72.5	42	27.5
<b>Age (p=0.838)</b>	<19	4	80.0	1	20
	between 20-49	72	74.2	25	25.8
	>50	73	77.7	21	22.3
<b>Preoperative diagnosis (p=0.203)</b>	Multinodular goitre	118	79.2	31	20.8
	Basedow-graves	4	66.7	2	33.3
	Toxic nodular goitre	8	57.1	6	42.9
	Thyroid cancer	5	55.6	4	44.4
	Recurrent goitre	14	77.8	4	22.2
<b>Nodule diameter (p=0.052)</b>	< 3cm	41	67.2	20	32.8
	> 3cm	108	80.0	27	20
<b>Hormonal status (p=0.655)</b>	Hypothyroid	4	66.7	2	33.3
	Euthyroid	117	77.5	34	22.5
	Hyperthyroid	28	71.8	11	28.2
<b>Operative time (p=0.931)</b>	< 119 minutes	19	73.1	7	26.9
	120-179 minutes	88	76.5	27	23.5
	>180 minutes	42	76.4	13	23.6
<b>Experience of the surgeon (p=0.552)</b>	Less experienced	15	71.4	6	28.6
	Experienced	13	86.7	2	13.3
	Very experienced	121	75.6	39	24.4
<b>Damage to the parathyroid (p=0.036)</b>	No	146	77.2	43	22.8
	Yes	3	42.9	4	57.1
<b>The amount of bleeding (p=0.817)</b>	<99 cc	37	77.1	11	22.9
	between 100-199 cc	75	77.3	22	22.7
	between 200-299 cc	34	73.9	12	26.1
	>300 cc	3	60.0	2	40
<b>Preoperative drug use (p=0.167)</b>	Yes	56	70.9	23	29.1
	No	93	79.5	24	20.5
<b>Vitamin D (p=0.011)</b>	Normal	124	80.0	31	20
	Low	25	61.0	16	41

## Discussion

Thyroid nodule is a common clinical problem in the general population. In regions with iodine deficiency, palpable thyroid nodule is observed at a rate of 5% in women and in 1% in

men [3]. On ultrasonography, the thyroid nodule was found to have an incidence of 50% in individuals over 50; this rate was reported as 19-67% in some randomized studies [3-5]. There are more than 200 million goitre patients throughout the world. While goitre is commonly observed as endemic in

**Table 5. Logistic regression model**

Parameters	Chi-square	Logistic regression	The estimated relative risk
Gender	0.032	0.012	4.246
Preoperative diagnosis	0.020	0.008	3.943
Nodule diameter	0.052	0.121	0.560
Damage to the parathyroid	0.036	0.036	6.840
Vitamin D	0.011	0.003	3.439

our country, the prevalence of this disease has been determined to be about 30.5% [6].

Since the beginning of the twentieth century, there has been a decrease in complications and mortality after thyroid surgery [7]. However, thyroidectomy operations result in various complications, particularly hypocalcaemia. Because of these complications, many biochemical and hormonal tests are performed and the length of hospital stay increases. In order to alleviate the clinical symptoms and to decrease the severe complications, intravenous Ca treatment is necessary. Although hypocalcaemia spontaneously regresses in many patients, it may be permanent when an irreversible injury occurs in the parathyroid glands. As a result, this complication has increased the cost of thyroidectomy [8]. The incidence of hypocalcaemia has been reported to be between 6.9% and 49% in many studies [7, 9-13]. Consistent with the literature, 47 of 196 patients (24%) with total thyroidectomy displayed postoperative hypocalcaemia.

Various biological, clinical and surgical factors may contribute to the decrease in serum Ca levels following thyroid operation. Moderate asymptomatic hypocalcaemia is observed in 12 hours following bilateral or unilateral thyroidectomy, and in most cases this resolves spontaneously in 24 hours. Besides, serum P somewhat decreases in 24 hours. Haemodilution in the perioperative period may be responsible for the changes [8].

