

The role and timing of parathyroid hormone determination after total thyroidectomy

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Abstract: Postoperative hypocalcemia is a common complication of total thyroidectomy resulting from manipulation, resection, or devascularization of the parathyroid glands. Parathyroid hormone (PTH) levels assessed in the perioperative period have been used to predict development of hypocalcemia. Articles examining the role of PTH measurement in the perioperative period following total or completion thyroidectomy are reviewed. Focus is placed on the timing of PTH measurement and the ability to predict which patients will develop hypocalcemia requiring supplementation. Postoperative PTH determination is highly accurate in predicting the development of hypocalcemia. Studies have examined PTH levels drawn at differing time points, ranging from intraoperatively until postoperative day 1 (POD1) with similar accuracy. This data is used to guide postoperative selective calcium and calcitriol supplementation in patients at highest risk for hypocalcemia. When evaluated within the first 4 hours postoperatively, predictive accuracy is maintained but can allow for earlier discharge for those patients at lower risk. Alternatively, some authors argue for routine supplementation, which can reduce the rate of postoperative hypocalcemia but increases the rate of unnecessary supplementation and potential risks associated with hypercalcemia. PTH determination at four hours after total thyroidectomy is an accurate predictor of hypocalcemia and can guide selective calcium supplementation for those at high risk, as well as facilitate a safe earlier hospital discharge for those at low risk of developing postoperative hypocalcemia.

Keywords: Hypocalcemia; hypoparathyroidism; parathyroid hormone (PTH); thyroidectomy

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Introduction

Postoperative hypocalcemia is the most common complication after total thyroidectomy. It occurs as a result of unintentional resection, manipulation, or devascularization of the parathyroid glands during thyroidectomy leading to hypoparathyroidism. Clinical manifestations are primarily neurologic and cardiac in nature, and include perioral and acral paresthesias, muscle cramps, tetany, seizures, prolonged QT syndrome, and congestive heart failure. Postoperative hypocalcemia lasting up to 6 months is considered transient

and has been reported to occur in 3–53% of patients. The wide variability in reported rates of hypocalcemia secondary to transient hypoparathyroidism is in part due to differing definitions in the literature of hypocalcemia based on biochemical evaluation, patient symptoms, or both. However, in up to 2% of patients, hypoparathyroidism may last longer than 6 months and is considered permanent (1-11).

Multiple studies have investigated potential predictive factors to better determine which patients are at higher risk for postoperative hypocalcemia. In the majority of studies, demographic factors including age, sex, and other

comorbidities play a minimal role (6,7,12-15). Results regarding preoperative factors including 25-OH vitamin D, serum calcium, or parathyroid hormone (PTH) levels, or indications for surgery such as Graves' disease have been variable with no clear association to the development of postoperative hypocalcemia. Potential intraoperative factors that have been investigated include performance of a central compartment neck dissection as it is associated with increased parathyroid manipulation, as well as potential devascularization of the inferior parathyroid glands requiring autotransplantation; again, results have been mixed (5,16).

Postoperatively, numerous studies have demonstrated that measurement of serum PTH levels can be utilized as a predictor of the development of post-thyroidectomy hypocalcemia. However, there has not been consensus on the most appropriate timing or threshold value for PTH measurement that would optimally guide the management of postoperative hypocalcemia, as there is also not universal consensus as to the routine or selective use of calcium and/or calcitriol supplementation. This review article will focus on the role and timing of PTH measurement in the perioperative period to guide treatment of postoperative hypocalcemia for patients undergoing total thyroidectomy.

