Int Surg 2018;**103:**344–350
DOI: 10.9738/INTSURG-D-18-00024.1

Occurrence of Clinically Significant Hypocalcemia 6 to 12 Months After Total Thyroidectomy Could Be Overrated: Results of a Prospective Multicenter Study

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Objective: The aim of this study was to compare 2 groups of patients, normocalcemic and hypocalcemic, 6 to 12 months after total thyroidectomy and to determine the clinical value of the calcium levels on hospital discharge.

Summary of background data: Thyroid surgeries are among the most common operations performed in the world. Hypocalcemia after total thyroidectomy is a common complication that is sometimes difficult to correct.

Methods: From January 2015 through April 2017, 400 patients were included in this prospective multicenter study. All the patients underwent total thyroidectomy. By way of random of selection, 2 groups of patients were formed: 30 patients who had a normal level of calcium detected in the blood on discharge from the hospital after total thyroidectomy (normocalcemia group), and 30 patients who had a reduced level of calcium in the blood on discharge from the hospital (hypocalcemia group). In these groups of patients, various parameters were determined.

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Results: The comparison of patient groups with normocalcemia and hypocalcemia on discharge from the hospital and 6 to 12 months after surgery demonstrated that there were no statistically significant factors for postoperative hypocalcemia. Generally, there were no differences between the groups 6 to 12 months after surgery.

Conclusions: Treatment with calcium and 25-hydroxyvitamin D preparations after surgery leads to disappearance of both biochemical and clinical expression of hypocalcemia in most cases. On discharge from the hospital, patients with more pronounced hypocalcemia should be administered calcium and calcitriol preparations, even in the absence of clinical symptoms.

Key words: Total thyroidectomy – Hypocalcemia – Thyroid – Predictors

Thyroid surgeries are among the most common operations in the world.[1] Thyroid surgery is the definitive management option for thyroid malignancies and for benign diseases such as multinodular goiter with compression symptoms.[2] Hypocalcemia following total thyroidectomy (TT) is a relatively frequent complication, which is sometimes difficult to correct. Temporary hypocalcemia occurs in 50%–68% of post-TT patients,[3,4] whereas permanent hypocalcemia occurs in 3% of post-TT patients.[5–7] Temporary hypocalcemia is defined by various authors as a postsurgery decrease in calcium (Ca), lasting for 6 to 12 months; permanent hypocalcemia is a post-TT decrease in Ca lasting for more than 12 months.[8] Post-TT hypocalcemia depends on a number of factors including biochemical blood parameters before and after surgery, clinical effects and factors related to surgery, surgical technique, surgeon's experience, the patient, and the disease.[9]

The aim of this study was to compare 2 patient groups: those with normocalcemia and those with post-TT hypocalcemia on discharge from the hospital and to assess the frequency of hypocalcemia and risk factors for its development in the long term (6–12 months) after surgery.

Materials and Methods

From January 2015 to April 2017, 400 patients underwent surgeries for various thyroid diseases at Klaipėda University Hospital, Lithuania, and Vilnius University Hospital Santaros Klinikos, Lithuania. Permission from the Lithuanian Bioethics Committee was obtained for this prospective multicenter research (02/12/2014, No. L-14-09/1, No. L-14-09/2). All patients signed a consent form before surgery. The inclusion criteria for this study were age >18 years and thyroid nodules, thyroid carcinoma, or thyroiditis. Some patients had more than 1 indication for surgery. The exclusion criteria for this study were previous hemithyroidectomy, lobectomy, resection of the thyroid gland, and diagnosed pathology of parathyroid glands (PGs).