Different results have been reported in studies demonstrating the relationship between gender and hypocalcaemia. Although some studies show that gender has no significant effects on hypocalcaemia [8, 14, 15], in their study on 1022 patients, Unal et al. [16] found that the rates of transient and permanent hypocalcaemia were significantly high in women. In the present study, gender was found to be a significant risk factor in hypocalcaemia. In the logistic regression model, the estimated relative risk was determined as 4.246. Although this result is not concordant with most of the literature, we think that other risk factors have led to these findings. Furthermore, with women being affected to a higher extent than men by the psychological and social conditions, the effect of this on calcium metabolism should be investigated.

Postoperative hypocalcaemia as a significant risk factor in women has shown that supportive treatment is necessary in the early period, both before and after the operation.

In patients in whom thyroidectomy is performed for thyroid carcinoma, there are studies demonstrating hypocalcaemia following the operation. In these studies, significant hypocalcaemia is observed when neck dissection and paratracheal lymph node dissection are carried out together with thyroidectomy [14, 17]. It has also been shown in some studies that there is no significant relationship between the diagnosis in surgery and the hypocalcaemia findings after the operation [15, 16]. In the present study, it was discovered that the preoperative diagnosis did not have a significant effect on the development of hypocalcaemia findings. Patients undergoing surgery for toxic nodular goitre and thyroid carcinoma (with neck dissection) showed hypocalcaemia symptoms at the rates of 42.9% and 44.4%, respectively. When these two groups of patients were regarded as the first group and the other preoperative diagnosis groups as the second group, the hypocalcaemia findings were found to be significant in the first group. In the logistic regression model, the estimated relative risk was determined as 3.943. We believe that neck dissection in malignant cases should not be performed at the same session, and while thyroidectomy is performed, the parathyroid glands should be completely explored and protected in order to decrease the risk of hypocalcaemia.

In two different studies carried out by Filho et al. [7, 14], they found that the size of thyroid nodule had no effect on the incidence of hypocalcaemia. Akgün et al. [18] stated that patients with larger nodules more frequently had hypocalcaemia, although not significant. In the present study, patients with thyroid nodules less than 3cm showed significantly higher rates of hypocalcaemia. In the logistic regression, the estimated relative risk was determined as 0.560.

Parathyroid injury during thyroidectomy and related autotransplantation and incidental parathyroidectomy are independent factors for hypocalcaemia. Moreover, with an increase in the number of injured parathyroid glands, the findings of hypocalcaemia are observed earlier and last longer [8, 19-21]. In this study, it was found that parathyroid

injury and autotransplantation and incidental parathyroidectomy were significant risk factors for hypocalcaemia. The estimated relative risk was determined as 6.840 in the logistic regression analysis. We think that parathyroid glands can be protected following a careful operation, although when the blood supply of the parathyroid glands are destroyed or when they are accidentally excised, they should be autotransplanted inside the sternocleidomastoid muscle.

Vitamin D deficiency occurs due to insufficient intake, covering the head and skin, and life style that causes inadequate exposure to sunlight [22]. Vitamin D deficiency is more common in elderly people. Insufficient nutrition, decreased skin vitamin D synthesis and decreased use of sunlight are the most significant causes of vitamin D deficiency in the elderly [23]. There are studies showing that there are less findings of hypocalcaemia in patients who received vitamin D and Ca postoperatively than those who did not [24, 25]. Erbil et al. [26] determined the findings of hypocalcaemia to be significantly higher in those with lower than normal preoperative vitamin D levels. Conversely, Chia et al. [27] stated that there was no relationship between preoperative vitamin D levels and postoperative hypocalcaemia findings. In the present study, the rate of hypocalcaemia was significantly high in patients with low Vit-D levels. According to the logistic regression model, the estimated relative risk was determined as 3.439. In patients for whom thyroidectomy is planned, Vit-D levels should be monitored to obtain normal values before thyroidectomy, or the postoperative vitamin D should be replaced in the postoperative period.

In conclusion hypocalcaemia, whether symptomatic or not, is one of the most common complications observed following thyroid operations. Therefore, calcium levels should be tested in the first 24 hours following thyroidectomy; in case one or more factors exist, medical treatment should be administered whether symptomatic or not. Hypocalcaemia following thyroidectomy may develop due to several causes. Sex, preoperative diagnosis, parathyroid injury, nodule size and Vit-D deficiency have all been found to be effective factors in the development of hypocalcaemia.

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**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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