Routine versus selective supplementation

Given the ease and low cost of calcium supplements, many have advocated for routine supplementation as the optimal method to prevent postoperative hypocalcemia. Bellantone *et al.* (17) compared administration of oral calcium alone, oral calcium and vitamin D supplementation, or no supplementation in a study of 79 patients that underwent total thyroidectomy. They defined hypocalcemia as serum calcium <8.0 mg/dL. Compared to no supplementation or calcium alone, the group that received both calcium and vitamin D had a significantly higher serum calcium level on postoperative days 2 and 3 ($P<0.05$), but there was no difference in the calcium levels among the three groups at 1 week postoperatively. The groups that received calcium alone or calcium with vitamin D had a significant reduction in symptomatic hypocalcemia, compared to the group without routine supplementation (12% *vs.* 41%, $P=0.005$). Another study by Roh *et al.* (18) had a similar study design and compared no supplementation to routine supplementation with oral calcium and vitamin D in a series of 90 patients. Rates of biochemical (serum total calcium <8.0 mg/dL or ionized calcium <1.0 mmol/L) and

symptomatic hypocalcemia were significantly lower in the supplementation group (13% *vs.* 36%, $P=0.014$; and 7% *vs.* 24%, $P=0.02$, respectively). In both studies, addition of intravenous (IV) calcium for persistent symptoms was only needed in the group without routine supplementation, suggesting that routine supplementation could prevent the need for IV calcium and ameliorate postoperative hypocalcemia. However, despite routine supplementation, 12% of patients in the first study and 7% in the second developed symptomatic hypocalcemia, demonstrating that patients should still be counseled regarding the symptoms of hypocalcemia so they can be evaluated and treated promptly should symptoms arise.

There may be certain situations in which routine supplementation is appropriate. Roh *et al.* (16) examined the role of routine supplementation in patients undergoing total thyroidectomy with central compartment neck dissection, given the higher theoretical risk of devascularization of the inferior glands during this procedure. The authors compared groups who received oral calcium alone ($N=49$), oral calcium and vitamin D ($N=49$), or no supplementation ($N=50$) for the first two weeks postoperatively; a control group of 49 patients who underwent total thyroidectomy without central compartment neck dissection and who did not receive supplementation was included. In comparing groups who did not receive supplementation, the rate of biochemical hypocalcemia (<8.0 mg/dL) was overall higher in patients with central compartment neck dissection compared to total thyroidectomy alone (44% *vs.* 14%, $P=0.002$). Routine supplementation with calcium and vitamin D reduced this rate to 8%. It also completely eliminated the need for IV calcium for persistent symptomatic hypocalcemia, which was required for 14% of the group who underwent a central compartment neck dissection and that did not receive any supplementation. Overall, the rate of permanent hypocalcemia was 2.5%, and was similar in all four groups. The authors concluded that the addition of a central compartment neck dissection to total thyroidectomy significantly increased the risk of hypocalcemia and therefore, this group of patients should receive routine supplementation with calcium and vitamin D.

From a cost perspective, a recent analysis (19) demonstrated a reduction in cost per quality-adjusted life-years (QALYs) using a Markov decision model on a hypothetical cohort of patients. Patients were divided into routine supplementation or selective supplementation groups. All patients in the routine supplementation group received a standardized regimen of calcium 1 g 3 times a

day and calcitriol 0.5 mcg every 12 hours for 1 week. The selective supplementation group received calcium/calcitriol per the Australian Endocrine Surgeons guidelines (20). For PTH >20 pg/mL, no supplementation was given. For PTH 3–20 pg/mL, calcium carbonate 1,200 mg was given twice daily, and for a PTH ≤3 pg/mL calcium carbonate 1,200 mg and calcitriol 0.5 mcg were each given twice daily. Routine supplementation was associated with a savings of \$62 per patient, and a small increase in QALYs. The model was very sensitive to hypocalcemia, which was a factor that varied by surgeon. The effect on quality of life at the individual level was also not well-characterized. The authors concluded that prospective studies are needed to better determine the cost/benefit of routine supplementation on both the individual and societal level.

Although the theoretical cost may be lower and the risk of hypocalcemia despite supplementation is low, this must be balanced against the risks of over supplementation. Patients receiving excessive amounts of calcium unnecessarily can develop hypercalcemia (21), which can increase the risk of developing renal calculi, constipation, and altered absorption of iron and zinc. There is also evidence that parathyroid inhibition can occur as a result of prolonged exposure to calcitriol. These factors may necessitate additional phlebotomies or clinic follow up in the postoperative period which can increase cost and discomfort for the patient (5). All of these factors have led to the examination of the use of selective supplementation following thyroidectomy based on postoperative serum calcium and/or PTH levels.

