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ORIGINAL ARTICLE

Rate of drop in serum calcium as a predictor of hypocalcemic symptoms post total thyroidectomy

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Abstract

Summary The rate of drop in serum calcium post total thyroidectomy is a predictor of hypocalcemic symptoms in adults, after adjusting for other significant covariates.

Introduction Test the hypothesis that rate of drop in calcium is a significant and independent predictor of post-operative hypocalcemic symptoms post total thyroidectomy.

Methods A retrospective chart review (electronic and hard copy) for 429 patients who underwent total thyroidectomy from January 2011 to December 2016. We collected information on demographics, clinical characteristics, information on surgical intervention, histopathology reports, clinical course, biochemistries, treatments and discharge instructions.

Results Sixty-one patients (14%) developed post-operative hypocalcemic symptoms. The rate of calcium drop, younger age, female gender, and lower body mass index, and the presence of parathyroid tissue in resected specimen all correlated significantly with the development of symptoms. The rate of drop in serum calcium and the post-operative serum calcium level remained the only significant predictors of symptom development, after adjustment for other significant co-variates. Using a receiver operating characteristics curve, a cutoff rate of calcium drop > 0.083 mg/dl/h, that is 1 mg/dl over 12 h, has a sensitivity of 71% and specificity of 73% for detecting hypocalcemic symptoms.

Conclusion The rate of drop of serum calcium post total thyroidectomy significantly and independently correlated with the development of hypocalcemic symptoms. Patients with a rate of drop < 1 mg/dl/12 h may be considered for earlier discharge and less aggressive management peri-operatively.

Keywords Rate of calcium drop · Symptomatic hypocalcemia · Thyroidectomy · Transient hypoparathyroidism

Introduction

Post-operative hypocalcemia is a major complication following total thyroidectomy [1–3]. Depending on the definition used, the risk of transient hypocalcemia varies between 7 and 37% [2, 4] and the risk of permanent hypocalcemia between < 1 [1] and 2.3% [3]. Post-thyroidectomy hypocalcemia typically occurs early on [5] and is defined as a serum calcium (Ca) level < 8.0–8.6 mg/dl [1, 3, 5, 6], depending on the study and laboratory reference used. Patients may remain asymptomatic or may develop peri-oral or digital numbness, carpopedal spasms, tetany [6, 7], seizures, or even cardiac arrhythmias [1]. Although in the majority of cases, hypocalcemia is transient [1, 7], the presence of symptoms can prolong hospitalization [7, 8], necessitate frequent blood draws [3], and cause readmissions [7], thus increasing patient discomfort and cost of care [7, 8]. Many previous studies have evaluated the risk factors and predictors of post-thyroidectomy hypocalcemia and hypoparathyroidism [3, 5–7, 9–15], but few investigated predictors of symptomatic hypocalcemia [16–18].

The primary objective of our study is to test the hypothesis that the rate of drop in Ca is a significant predictor of post-operative hypocalcemic symptoms, in patients undergoing total thyroidectomy. If so, it could be a useful guide in the post-operative management of these patients. We also investigated the incidence of symptomatic hypocalcemia post-total thyroidectomy at our center and its predictors.

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Methods

This is a retrospective chart review of all total thyroidectomies conducted on adults between January 2011 and December 2016, at the American University of Beirut-Medical Center (AUB-MC), a university-based tertiary care center. We collected all relevant information from the electronic and hard copy medical records of each patient. This included demographics, clinical characteristics, information on surgical intervention, histopathology reports, clinical course, biochemistries, treatments, and discharge instructions.

Exclusion criteria were cases who underwent re-do thyroidectomies, received radioactive iodine pre-operatively, underwent concomitant or prior parathyroidectomy, were known to have hyperparathyroidism or a solid or hematological malignancy, and had a head or neck malignancy surgery, renal insufficiency (with estimated glomerular filtration rate eGFR < 60 ml/min/1.73 m^2), pre-operative hypocalcemia (Ca level < 8 mg/dl), or in whom pre-operative Ca level was not measured.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was followed [19].

Survey data

Demographics and clinical profile

The information we collected included demographics, such as gender, age (years), body mass index (BMI, kg/m^2); number of comorbidities, including diabetes mellitus; and pre-operative home medications, including Ca and vitamin D (vit D) supplementation. We also retrieved the pre-operative cytologic diagnosis from fine needle aspirate (FNA) reports if the procedure was performed at AUB-MC, or from physician notes, as available. The categories were Graves' disease (GD), toxic nodular goiter (TNG), toxic nodule (TN), simple goiter, and nodules suspicious for malignancy or found to harbor a malignancy.

The chemistry and hormone levels we obtained were pre-operative Ca, phosphorus (PO_4), magnesium (Mg), and thyroid stimulating hormone (TSH), if done within 3 months prior to the thyroidectomy, and 25-hydroxy vitamin D level if done within 6 months of the thyroidectomy.

Surgical and pathology findings

We also obtained information on the length of surgery, on whether lymph node dissection was performed, and if so whether dissection was only central or central in addition to lateral neck dissection (unilateral or bilateral). We retrieved the histopathological diagnosis as recorded: differentiated or un-differentiated thyroid malignancy, GD, TNG, TN or simple goiter. We gathered information on the presence or absence of parathyroid tissue in the resected specimen, and the weight of the thyroid tissue removed from the pathology report.

Biochemical and clinical hypocalcemia

We retrieved information on signs and symptoms of hypocalcemia from the notes of the registered nurses and the medical and surgical teams involved. These were peri-oral or chin numbness, extremity paresthesia or tingling, carpo-pedal spasm, tetany, seizures, or positive Chvostek sign. Patients were educated pre-operatively and directly post-operatively by both the surgical team and the endocrinology consult service, with regard to possible post-operative hypocalcemia symptoms. Patients were instructed to report on any symptoms once they occur. Furthermore, our hospital has been accredited by the Magnet Recognition Program, and our nurses are trained to actively ask about hypocalcemia symptoms in every post-thyroidectomy patient. Surgical residents round on patients directly on post-operative admission to the floor and pass by again with the surgeon at night and then once more the next morning. The endocrinology consult service visits the patient directly post-operatively and again the next morning.

