Hypocalcemia after Total Thyroidectomy in Graves Disease

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ABSTRACT

Context: Total thyroidectomy has been shown to provide a cost-effective and efficient method of permanently treating Graves disease; however, hypocalcemia can be a common complication.

Objective: To evaluate the risk of hypocalcemia after total thyroidectomy in patients with vs without Graves disease.

Design: The 2016 American College of Surgeons National Surgical Quality Improvement Program participant use data files for procedure-targeted thyroidectomy and from 5871 patients were merged. This study included any patient who underwent total thyroidectomy.

Main Outcome Measures: Whether symptomatic hypocalcemia developed anytime within 30 days after the thyroidectomy. A clinically severe hypocalcemic event was also evaluated as a secondary outcome measure.

Results: Of the 2143 patients who underwent total thyroidectomy, 222 patients experienced hypocalcemia after surgery, 124 of whom had symptomatic hypocalcemia postoperatively. Among patients with hypocalcemia, 16.3% had Graves disease, whereas only 9.4% of patients without Graves disease experienced significant hypocalcemia. Multivariable logistic regression analysis revealed that women (odds ratio = 1.79; 95% confidence interval = 1.16-2.76; p = 0.009) and patients who underwent parathyroid autotransplantation (odds ratio = 1.91; 95% confidence interval = 1.30-2.81; p = 0.001) were at greater risk of development of hypocalcemia. Older patients were less likely to experience hypocalcemia postoperatively (odds ratio = 0.586; 95% confidence interval = 0.44-0.79; p = 0.0001).

Conclusion: Patients with Graves disease are about twice as likely to experience hypocalcemia or clinically severe hypocalcemia postoperatively than are patients without the disease.

INTRODUCTION

Graves disease is the most common autoimmune disorder in the US and the most common cause of hyperthyroidism.[1] Although the initial treatment may be antithyroid medications or radioactive iodine, surgery is an excellent definitive treatment and may be indicated because of goiter, local compressive symptoms, or nodules that may harbor malignancy.[2] Likewise, patients may prefer surgery to avoid radioactive iodine therapy and the potential adverse effects of antithyroid medication. However, there are complications associated with surgery, including hematoma, recurrent laryngeal nerve palsy, and most commonly, hypoparathyroidism.[2-4] Up to 50% of patients who undergo total thyroidectomy may experience hypoparathyroidism.[1,3,4] Patients with Graves disease are apparently more prone to tetany developing after total thyroidectomy than any other patients who do not have Graves disease.[1,5-12] Most studies are smaller case series, and to our knowledge, no population-based studies to date have compared patients with and without Graves disease after total thyroidectomy.

The objective of this study was to use the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database to evaluate the risk of hypocalcemia after total thyroidectomy in patients with Graves disease compared with those without Graves disease.

METHODS

Data Sources and Study Subjects

The 2016 NSQIP participant use data files for procedure targeted thyroidectomy were merged with 2016 NSQIP participant use files into a file that contained data for 5871 patients. Any patient who underwent a total thyroidectomy was then identified from this group using Current Procedural Terminology (CPT) codes 60240 or 60271. Those patients who underwent synchronous parathyroidectomy (CPT code 60500) were excluded. Patients who underwent a neck dissection—either limited or modified radical or radical—or any other surgical procedure were also excluded.

Perioperative Variables

Patient demographic variables that were collected included age (< 50 years old vs ≥ 50 years), sex, body mass index (BMI), and presence or absence of Graves disease. Status of parathyroid autotransplantation was also collected.