Defining hypocalcemia and the hypoparathyroid state

Predictive factors for hypocalcemia after thyroidectomy have been extensively investigated, but the definition of hypocalcemia has not been consistent across studies. Many studies on the topic of postoperative hypocalcemia have commented on the presence of symptoms and stratified hypocalcemia as “symptomatic” or “biochemical” if it was only based on laboratory values. The threshold calcium level also varied from 7.2 to 8.5 mg/dL depending on the study. Others have used more complicated algorithms to classify hypocalcemia by combining different thresholds with or without symptoms. As an example, one study (22) defined hypocalcemia as anyone with total calcium less than 7.2 or 7.2–8.6 mg/dL and symptomatic. These definitions were used in many studies to guide calcium supplementation, while others based a supplementation schedule on the

postoperative PTH level. Still others only counted patients with symptomatic hypocalcemia as they felt this was most clinically significant. These factors explain why there is such great variability in the incidence of postoperative hypocalcemia across different studies.

Both serum calcium and PTH levels in the perioperative period have been studied to determine their ability to predict postoperative hypocalcemia, with PTH being favored for several reasons. The nadir of serum calcium levels occurs 48–72 hours postoperatively and serum calcium levels obtained on postoperative day 1 (POD1) have been associated with a positive predictive value as low as 4% for determining persistent hypocalcemia. Given this fact, which is in part because the nadir of serum calcium typically occurs after patients have been discharged, there has been a need for an earlier predictor in order to facilitate postoperative management and prevent potential readmissions. In patients who develop hypoparathyroidism, PTH levels decline more rapidly than serum calcium, with significant changes noted within the first 3 hours (23). Postoperative PTH levels have become a more useful predictor of hypocalcemia following total thyroidectomy, as it is associated with the highest accuracy, particularly when compared to measuring postoperative calcium levels. The studies discussed below will outline the utility and timing of postoperative PTH measurements in determining the need for calcium and/or calcitriol supplementation after thyroidectomy (Table 1).

Timing of PTH measurement to guide selective supplementation

POD1

Multiple studies have examined the role of a single measurement of serum PTH level on POD1. Landry *et al.* (5) retrospectively reviewed 156 patients who underwent total or completion thyroidectomy and stratified patients into groups based on their risk of developing hypocalcemia. The high-risk group included patients with symptoms of hypocalcemia, and serum PTH <3 pg/mL and/or serum calcium <7 mg/dL on POD1. The low-risk group included all other patients. PTH and calcium levels were checked at 2 hours postoperatively, on the day of surgery at 5 PM, and on POD1 at 5 AM. The high-risk group consisted of 34 (22%) patients, 25 (74%) of whom became symptomatic. The high-risk group was more likely to be women (91% *vs.* 74%, $P=0.04$), to have malignant disease (88% *vs.* 65%, $P=0.01$), to have a concomitant

Table 1 Summary of studies demonstrating differing definitions and rates of hypocalcemia, as well as the ability of PTH levels to predict hypocalcemia