We assumed that the time at which the symptoms occurred corresponds to the time at which symptoms were documented in the medical chart. This was matched to the corresponding serum Ca, PO_4, and Mg levels entered for the same time in the laboratory electronic records. For patients who did not develop symptoms, we collected the results of the first set of routine post-operative serum Ca, PO_4, and Mg levels, and noted the time at which these levels were withdrawn.

Post-operative treatment and discharge medications

We gathered information on post-operative treatment with Ca and Mg, as intravenous runs or continuous infusions, or as oral supplementation, in addition to the time at which these treatments were given. We also collected any record of in-hospital supplementation with alfacalcidol, vit D, and/or a thiazide. We noted the prescription for discharge medications, including any Ca, Mg, vit D, alfacalcidol, or thiazide.

Statistical analysis

The primary outcome was hypocalcemic symptoms, and the major predictor was the rate of drop in serum Ca. The rate of drop in serum Ca was calculated as follows:

$$\frac{\text{Ca preoperatively} - \text{Ca postoperatively}}{\text{Time at which Ca level was taken (hours postoperatively)}} = \frac{\text{mg}}{\text{hour}}$$

We defined pre-operative Ca as any serum Ca level taken within 3 months prior to the surgery, and post-operative Ca as the serum Ca level withdrawn at the time of symptoms or the first post-operative serum Ca level withdrawn if symptoms do not occur.

The covariates investigated [7, 14] included age, gender, BMI, diabetes mellitus, pre-operative cytologic or clinical diagnosis, pre-operative serum biochemistries and hormone levels, length of surgery, lymph node dissection, histopathology, presence of parathyroid tissue in resected specimen, thyroid weight, and post-operative serum chemistries associated with symptoms.

We summarized baseline demographic characteristics using frequencies and percentages, *n* (%), for categorical variables, and mean ± standard deviation, $n \pm SD$, for continuous variables. We assumed normality of all variables based on our large sample size (central limit theorem).

Variables for which less than 5% of the data was missing were imputed using the mean estimate for such variable. These included pre-operative dose of Ca supplementation, pre-operative Mg and PO_4 level, resected thyroid weight, and first post-operative PO_4 level (3%, 4%, 2%, 4%, and 1% missing, respectively). Variables for which more than 5% of the data was missing were pre-operative TSH level, 25-hydroxy-vitamin D level, and cytology and post-operative Mg level (missing in 21%, 35%, 51%, and 31% of cases, respectively). We analyzed these according to the number of results available, with no imputation for missing values.

We compared between groups using chi-squared test or Fischer's exact test for the categorical variables and *t* test for continuous variables. We implemented a multiple logistic regression model and included the covariates, defined above, that were significant at the bivariate level ($p < 0.1$). We presented the magnitude of association between the predictors and the development of hypocalcemic symptoms as both crude and adjusted odds ratio (OR) with the corresponding 95% confidence interval (CI) and did not adjust for multiple *t*-testing. We rounded numbers to the nearest integer unless otherwise specified. SPSS version 23 (IBM, Chicago, USA) was used to conduct all statistical analysis, and a two-sided *p* value of < 0.05 was considered as significant.

Results

Demographics

Of the total of 548 patients who underwent total thyroidectomy during the specified period at AUB-MC, 429 patients were included in the analysis (Fig. 1). Table 1 summarizes the patients baseline characteristics. Patients were on the average 47 ± 13 years, and the majority (76%) were females. Nearly all the patients were of Lebanese origin (92%), most were non-smokers (56%), and almost half of the population were otherwise healthy (49%). Less than one third were on Ca or vit D supplementation preoperatively. Pre-operative diagnosis was available for 278 patients (65%), either from an FNA cytology report or documented in the medical notes: 11% of cases had an indeterminate cytology on FNA, while 38% had nodules that were either malignant or suspicious for malignancy.

The majority of surgeries were done by general surgeons and lasted on average 156 ± 74 min (Table 2). Lymph node dissection was performed in 174 (41%) cases: 144 (34%) only had central nodal dissection, and 55 (13%) also underwent concomitant lateral dissection. The mean length of hospital stay was 2 ± 1 days. Histopathology confirmed malignancy in 190 cases (44%), and parathyroid tissue was present in 16% of the resected specimens. The mean weight of the resected thyroid tissue was 57 ± 72 g (Table 2).

Post-operative symptoms of hypocalcemia and their predictors

A total of 61 patients (14%) developed hypocalcemic symptoms, including paresthesia, perioral numbness, muscle spasm, and/or tetany (Table 2). Younger age, female gender, lower BMI, absence of diabetes mellitus, higher pre-operative PO_4 level, and the presence of parathyroid tissue in the resected specimen predicted the development of hypocalcemic symptoms. Length of surgery tended to be longer in symptomatic subjects.

Pre-operative serum Ca was drawn on average 3 ± 5 days prior to the surgery, and only a minority, 27 (6%), had their serum Ca checked the morning of the surgery. Post-operatively, serum chemistry levels were drawn, on average, 13 ± 6 and 16 ± 6 h post-surgery in symptomatic and asymptomatic patients, respectively, $p < 0.001$. The post-operative Ca (7.8 ± 0.5 mg/dl), PO_4 (4.2 ± 0.8 mg/dl), and Mg (1.7 ± 0.2 mg/dl) levels significantly correlated with the development of symptoms. The rate of Ca drop was significantly associated with the development of hypocalcemic symptoms. Symptomatic patients had a mean rate of drop in serum Ca that was almost twice that in patients who remained asymptomatic (0.120 versus 0.072 mg/dl/h). Using a receiver operating characteristics (ROC) curve, a cutoff rate of Ca drop of 0.083 mg/dl/h has a sensitivity of 71% and specificity of 73% for detecting hypocalcemic symptoms, with an area under the curve of 0.74 (Fig. 2). This cutoff is equivalent to a drop of 0.5 mg/dl over 6 h, or 1 mg/dl over 12 h, and has a positive predictive value (PPV) of 30% (95% CI 25, 35) and a negative predictive value (NPV) of 94% (95% CI 91, 96) for the occurrence of symptoms.