Various factors that may influence post-TT hypocalcemia were investigated, including preoperative and postoperative biochemical blood parameters, clinical effects and factors related to surgery, the patient, and the disease. Postoperative hypocalcemia was diagnosed when the level of Ca in the blood was <2.10 mmol/L. Before surgery, Ca, ionized calcium (iCa), parathyroid hormone (PTH), 25-hydroxyvitamin D (25-hydroxy Vit D), and thyroid hormones were measured. Length of stay in hospital for patients after surgery was 2 days. Measurements following TT on hospital days 1 and 2 at 6:00 AM in the morning were performed. On hospital day 1 after surgery, Ca, iCa, and PTH were measured. On hospital day 2 after surgery, Ca and iCa were measured. Clinical expression of postoperative hypocalcemia and the time when the disease manifested were assessed. The impact of surgery-related factors on postoperative hypocalcemia was analyzed, including the number of PGs observed during the surgery, number of autotransplanted PGs, and ligation of vessels supplying blood to the thyroid gland.

By way of random selection, 2 groups of patients were formed: 30 patients who had a normal level of Ca detected in the blood on discharge from the hospital following TT (normocalcemia group) and 30 patients who had a reduced level of Ca in the blood on discharge from the hospital (hypocalcemia group). In these groups of patients, the following parameters were determined: Ca, iCa, 25-hydroxy Vit D, PTH, clinical expression of hypocalcemia, and the use of Ca and calcitriol preparations on

discharge from the hospital and 6 to 12 months after surgery.

All blood samples were taken from a peripheral vein. PTH and 25-hydroxy Vit D were measured with a Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany). The normal range of 25-hydroxy Vit D in the blood is 75.00 to 106.75 nmol/L for men and 75.00 to 124.75 nmol/L for women. The normal PTH range is 15.00 to 65.00 pg/mL. The levels of Ca and iCa were determined with an Architect ci8200 analyzer (Abbot, Wiesbaden, Germany).

The normal range of Ca in the blood is 2.10 to 2.55 mmol/L, and the normal range of iCa in the blood is 1.00 to 1.30 mmol/L.

Statistical analysis

Comparison of health variables between hypocalcaemia [no (0), yes (1)] groups was performed using Student *t*-tests and Mann-Whitney *U* tests. The χ^2 test or Fisher's exact test was used to estimate association between categorical variables. The comparison of proportions between categories was performed using the z-test. After testing for normality, we used parametric or nonparametric tests. $P < 0.05$ was assumed to indicate significance. Computation was performed using SPSS v24.0 statistical software (SPSS, Chicago, Illinois).

Results

The inclusion criteria for this study were thyroid nodules in 361 patients (90.3%), thyroid carcinoma in 84 patients (21%), and thyroiditis in 37 patients (9.3%). Some patients had a few pathologies. By way of random selection, 2 groups of patients were formed: 30 patients who had a normal postoperative level of Ca (normocalcemia group) and 30 patients who had a reduced level of Ca (hypocalcemia group). There were 8 women (26.7%) and 22 men (73.3%) in the normocalcemia group and 3 women (10%) and 27 men (90.04%) in the hypocalcemia group ($P = 0.095$). The mean age of the subjects was 56.7 years in the normocalcemia group and 61.1 years in the hypocalcemia group ($P = 0.195$). The mean weight was 82.7 and 83.4 kg in the normocalcemia and hypocalcemia groups, respectively ($P = 0.867$).

In our study, Graves' disease was present in 2 patients (6.7%) in the hypocalcemia group. We did not observe any patients with Graves' disease in the normocalcemia group ($P = 0.150$). Recurrent multinodular goiter was diagnosed in 1e case (3.3%) in the normocalcemia group. We did not observe any patients with recurrent multinodular goiter from the hypocalcemia group ($P = 0.313$). Retrosternal multinodular goiter was present in 2 patients (6.7%) in the hypocalcemia group, but there were no patients with this condition in the normocalcemia group ($P = 0.150$). Thyrotoxicosis before surgery for <10 years was present in 7 patients (23.3%) in the normocalcemia group and in 9 patients (30%) in the hypocalcemia group ($P = 0.841$). Thyrotoxicosis before surgery for ≥10 years was diagnosed in 1 case (3.3%) in the normocalcemia group and in the hypocalcemia group (3.3%).