Article	Number of patients	Number of hypocalcemic patients (%)	Hypocalcemia definition	Timing of PTH	Threshold PTH (pg/mL)	Sensitivity (%)	Specificity (%)	Supplementation schedule
Landry <i>et al.</i> 2012 (5)	156	34 (21.8)	Ca <7 mg/dL	POD1	6	NR	NR	Oral calcium and/or calcitriol if PTH <6 or Ca <8 mg/dL, dose not specified
Selberherr <i>et al.</i> 2015 (4)	237	30 (12.7)	Ca <2 mmol/L	POD1	15	100	92	Oral calcium 1,000 mg, 25-OH-vitD 880 IU, and calcitriol 0.25 mcg all BID if PTH <10
Cayo <i>et al.</i> 2012 (1)	143	26 (18.2)	Symptomatic	POD1	10	58	86	Oral calcium vs. no supplementation if PTH 5–10, oral calcium vs. calcium + calcitriol if PTH <5
Toniato <i>et al.</i> 2008 (11)	160	66 (41.3)	Ca <8.5 mg/dL	POD1	9.6	NR	NR	Oral calcium/vitamin D if symptomatic, dose not specified
Lombardi <i>et al.</i> 2004 (24)	53	16 (30.2)	Ca <8 mg/dL	2, 4, 6, 24, 48 hours	10	94	100	Oral calcium 1 g TID and calcitriol 0.5 mcg BID if hypocalcemic regardless of symptoms
Carr <i>et al.</i> 2014 (9)	77	21 (27.3)	Symptomatic or PTH <10 ng/mL	4 hours, POD1	10	98	90	Oral calcium 3 g if PTH <10, add calcitriol if PTH <5 and/or at attending's discretion
Sywak <i>et al.</i> 2007 (25)	100	18 (18.0)	Ca <2 mmol/L	4 hours, POD1	10	90	84	Routine calcium 1.2 g BID. Add calcitriol 0.5 mcg BID if PTH <3 or if PTH 3–10 and hypocalcemic
Lecerf <i>et al.</i> 2012 (14)	137	39 (28.5)	Ca <2 mmol/L	4 hours	19.4	85	93	Oral calcium 600 mg TID plus calcitriol 1 mcg/day if hypocalcemic, add IV calcium if symptomatic
Lombardi <i>et al.</i> 2006 (10)	523	199 (38.0)	Ca <8 mg/dL	4 hours	10	65	90	Oral calcium 3 g/day and calcitriol 1 mcg/day if hypocalcemic regardless of symptoms
Puzziello <i>et al.</i> 2015 (3)	75	28 (37.3)	Ca <8.0 mg/dL	2 hours	14	NR	NR	Oral calcium 3 g/day and 1 mcg calcitriol daily if hypocalcemic regardless of symptoms
Graff <i>et al.</i> 2010 (7)	69	11 (15.9)	Ca <7.5 mg/dL	1 hour	14	100	83	Not specified
Richards <i>et al.</i> 2003 (26)	30	10 (33.3)	Symptomatic	IOPTH	10	80	100	Oral calcium 1,500 mg daily if PTH <10 ng/mL
Lang <i>et al.</i> 2012 (13)	117	17	Ca <1.9 mmol/L or symptomatic	IOPTH, POD1	9.4	82	95	Oral calcium 500–1,500 mg/day if Ca <1.9 mmol/L, add calcitriol 0.25 BID if oral calcium alone failed
Reddy <i>et al.</i> 2016 (6)	100	23 (23.0) [†] , 53 (53.0) [‡]	Ca <8.0 mg/dL or symptomatic	IOPTH	9	91	83	Oral calcium if Ca <8.0 mg/dL, add IV calcium and/or vitamin D if symptomatic
Alia <i>et al.</i> 2007 (22)	39	15 (38.5)	Symptomatic	IOPTH	14	80	92	Oral calcium if Ca <7.2 or 7.2–8.6 mg/dL and symptomatic
Gupta <i>et al.</i> 2015 (8)	90	NR	Ca <8.5 mg/dL	IOPTH	11.3	92	97	Oral calcium if Ca <7.2 or 7.2–8.5 mg/dL and symptomatic

The supplementation regimens used in each study are outlined. [†], symptomatic hypocalcemia; [‡], biochemical hypocalcemia. Ca, serum calcium level; PTH, parathyroid hormone (displayed in pg/mL); POD1, postoperative day 1; NR, not reported; BID, twice per day; TID, three times per day.