Patients who developed hypocalcemic symptoms were more likely to have received parenteral Ca and Mg and oral alfacalcidol (Table 3). The doses of oral Ca and alfacalcidol

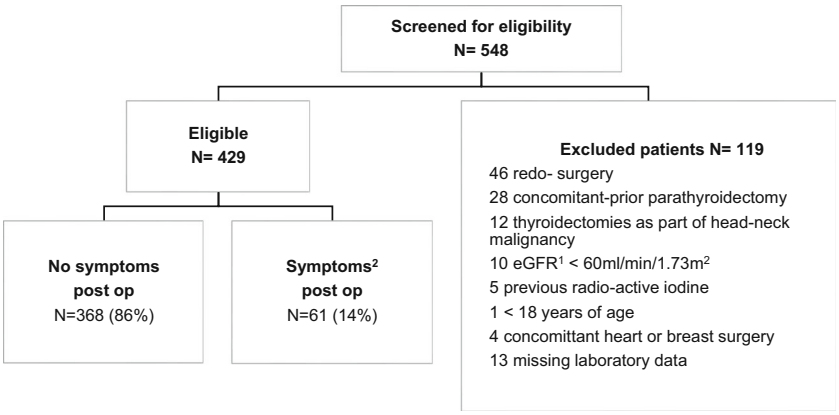

Fig. 1 Flow diagram detailing the selection of patients undergoing total thyroidectomy between January 2011 and December 2016 at AUB-MC. [1]eGFR estimated glomerular filtration rate, and [2] symptoms defined as peri-oral or chin numbness, extremity paresthesia or tingling, carpo-pedal spasm, tetany, or positive Chvostek sign

Table 1 Patient characteristics

Patient characteristics	Mean ± SD or *N* (%), *N* 429
Age (years)	47 ± 13
BMI (kg/m^2)	27.4 ± 5.0
Gender	
Female	325 (76)
Number of comorbidities[a]	
None	208 (49)
1	115 (27)
2	64 (15)
3	31 (7)
≥ 4	11 (2)
Diabetes mellitus	46 (11)
Pre-operative supplementation	
Vitamin D	116 (27)
Dose of vitamin D (IU/week)	18,345 ± 15,123
Calcium	91 (21)
Dose of calcium (mg/day)[b]	804 ± 292
Pre-operative cytologic[c] or clinical diagnosis	
Benign cytology	20 (5)
Indeterminate cytology[d]	47 (11)
Malignant cytology or suspicious for malignancy[e]	165 (38)
Toxic nodular goiter or toxic nodule[f]	33 (8)
Graves' disease[g]	17 (4)
Not available	151 (35)

[a] Comorbidities include coronary artery disease, hypertension, dyslipidemia, asthma or chronic obstructive pulmonary disease, hypothyroidism, pituitary disease, Addison disease, osteoporosis, steroid dependent rheumatic diseases, benign prostate hypertrophy, hematological disorder, neurologic diseases or psychiatric diseases

[b] Dose of elemental calcium

[c] Fine needle aspirate cytology result was available for 232 (54%) patients

[d] Indeterminate cytology includes Bethesda III and IV, i.e. atypia of undetermined significance (AUS), follicular lesion of undetermined significance (FLUS), follicular neoplasm (FN) and suspicious for FN

[e] Malignant cytology consisted of papillary thyroid cancer (PTC) but includes 6 medullary thyroid cancer (MTC) and 1 lymphoma

[f] Proportions do not add up to a 100% since two patients had both TNG and PTC

[g] Two patients had both Graves' disease and PTC

Table 2 Clinical, surgical, and pathological predictors of hypocalcemia symptoms

Characteristic	Symptoms, $N = 61$ (14)	No symptoms, $N = 368$ (86)	p value*
Age (years)	40 ± 12	48 ± 13	< 0.001
BMI (kg/m^2)	25.2 ± 5.1	27.8 ± 4.9	0.012
Gender			< 0.001
Female	54 (89)	271 (74)	
Diabetes mellitus	2 (3)	44 (12)	0.042
Pre-operative levels			
Calcium (mg/dl)	9.5 ± 0.4	9.5 ± 0.4	0.484
Magnesium (mg/dl)	2.0 ± 0.1	2.0 ± 0.2	0.682
Phosphorus (mg/dl)	3.6 ± 0.5	3.5 ± 0.5	0.037
25-Hydroxy vitamin D (ng/ml), (N = 209)	21.9 ± 12.7	25.1 ± 11.9	0.122
Thyroid stimulating hormone (mcU/mL), ($N = 338$)	2.11 ± 1.77	1.83 ± 2.19	0.394
Pre-operative cytologic[a] or clinical diagnosis			
Benign cytology	1 (2)	19 (5)	0.212
Indeterminate cytology[b]	8 (13)	39 (11)	0.561
Malignant cytology or suspicious for malignancy[c]	29 (47)	136 (37)	0.415
Toxic nodular goiter or toxic nodule[d]	5 (8)	28 (8)	0.774
Graves' disease[e]	4 (7)	13 (4)	0.501
Not available	14 (23)	137 (37)	
Length of surgery (minutes)	171 ± 79	154 ± 73	0.09
Lymph node dissection	31 (51)	143 (39)	0.078
Central dissection	27 (44)	117 (32)	0.056
Lateral dissection	10 (16)	45 (12)	0.367
Histopathology			
Benign	27 (44.3)	204 (55.4)	0.105
Malignant	31 (50.8)	159 (43.2)	0.268
Toxic nodular goiter or toxic nodule	1 (1.6)	1 (0.3)	0.264
Graves' disease	2 (3.3)	4 (1.1)	0.205
Presence of parathyroid tissue	15 (25)	53 (14)	0.044
Thyroid weight (g)	43 ± 49	59 ± 75	0.113
Post-operative levels (mg/dl)[f]			
First calcium level	8.1 ± 0.5	8.6 ± 0.6	< 0.001
Calcium level associated with symptoms	7.8 ± 0.5	NA	
First magnesium level (N = 295)	1.6 ± 0.2	1.8 ± 0.2	< 0.001
Magnesium level associated with symptoms	1.7 ± 0.2	NA	
First phosphorus level	4.2 ± 0.8	3.9 ± 0.7	0.002
Phosphorus level associated with symptoms	4.2 ± 0.8	NA	
Rate of drop in calcium (mg/h)	0.120 ± 0.120	0.072 ± 0.090	< 0.001