On discharge from the hospital (day 2), symptomatic hypocalcemia developed in 7 patients (23.3%) of the patients from the hypocalcemia group ($P = 0.019$). Numbness of the fingers was present in 7 patients (23.3%). Chvostek's symptoms were detected in 1 patient (3.3%) from the hypocalcemia group ($P = 0.313$). We did not observe any patients with Trousseau's symptoms. Six and 12 months after surgery, numbness of fingers was present in 1 patient from the hypocalcemia group.

Histopathologic analysis revealed colloidal nodules in 47 patients (78.3%), adenomatous nodules in 8 patients (13.3%), follicular adenoma in 3 patients (5%), papillary carcinoma in 9 patients (15%), and autoimmune thyroiditis in 6 patients (10%).

Thyroidectomy with 1-sided central lymphadenectomy was performed in 7 cases of cancer.

During the surgery, the surgeon tried to preserve PGs, and PG autotransplantations were performed in 6 patients (10%). In our study, 2 PGs were observed in 20 patients (33.3%), 3 PGs were observed in 28 patients (46.7%), and 4 PGs were observed in 12 patients (20%). Four patients (6.7%) developed PG hematoma.

To preserve the blood supply of each identifiable PG, careful extracapsular dissection was performed. The upper branch of left inferior thyroid artery, lower branch of left inferior thyroid artery, upper branch of right inferior thyroid artery, and lower branch of right inferior thyroid artery were not ligated in all 60 patients (normocalcemia and hypocalcemia groups). The trunk of the left inferior thyroid artery and the trunk of the right inferior thyroid artery were ligated in all 60 patients (normocalcemia and hypocalcemia groups). The demographic data of the subjects are presented in Table 1.

On discharge from the hospital (day 2), Ca and calcitriol preparations were administered in 37 of

Table 1 Patients demographics and clinical characteristics

Variables[a]	Normocalcemia	Hypocalcemia	*P*
Preoperative calcium, mmol/L			
Mean (SD)[b]	2.374 (0.076)	2.336 (0.083)	0.072
MD (IQR)	2.38 (0.11)	2.36 (0.08)	
Preoperative ionized calcium, mmol/L			
Mean (SD)[b]	1.038 (0.042)	1.0124 (0.099)	0.027
MD (IQR)	1.03 (0.07)	1.02 (0.06)	
Preoperative PTH, ng/L(pg/mL)			
Mean (SD)[b]	53. 23 (18.54)	56.22 (15.50)	0.501
MD (IQR)	51.09 (19.57)	54.62 (25.035)	
Preoperative 25-hydroxyvitamin D, nmol/L,			
Mean (SD)[c]	45.03 (24.20)	43.44 (19.15)	0.779
MD (IQR)	42.63 (30.44)	40.32 (29.75)	
Preoperative TSH, mlU/L			
Mean (SD)[c]	0.897 (0.883)	0.959 (0.843)	0.782
MD (IQR)	0.76 (0.77)	0.67 (1.34)	
Preoperative FT3, pmol/L			
Mean (SD)[b]	5.034 (1.227)	4.645 (.480)	0.111
MD (IQR)	4.84 (0.75)	4.71 (0.67)	
Preoperative FT4, pmol/L			
Mean (SD)[b]	13.14 (1.71)	13.665 (2.118)	0.615
MD (IQR)	13.11 (2.46)	13.52 (3.35)	
Thyroidectomy without lymphadenectomy, n (%)	30	30	
No	3 (10.0)	4 (13.3)	$\chi^2 = 0.16$, $\delta\phi = 1$, $\pi = 0.688$
Yes	27 (90.0)	26 (86.7)	
Thyroidectomy with bilateral central lymphadenectomy, n (%)			
No	30 (100)	30 (100)	
Number of darkened parathyroid glands at the end of surgery, n (%)			
0	28 (93.4)*	22 (73.3)*	$\chi^2 = 7.16$, $\delta\phi = 2$, $\pi = 0.028$
1	1 (3.3)*	8 (26.7)*	
3	1 (3.3)	0	

FT3, free triiodothyronine; FT4, free thyroxine; IQR, interquartile ratio; TSH, thyroid stimulating hormone.