central compartment neck dissection (73% *vs.* 43%, $P=0.001$), or an incidental parathyroidectomy (29% *vs.* 11%, $P=0.013$). On further analysis of the high-risk group, the authors found that all symptomatic patients had a PTH value <6 pg/mL and/or a calcium <8 mg/dL. By expanding criteria to capture all symptomatic patients, an additional 32 (26%) patients from the 122 patients in the low-risk group would receive supplementation based on a PTH of 3–6 pg/mL or calcium of 7–8 mg/dL. This left 90 patients in the low-risk group without supplementation, which made up 58% of the total cohort. While this supplementation schedule meant unnecessary supplementation for some patients who would not have become symptomatic, the authors concluded that it could lead to safe early discharge and reduction in postoperative need for medication, follow-up assessments, and phlebotomies for a substantial proportion of patients. They therefore recommended calcium and/or calcitriol supplementation for all patients with PTH <6 pg/mL or calcium <8 mg/dL on the morning after total thyroidectomy.

Selberherr *et al.* (4) prospectively stratified 237 patients who underwent total thyroidectomy without lymphadenectomy by POD1 PTH values and classified them as having “normal” parathyroid function (PTH >15 pg/mL), “disturbed” function (PTH <10 pg/mL), or “uncertain” function (PTH 10–15 pg/mL). They studied the rate of hypocalcemia, which they defined as serum calcium <2 mmol/L, and the effectiveness of each threshold value of predicting hypocalcemia. The standard supplementation regimen included oral calcium, 25-OH vitamin D, and calcitriol as outlined in the table (Table 1). Threshold PTH values of 10 and 15 pg/mL had a sensitivity of 83% and 100% and specificity of 99% and 92%, respectively. These data suggested that patients with PTH >15 pg/mL were safe for early discharge without supplementation, those with PTH <10 pg/mL were at highest risk and should receive supplementation with calcium, 25-OH vitamin D, and calcitriol, and those with PTH in the 10–15 pg/mL range warrant close observation.

In a prospective, randomized study of 143 patients undergoing total or completion thyroidectomy, Cayo *et al.* (1) evaluated predictive factors for hypocalcemia and hypoparathyroidism in an effort to appropriately tailor postoperative calcium and vitamin D supplementation for the patients at highest risk of postoperative hypocalcemia. Serum calcium and PTH levels were obtained on the evening of surgery and in the morning of POD1. Patients were stratified by the POD1 PTH level, which was used as a guide for supplementation. In the highest risk group with PTH

<5 pg/mL, patients were randomized to supplementation with calcium alone or calcium and calcitriol. With a PTH between 5–10 pg/mL, patients received either calcium alone or no supplementation. No supplements were given to any patient with PTH >10 pg/mL. Calcium supplementation consisted of calcium carbonate 2,500 mg 3 times daily, or calcitriol 0.25–0.50 mcg twice daily. Follow-up serum calcium and PTH levels were obtained at the first postoperative visit. Of the 143 patients, 31 patients (22%) had PTH <10 pg/mL, and 15 of them (48%) developed symptoms of hypocalcemia. Ten of these patients required additional calcitriol or oral calcium, and 5 required prolonged admission for IV calcium. In contrast, only 11 of 112 (10%) patients with PTH >10 pg/mL were symptomatic, none required scheduled supplemental calcium, and PTH levels remained >10 pg/mL in all patients at the time of the postoperative visit (Figure 1). The authors concluded that a POD1 PTH <10 pg/mL had a sensitivity of 86% and negative predictive value of 90% for symptomatic hypocalcemia. On multivariate analysis, younger age and lower postoperative PTH levels were associated with hypocalcemic symptoms. No statistically significant predictors were found for postoperative PTH <10 pg/mL, including performance of a central compartment neck dissection, although the removal and/or autotransplantation of parathyroid glands had a trend toward being predictive (Table 2). The authors acknowledged that sample size was a limitation in finding predictive factors. This limitation notwithstanding, they concluded that PTH <10 pg/mL on the first postoperative day is highly predictive of patients at highest risk for developing symptomatic hypocalcemia after total thyroidectomy and these patients should receive supplementation. In contrast, patients with PTH >10 pg/mL are at low risk for postoperative hypocalcemia and can be discharged safely without supplementation and without the need for laboratory assays in the absence of symptoms.