Values are presented as mean ± SD or frequency (%)

NA not applicable

*p value < 0.05 indicates significant difference between patients who developed symptoms and those who remained asymptomatic

[a] Fine needle aspirate cytology result was available for 232 (45%) patients

[b] Intermediate cytology includes atypia of undetermined significance (AUS), follicular lesion of undetermined significance (FLUS), follicular neoplasm (FN) and suspicious for FN

[c] Malignant cytology consisted of papillary thyroid cancer (PTC) but includes 6 medullary thyroid cancer (MTC) and 1 lymphoma

[d] Proportions do not add up to a 100% since two patients had both toxic nodular goiter/ toxic nodule and PTC

[e] Two patients had both Graves' disease and PTC

[f] Symptoms documented in the medical chart were matched to the corresponding chemistries entered for the same time in the laboratory electronic records. For patients who did not develop symptoms, the first set of post-operative serum Ca, PO_4, and Mg levels is noted

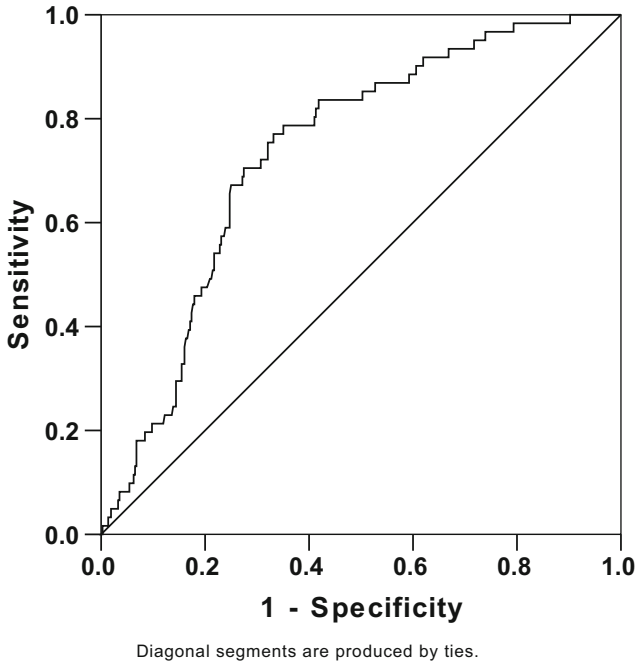

Fig. 2 Receiver operator characteristics curve for the rate of calcium drop post total thyroidectomy conducted in the study cohort, with area under the curve (AUC) of 0.74 (95% confidence interval [0.68, 0.8])

supplementation were also significantly higher in patients who developed post-operative symptoms. Patients who developed symptoms stayed one extra day in the hospital compared to those who remained asymptomatic. Symptomatic patients were also more likely to have been discharged on oral Ca, Mg, vit D, and/or alfacalcidol, with doses that were double those given to patients without symptoms (Table 3).

Our main predictor, the rate of drop in serum Ca, and post-operative serum Ca level were significantly associated with the development of symptoms at both the bivariate level, OR 6.2 (95% CI 3.4, 11.3) and OR 6.4 (3.7, 11.0), respectively, and at the multivariate level, OR 3.2 (3.2, 1.5) and OR 3.7 (2.0, 7.0), respectively (see Table 4). Using a lower ($p < 0.05$) or a higher ($p < 0.2$) cutoff, for entry of variables at the bivariate level into the multivariate model, gave the same results.

Normo-calcemic patients with symptoms

Out of the 61 symptomatic patients, 12 (20%) had a serum Ca level ≥ 8.5 mg/dl. Of these 12 patients, 6 (50%) had a rate of Ca drop ≥ 0.083 mg/dl/h. Using logistic regression, a normo-calcemic person with a rate of drop ≥ 0.083 mg/dl/h was 3.7 (95% CI 1.1, 12.5) more likely to develop symptoms compared to a person with a rate of drop < 0.083 mg/dl/h, after adjusting for serum Ca level. The number of subjects in this category ($N = 12$) was too small for a multivariate analysis.

Discussion

Hypocalcemia post-thyroidectomy is a common complication of thyroid surgery [1–3], and the development of symptoms can prolong hospitalization and increase the financial burden on both the patient and society [7, 8]. Hypocalcemia treatment is guided by both serum Ca level and concomitant symptoms [20]. Identifying high-risk patients is crucial for potential closer monitoring, earlier intervention, and thus hospital discharge [7].