[a]Continuous variables are presented as mean (SD) and median (IQR); categorical variables are presented as n (%).

[b]Student *t*-test.

[c]Mann-Whitney *U* test.

*$P < 0.05$, z-test.

the 60 patients. At the end of the study (6–12 months after surgery), 18 patients received Ca and calcitriol preparations. Of them, 14 patients used Ca and calcitriol preparations irregularly due to osteoporosis. They had a normal range of Ca in the blood. Three patients used Ca and calcitriol preparations regularly due to osteoporosis. They had a normal range of Ca in the blood also. No clinical symptoms were observed 6 to 12 months after surgery in 1 of the 2 patients with hypocalcemia. The patient did not take Ca and calcitriol preparations. The other patient complained of numbness of fingers and was taking Ca and calcitriol preparations. These data are presented in Table 2.

Based on the data of our study, the comparison of patient groups with normocalcemia and hypocalcemia on discharge from the hospital and 6 to 12 months after surgery demonstrated that there were no statistically significant factors for postoperative hypocalcemia. Generally, there were no differences between the groups 6 to 12 months after surgery.

A reduced level of Ca in the blood was determined in the group of patients with hypocalcemia on discharge from the hospital; meanwhile, 6 to 12 months after surgery, reduced Ca in the same group was determined only in 2 subjects. Other subjects in this group had normal Ca levels in the blood. In the normocalcemia group, Ca remained normal both on discharge from the hospital and 6 to 12 months after surgery. We used McNemar's test and found that, in the group with postoperative normocalcemia, there were no patients with hypocalcemia after 6 to 12 months, and long-term hypocalcemia was determined only in 2 of 30 patients in the group with postoperative hypocalcemia. These data are presented in Table 3.

Table 2 Clinical and biochemical data on discharge from the hospital (day 2) and after 6 to 12 months

Variables[a]	On discharge from the hospital (day 2)			6 to 12 months after surgery		
	Normocalcemia (n = 30)	Hypocalcemia (n = 30)	*P*	Normocalcemia (n = 58)	Hypocalcemia (n = 2)	*P*
PTH, ng/L(pg/mL)						
Mean (SD)	42.67 (14.460)	27.31 (19.491)	0.001	58.89 (31.57)	24.96 (28.02)	0.163
MD (IQR)	38.67 (17.21)	27.26 (27.41)		50.89 (29.34)	24.96	
25-hydroxyvitamin D, nmol/L						
Mean (SD)	45.03 (24.20)	43.44 (19.15)	0.779	54.12 (27.88)	22.81 (15.05)	0.081
MD (IQR)[c]	42.63 (30.44)	40.32 (29.75)		49.33 (37.03)	22.81	
Calcium, mmol/L						
Mean (SD)	2.159 (0.087)	1.933 (0.110)	<0.001	2.362 (0.091)	1.93 (0.142)	0.001
MD (IQR)	2.15 (0.11)	1.94 (0.18)		2.37 (0.13)	1.93	
Ionized calcium, mol/L						
Mean (SD)	1.019 (0.045)	0.917 (0.049)	<0.001	1.007 (0.045)	0.860 (0.113)	0.018
MD (IQR)	1.016 (0.04)	0.920 (0.08)		1.005 (0.06)	0.86	
Treatment administered upon discharge						
n (%)	23 (76.7)	0	$\chi^2 = 34.13$, $\delta\phi = 1$, $\pi < 0.001$			
No	7 (23.3)	30 (100)				
Yes						
Have been taking calcium and calcitriol preparations, n (%)						
No				41 (70.7)	1 (50.0)	$\chi^2 = 13.98$, $\delta\phi = 2$, $\pi = 0.066$
Irregularly				14 (24.1)	0	
Regularly				3 (5.2)	1 (50.0)	

Association between categorical variables estimated using χ^2 test or Fisher's exact test.

[a]Continuous variables are presented as mean (SD) and median (IQR); categorical variables are presented as n (%).