Outcomes

The main outcome measure was whether patients experienced symptomatic hypocalcemia anytime within 30 days after the thyroidectomy. As a secondary outcome measure, *clinically severe hypocalcemic event* was evaluated, and it was defined by NSQIP as: "emergent evaluation in clinical office/Emergency Department," and/or "readmitted for low calcium, and/or "IV [intravenous] calcium supplementation."[13]

Statistical Analysis

Categorical predictor variables were compared between the 2 age groups using the χ^2 test. The likelihood of hypocalcemia within 30 days and a clinically severe hypocalcemic event was estimated using multivariable logistic regression models adjusting for age (< 50 years old vs ≥ 50 years), sex, BMI, Graves disease (yes, no), and parathyroid autotransplantation. Odds

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ratios (ORs) with 95% confidence intervals (CIs) were calculated. All p values were 2-tailed, and $p < 0.05$ was the criterion for statistical significance on final multiple regression models. All analyses were performed using statistical software (SPSS Version 25, IBM, Armonk, NY).

RESULTS

Patient Demographics

There were 2143 patients who underwent total thyroidectomy, and of these, 294 had Graves disease. A total of 915 patients (42.7%) were younger than age 50 years (Table 1). Most patients (81.2%) were women. There were 218 patients (10.8%) who required autotransplantation (Table 1).

Patients were similar in most characteristics when evaluated by Graves disease status; however, patients with Graves disease were younger, with 71.1% less than age 50 years (Table 1).

Table 1. Characteristics of 2143 patients who underwent total thyroidectomy stratified by Graves disease status

Characteristic	Graves disease (n = 294), no. (%)	Non-Graves disease (n = 1849), no. (%)
Age, y		
< 50	209 (71.1)	706 (38.2)
≥ 50	85 (28.9)	1143 (61.8)
Sex		
Women	234 (79.6)	1507 (81.5)
Men	60 (20.4)	342 (18.5)
Mean BMI, kg/m^2 (SD)	29.3 (6.7)	31.3 (7.6)
Parathyroid autotransplantation		
Yes	33 (11.2)	185 (10.0)
No	261 (88.8)	1664 (90.0)

BMI = body mass index; SD = standard deviation.

Symptomatic Hypocalcemia within 30 Days after Thyroidectomy

Of the 2143 patients who underwent total thyroidectomy, 222 patients (10.4%) experienced symptomatic hypocalcemia. By Graves disease status, 48 (16.3%) of 294 patients with Graves disease had hypocalcemia compared with 174 (9.4%) of the 1849 patients in the non-Graves disease group ($p = 0.001$). We evaluated the following risk factors and analyzed their independent effect on symptomatic hypocalcemia: Age, sex, BMI, Graves vs non-Graves disease, and parathyroid autotransplantation. Women were independently at greater risk of hypocalcemia compared with men (OR = 1.79; 95% CI = 1.16-2.76; $p = 0.009$), as were patients with Graves disease (OR = 1.57; 95% CI = 1.09-2.25; $p = 0.015$) and those who had parathyroid autotransplantation (OR = 1.91; 95% CI = 1.30-2.81; $p = 0.001$; Table 2). The older group of patients in the study were less likely to experience hypocalcemia (OR = 0.586; 95% CI = 0.44-0.79; $p = 0.0001$). The BMI had no significance on whether a patient would be more prone to development of hypocalcemia (OR = 0.99; 95% CI = 0.97-1.01; $p = 0.194$).

Table 2. Predictors of symptomatic hypocalcemia in patients who underwent total thyroidectomy

Predictor	Odds ratio	95% CI	p value
Age, y			
< 50	1 [Reference]	—	—
≥ 50	0.59	0.44-0.79	< 0.0001
Sex			
Men	1 [Reference]	—	—
Women	1.79	1.16-2.76	0.009
BMI	0.99	0.97-1.01	0.194
Graves disease			
No	1 [Reference]	—	—
Yes	1.57	1.09-2.25	0.015
Parathyroid autotransplantation			
No	1 [Reference]	—	—
Yes	1.91	1.30-2.81	0.001

BMI = body mass index; CI = confidence interval.