In our study, 61 patients (14%) had hypocalcemic symptoms, of which most ($N = 49$, 80%), but not all, had true hypocalcemia (Ca < 8.5 mg/dl). Our main study variable, the rate of drop in serum Ca, and also the post-operative serum Ca level were significant predictors of hypocalcemic symptoms, even after adjustment for other significant covariates. Some patients developed symptoms of hypocalcemia in the presence of normal post-operative serum Ca level (≥ 8.5 mg/dl). In this subgroup of patients, the rate of serum Ca drop was a significant predictor of symptoms, independent of serum calcium, an interesting finding that can potentially guide management of symptomatic patients with normo-calecemia.

Several studies have specifically evaluated predictors of hypocalcemic symptoms [7, 10, 16–18, 21–28]. Most of these studies, however, evaluated the effectiveness and accuracy of parathyroid hormone (PTH), as a predictor of the occurrence of hypocalcemia symptoms, when measured perioperatively (i.e., at skin closure or 10 to 20 min post-thyroid removal) [22–25], 1 to 6 h post-operatively [16, 18, 21, 26, 27], 1 day post-operatively [17], or when calculated as a post-operative PTH decline from baseline [16, 17, 22, 24, 28]. A recent prospective cohort of 328 total thyroidectomy patients, using multilogistic analysis, concluded that malignant pathology and central neck dissection were the only significant predictors of symptomatic hypocalcemia [7]. This was not evident in our study, where only central neck dissection bordered on significance at the bivariate level but was not significant in adjusted analysis.

To our knowledge, no previous study has investigated the rate of serum Ca drop as a predictor of the occurrence of hypocalcemic symptoms. The parathyroid glands are exquisitely sensitive to minute to minute changes in serum ionized Ca [29]. The change of calcium as a predictor of hypocalcemia, but not of hypocalcemic symptoms, was investigated in few studies [30–32]. In 1995, a prospective study followed 150 patients undergoing total or near total thyroidectomy, and plotted serum Ca levels at 8, 14, and 20 h post-operatively. All patients with an upward trend in serum Ca at 20 h developed no hypocalcemia problems up to 1 week post-surgery, allowing for discharge within 23 h of surgery [30]. In 1998, another study showed similar results by calculating the slope between the first two Ca levels taken post-operatively as a percentage of change in Ca per hour [31]. Those with post-

Table 3 Length of hospital stay, in-hospital management and discharge medications

Characteristic	Symptoms, *N* (%) = 61 (14)	No symptoms, *N* (%) = 368 (86)	*p* value*
Post-operative in hospital management			
Received calcium (IV[a] and oral)	51 (84)	93 (25)	< 0.001
Received oral calcium only[b]	10 (17)	71 (19)	0.004
Oral calcium dose (mg/day)	1963 ± 936	1190 ± 647	0.001
Received alfacalcidol	30 (49)	32 (9)	< 0.001
Alfacalcidol dose (mcg/day)	1.23 ± 0.53	0.94 ± 0.49	0.027
Received IV magnesium sulfate	25 (41)	40 (11)	< 0.001
IV magnesium sulfate dose (g/day)	3 ± 2	2 ± 0	0.011
Received vitamin D	22 (36)	48 (13)	< 0.001
Vitamin D dose (IU/week)	29,102 ± 27,007	17,446 ± 16,580	0.072
Length of hospital stay (days)	3 ± 1	2 ± 1	0.001
Discharge medication			
Calcium	56 (92)	280 (76)	0.006
Dose of calcium (mg/day)[c]	2641 ± 1902	1518 ± 874	< 0.001
Magnesium	20 (33)	49 (13)	< 0.001
Dose of magnesium (mg/day)[d]	192 ± 96	96 ± 48	0.001
Alfacalcidol	38 (62)	96 (26)	< 0.001
Dose of alfacalcidol (mcg/day)	2 ± 1	1 ± 1	< 0.001
Thiazide	3 (5)	5 (1)	0.091
Thiazide (mg/day)	17 ± 7	15 ± 6	0.725
Vitamin D	35 (57)	187 (51)	0.342
Dose of vitamin D (IU/week)	29,629 ± 24,611	17,492 ± 17,009	0.008

*p value < 0.05 indicates significant difference between patients who developed symptoms and those who remained asymptomatic

[a] IV intravenous

[b] Calcium gluconate used for IV supplementation and calcium carbonate as oral supplementation

[c] Dose of elemental calcium (Ca^{2+})

[d] Dose of elemental magnesium (Mg^{2+})

operative hypocalcemia had a more negative slope (− 0.84% change/h) compared to those who remained normocalcemic (− 0.49% change/h). It also showed that a positive slope has a very high likelihood of remaining positive, i.e., remaining normocalcemic [31], and a negative slope was predictive of the occurrence of hypocalcemia and of its magnitude [30, 31]. In a retrospective study of 52 total and subtotal thyroidectomy patients, a Ca slope from baseline to 6 h postoperatively correlated with Ca level at 24 h, thus facilitating discharge [32]. In an observational study of 136 total/completion thyroidectomy patients that looked at the change in serum Ca from baseline, the absolute Ca level at 20 h post-surgery was more predictive of hypocalcemia (defined as Ca ≤ 7.6 mg/dl in this study), as compared to change in serum Ca at 6 or 12 h postoperatively [11]. The latter study was limited by its definition of hypocalcemia, its exclusion of normo-calcemic symptomatic patients, and by the fact that it requires a fixed measurement of Ca 20 h post-surgery, whereas using a rate of drop in calcium allows flexibility to use Ca at any point in time [11].