[b]Student *t*-test.

[c]Mann-Whitney *U* test.

Discussion

Post-TT hypocalcemia is one of the most common complications of surgery.[10] In the literature, most patients exhibit asymptomatic hypocalcemia and need no treatment or only oral administration of Ca and calcitriol preparations.[11] Based on the data from our study, 23 patients (76.7%) in the hypocalcemia group had asymptomatic hypocalcemia on hospital day 2, and 28 patients (93.3%) had it 6 to 12 months after surgery. Numbness of fingers on hospital day 2 after surgery was observed in 7 patients (23.3%) in the hypocalcemia group. However, 6 to 12 months after surgery, only 1 patient complained about numbness of fingers. In a multicenter study with 14,934 patients, Rosato *et al*[3] found that 10% of patients had symptomatic hypocalcemia. However, that study included patients who had TT (64.3%) and smaller-scale surgeries on the thyroid (35.7%).[3]

Table 3 Calcemia on discharge from the hospital (day 2) and after 6 to 12 months (McNemar's test)

Calcemia on day 2 after surgery	Calcemia 6 to 12 months after surgery		
	Normocalcemia	Hypocalcemia	Total
Normocalcemia	30 (51.7)	0	30 (50.0)
Hypocalcemia	28 (48.3)	2 (100)	30 (50.0)
Total	58 (100)	2 (100)	60 (100)

($\chi^2 = 2.1$, df = 1, $P = 0.150$); $P < 0.01$.

Post-TT–reduced PTH recovers in many patients within several weeks to 1 month after surgery.[12,13] According to the data of some studies, the function of PGs after TT normally recovers when PTH in the blood is 10 pg/mL or more and no hypocalcemia symptoms are present.[13,14] In other studies, the function of PGs returns to normal when patients do not need to take Ca and calcitriol preparations.[1,15] Many authors claim that post-TT function of PGs becomes normal when a normal PTH value is determined in the blood, and patients do not need to take Ca and calcitriol preparations.[16–19] Lorente-Poch *et al*[20] reported that approximately 20% of

patients who recover from protracted hypoparathyroidism do so after 6 months. In our study, reduced PTH in the blood was determined in 9 patients during the first 24 hours after surgery in the hypocalcemia group. However, after 6 to 12 months, only 1 patient had reduced PTH in this group. The patient complained about numbness of fingers and was taking Ca and calcitriol preparations.

A retrospective analysis with 1054 patients conducted by Ritter *et al*[19] demonstrated that only 1.9% of patients developed long-term hypoparathyroidism 1 year after surgery and needed Ca and calcitriol preparations. According to the data of our study, persistent hypocalcemia could be anticipated in 2 patients from the postoperative hypocalcemia group. Of the 2 mentioned patients with hypocalcemia, no clinical symptoms were observed in 1 patient 6 to 12 months after surgery. The patient did not take Ca and calcitriol preparations. The other patient, with remaining numbness of fingers, PTH of 5.14 pg/mL, and Ca of 1.77 mmol/L in the blood 6 to 12 months after TT, regularly takes Ca and calcitriol preparations.

The amount of Ca in the blood is significant for faster functional recovery of the PGs after TT. The greater the Ca, the higher the probability of recovery of affected PGs.[20] Therefore, Ca and calcitriol preparations are frequently administered on discharge from the hospital to patients with more pronounced hypocalcemia, even in the absence of clinical symptoms.

Many authors suggested routine administration of Ca and calcitriol preparations to all patients undergoing TT.[21] Others recommended postoperative Ca measurements as the standard protocol of care.[22]

Conclusions

Hypocalcemia is a frequent post-TT complication; however, in most cases, it regresses after 6 to 12 months (especially if Ca and calcitriol preparations are taken) and does not cause any long-term negative effects. Based on the data of our study, there were no statistically significant factors for postoperative hypocalcemia 6 to 12 months after thyroid surgery. Generally, there were no differences between the groups 6 to 12 months after surgery.

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