Clinically Severe Hypocalcemia Event within 30 Days after Thyroidectomy

Of the 222 patients who had hypocalcemia, 124 had clinically severe hypocalcemic-related events. A clinically severe hypocalcemic event occurred in 29 (9.9%) of the patients with Graves disease vs 95 patients without Graves disease (5.1%). Graves disease was an independent predictor of clinically severe hypocalcemic event (OR = 1.69; 95% CI = 1.07-2.66, $p = 0.024$, Table 3). Likewise, women were at a greater risk of hypocalcemia development compared with men (OR = 2.10; 95% CI = 1.14-3.87; $p = 0.017$). The older patients were less likely to experience a clinically severe hypocalcemic event (OR = 0.62; 95% CI = 0.43-0.91; $p = 0.014$). The BMI (OR - 0.98; 95% CI = 0.95-1.00; $p = 0.090$) had no significance on whether a patient would be more prone to experiencing significant hypocalcemia. Interestingly, parathyroid autotransplantation increased the risk for this outcome, but the difference was not statistically significant (OR = 1.56; 95% CI = 0.93-2.61; $p = 0.092$).

DISCUSSION

Results of this study confirm that patients with Graves disease have a higher likelihood of hypocalcemia developing within 30 days after total thyroidectomy compared with those without Graves disease. Other factors such as age, sex, and parathyroid autotransplantation also are associated with significant hypocalcemia, independent of Graves disease.

The preoperative state of the patient with Graves disease plays a pivotal role in causing postoperative tetany.[14-16] Before the surgery, in patients with Graves disease receiving antithyroid drugs, "hungry bone syndrome" can develop, in which bone restoration depletes the calcium and vitamin D reservoirs and causes a calcium and vitamin D deficiency.[9,14,17] This condition leads to secondary hyperparathyroidism, which causes hypocalcemia postoperatively.[6,18] High levels of parathyroid hormone (PTH) circulating for prolonged periods preoperatively decrease the organ sensitivity to calcium and induce downregulation of PTH

Table 3. Predictors of clinically severe hypocalcemia event in patients who underwent total thyroidectomy

Predictor	Odds ratio	95% CI	p value
Age, y			
< 50	1 [Reference]	—	—
≥ 50	0.62	0.42-0.91	0.014
Sex			
Men	1 [Reference]	—	—
Women	2.10	1.14-3.87	0.017
BMI	0.98	0.95-1.00	0.090
Graves disease			
No	1 [Reference]	—	—
Yes	1.69	1.07-2.62	0.024
Parathyroid autotransplantation			
No	1 [Reference]	—	—
Yes	1.56	0.93-2.61	0.092

BMI = body mass index; CI = confidence interval.

receptors peripherally.[15] Secondary hyperparathyroidism further increases vitamin D deficiency by producing 1,25-dihydroxyvitamin D that converts vitamin D in the liver to its inactive form that goes on to be excreted in the bile.[6]

Multiple risk factors have been shown to contribute to the hypocalcemic outcome after thyroidectomy in patients with Graves disease. Erbil et al[9] stated that vitamin D deficiency had the greatest contribution to causing hypocalcemia after surgery. Factors such as sex, the degree of parathyroid gland manipulation at the time of surgery, and the size of goiter may also be responsible.[1,14,19] Our data also showed that younger patients are more prone to experiencing significant hypocalcemia and clinically severe hypocalcemic events postoperatively compared with older patients. Aging can cause vitamin D deficiency and decreased intestinal calcium absorption and thus contributes to the hypocalcemic outcome.[9,11,14,20]

Our study results have shown that women are at higher risk of development of both significant hypocalcemia and a clinically severe hypocalcemic event postoperatively than men. The mechanism as to why women are more prone to hypocalcemia development after total thyroidectomy has been disputed.[16] One reason may be that women are at a higher risk of vitamin D deficiency.[9] A second reason may be a drop in the level of calcitriol in menopausal women.[16] Third, multiple regulatory genes in men have been found that heighten the parathyroid gland's ability to undergo mitosis to maintain calcium homeostasis when demands for calcium increase.[21] Fourth, genetic differences may be responsible for vulnerability to hypocalcemia in women.[21] Finally, parathyroid glands in women are smaller and differ in parenchymal and stromal fat composition compared with those in men, which may have contributed to women having a higher percentage of inadvertent parathyroidectomy during a total thyroidectomy.[21]