Covariates that we found to be significantly associated with the development of symptoms at the bivariate level were younger age, female gender, lower BMI, pre-operative serum PO_4 level, post-operative serum PO_4 and Mg levels, and the presence of parathyroid tissue in the resected specimen. Previous studies focused on predictors of transient post-operative hypocalcemia in general and not hypocalcemic symptoms in particular [5, 6, 11, 12, 14, 32–41]. In a systematic review of 115 studies, older age, female gender, GD, lower pre-operative Ca or 25-hydroxy vitamin D levels, larger decline in post-operative Ca, post-op hypomagnesemia, lower intra-operative and post-operative PTH levels, a larger drop in PTH level, and higher pre-operative alkaline phosphatase level were predictors of transient post-operative hypocalcemia [14]. Significant surgical factors included parathyroid gland auto-transplantation, greater number of transplanted glands, and inadvertent parathyroid gland excision [14]. The meta-analysis showed that GD, inadvertent parathyroid gland excision, and auto-transplantation were significant predictors of transient hypocalcemia post-thyroidectomy (four studies included for each predictor) [14].

Table 4 Multivariate logistic regression analysis of predictors of hypocalcemic symptoms, reported as unadjusted and adjusted odds ratios

Predictor	Unadjusted OR (95% CI)	*p* value	Adjusted* OR (95% CI)	*p* value
Age	0.95 (0.93, 0.98)	< 0.001	0.98 (0.95, 1.00)	0.060
BMI	0.89 (0.83, 0.95)	< 0.001	0.96 (0.90, 1.03)	0.296
Female gender	2.76 (1.22, 6.27)	0.015	1.05 (0.40, 2.78)	0.921
Diabetes mellitus	0.25 (0.06, 1.06)	0.06	0.34 (0.07, 1.66)	0.182
Pre-operative phosphorus level	1.86 (1.04, 3.32)	0.038	1.60 (0.76, 3.37)	0.211
Parathyroid tissue in resected specimen	1.94 (1.01, 3.72)	0.046	1.29 (0.56, 3.00)	0.553
Post-operative calcium level	6.38 (3.69, 11.02)	< 0.001	3.72 (1.97, 7.02)	<0.001
Post-operative magnesium level	16.75 (2.92, 96.01)	0.002	3.76 (0.38, 37.16)	0.257
Post-operative phosphorus level	1.56 (1.10, 2.22)	0.013	0.96 (0.62, 1.49)	0.867
Rate of drop in calcium ≥ 0.083 mg/dl/h	6.23 (3.43, 11.30)	< 0.001	3.20 (1.54, 6.64)	0.002
Lymph node dissection	1.63 (0.94, 2.81)	0.08	0.79 (0.39, 1.61)	0.518
Length of surgery	1.00 (1.00, 1.01)	0.108	1.00 (1.00, 1.00)	0.936

Logistic regression analysis with an entry criterion of $p < 0.1$

OR odds ratio, *CI* confidence interval

*Adjusted for all other variables reported in the table

Our study holds the limitations of retrospective chart reviews. We assumed that the time at which symptoms were documented in the medical notes corresponded to the time of symptom development, and this was matched to the time serum chemistries were logged in as drawn, unless specified otherwise. Symptoms may not have all been recorded, which might have led to some misclassification bias; however, we believe that this is unlikely since we reviewed all notes written by both physicians and registered nurses. Another potential limitation is that the majority of subjects had their serum Ca drawn a few days prior in the pre-admission, rather than on the morning of the surgery. However, serum total Ca is quite stable with minimal variations that are unlikely to affect the calculated rate of drop in Ca. Serum ionized Ca is not routinely measured, and the total Ca was not corrected to albumin. However, the majority of patients were healthy at baseline or only had a few co-morbidities (Table 1) that could affect albumin or ionized Ca levels. Another potential limitation is that patients complaining of symptoms had their serum chemistries checked earlier than asymptomatic patients and the denominators used to calculate the rates differ between symptomatic and asymptomatic patients, as shown under "Results." This limitation can only be addressed through a prospective study which we plan to conduct, in which chemistries are checked at the same pre-specified time. Although most recent studies have focused on PTH measurement in predicting symptomatic hypocalcemia, measurement of PTH level post-total thyroidectomy is not standard practice in several centers, including ours, due to the PTH assay cost and the lack of consensus on the best time to measure it post-operatively. Conversely, measurement of serum calcium measurement is included in the panel usually drawn in the event of hypocalcemic symptoms (including PO_4 and Mg) and does not incur extra cost.

Our study is representative of the Lebanese patient population, as 92% of the patients studied were of Lebanese origin, and since AUB-MC is a tertiary care center, there is an influx of patients from all over Lebanon.

To our knowledge, this is the only study that assesses the rate of Ca drop as a predictor of hypocalcemic symptoms. The rate of Ca drop post total thyroidectomy significantly predicted the development of hypocalcemic symptoms, and interestingly, this holds true even in symptomatic patients with a normal post-operative serum Ca level. Its high NPV of 94% (95% CI 91, 96) might allow its use for early institution of therapy when needed and might limit prolonged hospitalization and costs. Validation of these results, through randomized prospective trials that also include PTH, is needed before our findings can be incorporated in clinical care pathways (algorithms).

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval This study was given approval by the Institutional Review Board (IRB) at the American University of Beirut and has been done in agreement with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. The IRB granted this study an informed consent waiver due to the study's retrospective nature and since no identifying information was used.

References

1. Stack BC Jr, Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, Pallota J, Snyder SK, Wong RJ, Randolph GW (2015) American association of clinical endocrinologists and american college of endocrinology disease state clinical review: postoperative hypoparathyroidism - definition and management. Endocr Pract 21(6):674–685. https://doi.org/10.4158/ep14462.dsc
2. Ritter K, Elfenbein D, Schneider D, Chen H, Sippel RS (2015) Hypoparathyroidism after total thyroidectomy: incidence and resolution. J Surg Res 197(2):348–353. https://doi.org/10.1016/j.jss.2015.04.059
3. Almquist M, Hallgrimsson P, Nordenstrom E, Bergenfelz A (2014) Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg 38(10):2613–2620. https://doi.org/10.1007/s00268-014-2622-z
4. Chadwick D, Kinsman R, Walton P (2012) The British association of endocrine & thyroid surgeons fourth national audit report dendrite clinical systems Henley on Thames, United Kingdom. https://www.baets.org.uk/wp-content/uploads/2013/05/4th-National-Audit.pdf. Accessed 26 October 2018
5. Arer IM, Kus M, Akkapulu N, Aytac HO, Yabanoglu H, Caliskan K, Tarim MA (2017) Prophylactic oral calcium supplementation therapy to prevent early post thyroidectomy hypocalcemia and evaluation of postoperative parathyroid hormone levels to detect hypocalcemia: a prospective randomized study. Int J Surg 38:9–14. https://doi.org/10.1016/j.ijsu.2016.12.041
6. Cannizzaro MA, Okatyeva V, Lo Bianco S, Caruso V, Buffone A (2018) Hypocalcemia after thyroidectomy: iPTH levels and iPTH decline are predictive? Retrospective cohort study. Ann Med Surg 30:42–45. https://doi.org/10.1016/j.amsu.2018.04.032
7. Docimo G, Ruggiero R, Casalino G, Del Genio G, Docimo L, Tolone S (2017) Risk factors for postoperative hypocalcemia. Updat Surg 69(2):255–260. https://doi.org/10.1007/s13304-017-0452-x
8. Sauer N, Lautenbach A, Pohl K, Schon G, Brose HP, Schulze Zur Wiesch CA, Aberle JC (2018) Screening and management of postoperative hypoparathyroidism-induced hypocalcemia in thyroidectomized patients in the endocrine ward compared with the surgical ward. Ear Nose Throat J 97(4–5):E22–e26
9. Pfleiderer A, Ahmad N, Draper M, Vrotsou K, Smith W (2009) The timing of calcium measurements in helping to predict temporary and permanent hypocalcaemia in patients having completion and total thyroidectomies. Ann R Coll Surg Engl 91(2):140–146. https://doi.org/10.1308/003588409x359349
10. Maxwell AK, Shonka DC Jr, Robinson DJ, Levine PA (2017) Association of preoperative calcium and calcitriol therapy with postoperative hypocalcemia after total thyroidectomy. JAMA Otolaryngol Head Neck Surg 143(7):679–684. https://doi.org/10.1001/jamaoto.2016.4796
11. Lazard DS, Godiris-Petit G, Wagner I, Sarfati E, Chabolle F (2012) Early detection of hypocalcemia after total/completion thyroidectomy: routinely usable algorithm based on serum calcium level. World J Surg 36(11):2590–2597. https://doi.org/10.1007/s00268-012-1727-5
12. Inversini D, Rausei S, Ferrari CC, Frattini F, Anuwong A, Kim HY, Liu X, Wu CW, Tian W, Liu R, Dionigi G (2016) Early intact PTH (iPTH) is an early predictor of postoperative hypocalcemia for a safer and earlier hospital discharge: an analysis on 260 total thyroidectomies. Gland Surg 5(5):522–528. https://doi.org/10.21037/gs.2016.09.08
13. Falcone TE, Stein DJ, Jumaily JS, Pearce EN, Holick MF, McAneny DB, Jalisi S, Grillone GA, Stone MD, Devaiah AK, Noordzij JP (2015) Correlating pre-operative vitamin D status with post-thyroidectomy hypocalcemia. Endocr Pract 21(4):348–354. https://doi.org/10.4158/ep14264.Or
14. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP (2014) Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg 101(4):307–320. https://doi.org/10.1002/bjs.9384
15. Al-Dhahri SF, Mubasher M, Mufarji K, Allam OS, Terkawi AS (2014) Factors predicting post-thyroidectomy hypoparathyroidism recovery. World J Surg 38(9):2304–2310. https://doi.org/10.1007/s00268-014-2571-6
16. Vanderlei FAB, Vieira JGH, Hojaij FC, Cervantes O, Kunii IS, Ohe MN, Santos RO, Abrahão M (2012) Parathyroid hormone: an early predictor of symptomatic hypocalcemia after total thyroidectomy. Arq Bras Endocrinol Metabol 56:168–172
17. Jung D, J-k K, Kwon H, Lim W, Moon B-I (2017) Percentage decline of parathyroid hormone level is a predictor for post-thyroidectomy symptomatic hypocalcemia. J Endocr Surg 17(4):168–174
18. Youngwirth L, Benavidez J, Sippel R, Chen H (2010) Postoperative parathyroid hormone testing decreases symptomatic hypocalcemia and associated emergency room visits after total thyroidectomy. Surgery 148(4):841–844; discussion 844-846. https://doi.org/10.1016/j.surg.2010.07.038
19. von-Elm E, Altman D, Egger M, Pocock S, Gøtzsche P, Vandenbroucke J (2008) STROBE initiative; the strengthening the reporting of observational studies in epidemiology (STROBE)statement: guidelines for reporting observational studies. J Clin Epidemiol 61(4) (4)):344–349
20. Bilezikian JP, Brandi ML, Cusano NE, Mannstadt M, Rejnmark L, Rizzoli R, Rubin MR, Winer KK, Liberman UA, Potts JT Jr (2016) Management of hypoparathyroidism: present and future. J Clin Endocrinol Metab 101(6):2313–2324. https://doi.org/10.1210/jc.2015-3910
21. Soon PS, Magarey CJ, Campbell P, Jalaludin B (2005) Serum intact parathyroid hormone as a predictor of hypocalcaemia after total thyroidectomy. ANZ J Surg 75(11):977–980. https://doi.org/10.1111/j.1445-2197.2005.03593.x
22. McLeod IK, Arciero C, Noordzij JP, Stojadinovic A, Peoples G, Melder PC, Langley R, Bernet V, Shriver CD (2006) The use of rapid parathyroid hormone assay in predicting postoperative hypocalcemia after total or completion thyroidectomy. Thyroid 16(3):259–265. https://doi.org/10.1089/thy.2006.16.259
23. Richards ML, Bingener-Casey J, Pierce D, Strodel WE, Sirinek KR (2003) Intraoperative parathyroid hormone assay: an accurate predictor of symptomatic hypocalcemia following thyroidectomy. Arch Surg 138(6):632–635. https://doi.org/10.1001/archsurg.138.6.632
24. Scurry WC Jr, Beus KS, Hollenbeak CS, Stack BC Jr (2005) Perioperative parathyroid hormone assay for diagnosis and management of postthyroidectomy hypocalcemia. Laryngoscope 115(8):1362–1366. https://doi.org/10.1097/01.Mlg.0000166699.23264.37
25. Reddy AC, Chand G, Sabaretnam M, Mishra A, Agarwal G, Agarwal A, Verma AK, Mishra SK (2016) Prospective evaluation of intra-operative quick parathyroid hormone assay as an early predictor of post thyroidectomy hypocalcaemia. Int J Surg 34:103–108. https://doi.org/10.1016/j.ijsu.2016.08.010