It is interesting to note that parathyroid autotransplantation played a significant role in causing hypocalcemia postoperatively. Parathyroid autotransplantation during thyroidectomy is the placement of morcellated parathyroid tissue from a parathyroid gland that has been inadvertently removed or devascularized back into the patient, usually in an intramuscular pocket in the neck. Studies have shown that undergoing parathyroid autotransplantation puts patients at greater risk of transient hypocalcemia developing postoperatively[12,16]; however, permanent hypocalcemia is less likely to develop in these patients over time.[12,22-24] Because the ACS NSQIP collected data for only 30 days after the surgery, we were unable to assess whether parathyroid autotransplantation caused permanent hypocalcemia. The role of parathyroid autotransplantation has been debated, as it has also been shown to provide no benefit or to actually increase the risk of permanent hypocalcemia postoperatively.[20,25] We still believe that autotransplantation acts as insurance in salvaging functional parathyroid tissue; however, there has yet to be a study comparing autotransplantation with leaving a devascularized parathyroid gland in situ.

Surgeons can prepare for hypocalcemia in patients with Graves disease by recognizing the predictors of hypocalcemia. Before surgery, serum calcium and PTH levels, vitamin D concentrations, and alkaline phosphatase levels should be measured and adjustments should be made accordingly by using calcium and vitamin D supplements.[8] Postoperatively, calcium and PTH levels should be monitored closely in these patients. Low levels of calcium and PTH are highly predictive of postoperative hypocalcemia.[4,9] For example, patients who had their PTH levels measured after surgery and had low levels (< 6-35 pg/mL) 30 minutes to 5 days after total thyroidectomy were prone to development of transient hypocalcemia.[19] In a study that focused on PTH levels postoperatively, PTH levels less than 10 pg/mL increased the risk of tetany 23-fold higher.[9] It would be prudent to follow-up patients with Graves disease more closely than the routine testing that is normally done.

Indocyanine green florescence has recently been used to assess blood perfusion in the parathyroid glands.[26,27] Studies have shown that by using indocyanine green fluorescence angiography, surgeons can avoid postoperative hypocalcemia by ensuring at least one well-perfused parathyroid gland.[26,27] This has removed the necessity to measure PTH and calcium levels intraoperatively to determine whether hypocalcemia occurs postoperatively and has provided an alternative method to measure hypoparathyroidism immediately after thyroid excision.[26,27] Lang et al[27] developed a system that measures the numeric value of the blood perfusion of the parathyroid gland. This may potentially be useful in patients with Graves disease, if not used routinely, to try to reduce the risk of hypocalcemia in this disease.

Although this study has the potential to alter certain aspects of clinical management when it comes to treating patients with Graves disease, it does come with some limitations. The database we used did not provide calcium, vitamin D, and PTH levels of the patients with Graves disease preoperatively, intraoperatively, and postoperatively. Moreover, the severity of the Graves disease was not recorded. It was also unknown whether patients were taking antithyroidal medication. Our data also state that certain subjects had a clinically severe hypocalcemic event, but it is not noted exactly how long after surgery it occurred.

CONCLUSION

Our study findings have shown that patients with Graves disease are almost twice as likely to experience transient hypocalcemia and clinically severe hypocalcemic events after total thyroidectomy than patients without Graves disease. Age, parathyroid autotransplantation, and sex all are important risk factors in causing transient hypocalcemia postoperatively. Surgeons may adjust their routine biochemical follow-up after total thyroidectomy and follow-up patients with Graves disease more closely. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Guardian

In illness the physician is a father; in convalescence, a friend, when health is restored, he is a guardian.

— Brahmanic saying