26. Lombardi CP, Raffaelli M, Princi P, Dobrinja C, Carrozza C, Di Stasio E, D'Amore A, Zuppi C, Bellantone R (2006) Parathyroid hormone levels 4 hours after surgery do not accurately predict postthyroidectomy hypocalcemia. Surgery 140(6):1016–1023; discussion 1023-1015. https://doi.org/10.1016/j.surg.2006.08.009
27. Lombardi CP, Raffaelli M, Princi P, Santini S, Boscherini M, De Crea C, Traini E, D'Amore AM, Carrozza C, Zuppi C, Bellantone R (2004) Early prediction of postthyroidectomy hypocalcemia by one single iPTH measurement. Surgery 136(6):1236–1241. https://doi.org/10.1016/j.surg.2004.06.053
28. Noordzij JP, Lee SL, Bernet VJ, Payne RJ, Cohen SM, McLeod IK, Hier MP, Black MJ, Kerr PD, Richards ML, Lo CY, Raffaelli M, Bellantone R, Lombardi CP, Cohen JI, Dietrich MS (2007) Early prediction of hypocalcemia after thyroidectomy using parathyroid hormone: an analysis of pooled individual patient data from nine observational studies. J Am Coll Surg 205(6):748–754. https://doi.org/10.1016/j.jamcollsurg.2007.06.298
29. El-Hajj Fuleihan G, Gundberg CM, Gleason R, Brown EM, Stromski ME, Grant FD, Conlin PR (1994) Racial differences in parathyroid hormone dynamics. J Clin Endocrinol Metab 79(6):1642–1647
30. Marohn MR, LaCivita KA (1995) Evaluation of total/near-total thyroidectomy in a short-stay hospitalization: safe and cost-effective. Surgery 118(6):943–947 discussion 947-948
31. Adams J, Andersen P, Everts E, Cohen J (1998) Early postoperative calcium levels as predictors of hypocalcemia. Laryngoscope 108(12):1829–1831
32. Walsh SR, Kumar B, Coveney EC (2007) Serum calcium slope predicts hypocalcaemia following thyroid surgery. Int J Surg 5(1):41–44. https://doi.org/10.1016/j.ijsu.2006.03.006
33. Lam A, Kerr PD (2003) Parathyroid hormone: an early predictor of postthyroidectomy hypocalcemia. Laryngoscope 113(12):2196–2200. https://doi.org/10.1097/00005537-200312000-00029
34. Lee DR, Hinson AM, Siegel ER, Steelman SC, Bodenner DL, Stack BC Jr (2015) Comparison of intraoperative versus postoperative parathyroid hormone levels to predict hypocalcemia earlier after total thyroidectomy. Otolaryngol Head Neck Surg 153(3):343–349. https://doi.org/10.1177/0194599815596341
35. Wong C, Price S, Scott-Coombes D (2006) Hypocalcaemia and parathyroid hormone assay following total thyroidectomy: predicting the future. World J Surg 30(5):825–832. https://doi.org/10.1007/s00268-005-0478-y
36. Payne RJ, Hier MP, Tamilia M, Mac Namara E, Young J, Black MJ (2005) Same-day discharge after total thyroidectomy: the value of 6-hour serum parathyroid hormone and calcium levels. Head Neck 27(1):1–7. https://doi.org/10.1002/hed.20103
37. Payne RJ, Tewfik MA, Hier MP, Tamilia M, Mac Namara E, Young J, Black MJ (2005) Benefits resulting from 1- and 6-hour parathyroid hormone and calcium levels after thyroidectomy. Otolaryngol Head Neck Surg 133(3):386–390. https://doi.org/10.1016/j.otohns.2005.02.021
38. Vescan A, Witterick I, Freeman J (2005) Parathyroid hormone as a predictor of hypocalcemia after thyroidectomy. Laryngoscope 115(12):2105–2108. https://doi.org/10.1097/01.Mlg.0000181504.69230.87
39. Ghaheri BA, Liebler SL, Andersen PE, Schuff KG, Samuels MH, Klein RF, Cohen JI (2006) Perioperative parathyroid hormone levels in thyroid surgery. Laryngoscope 116(4):518–521. https://doi.org/10.1097/01.Mlg.0000202617.63668.Cc
40. Falch C, Hornig J, Senne M, Braun M, Konigsrainer A, Kirschniak A, Muller S (2018) Factors predicting hypocalcemia after total thyroidectomy - a retrospective cohort analysis. Int J Surg 55:46–50. https://doi.org/10.1016/j.ijsu.2018.05.014
41. Sahli Z, Najafian A, Kahan S, Schneider EB, Zeiger MA, Mathur A (2018) One-hour postoperative parathyroid hormone levels do not reliably predict hypocalcemia after thyroidectomy. World J Surg 42(7):2128–2133. https://doi.org/10.1007/s00268-017-4444-2