Taken together, these studies demonstrate that a PTH measurement on the first postoperative day is an effective determinant of postoperative hypocalcemia and the need for supplementation, although limitations of this approach include a potential delay in treatment and subsequent discharge by 1 day.

Immediate postoperative PTH determination

In an effort to reduce costs and target earlier discharge from the hospital without compromising safety, multiple studies have assessed whether a PTH level drawn in the immediate postoperative period can accurately predict

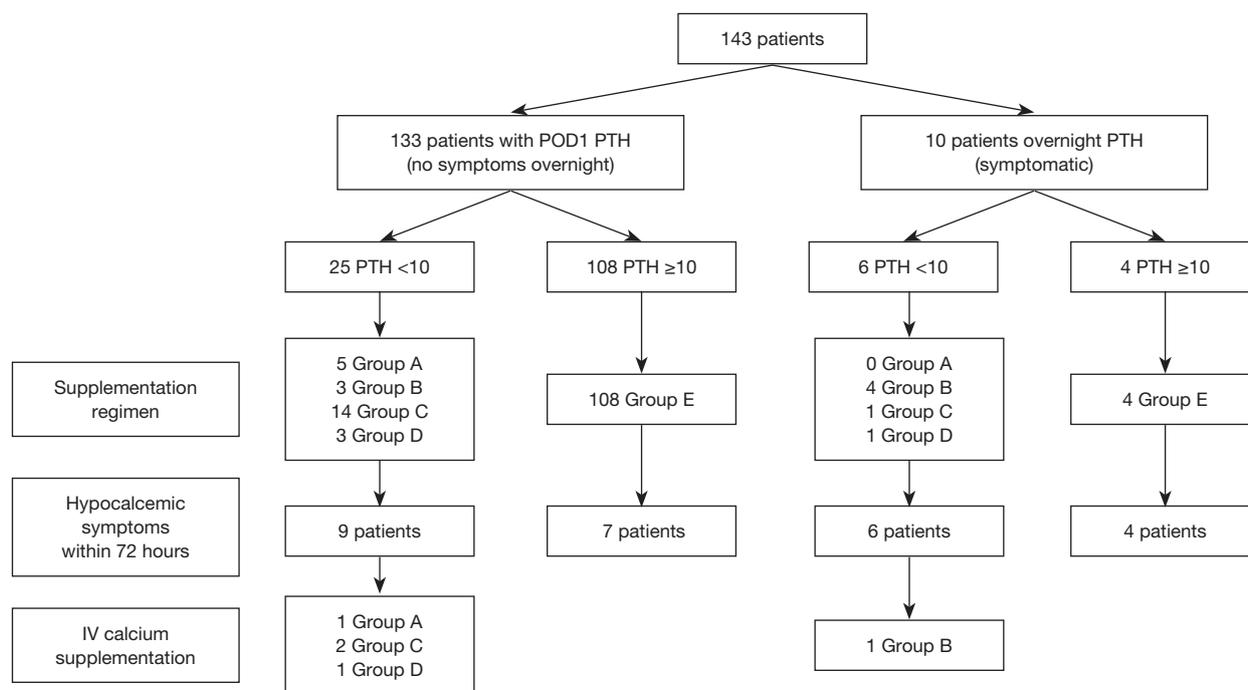


Figure 1 Breakdown of the study cohort by POD1 PTH level, supplementation regimen, hypocalcemic symptoms, and need for IV calcium [reprinted with permission from Cayo *et al.* (1)]. Group A, PTH <5, randomized to supplementation with oral calcium; Group B, PTH <5, randomized to supplementation with oral calcium and calcitriol; Group C, PTH 5–10, randomized to supplementation with oral calcium; Group D, PTH 5–10, randomized to no supplementation; Group E, PTH >10, did not receive routine supplementation.

hypocalcemia with the goal of earlier discharge in low-risk patients. The Australian Endocrine Surgeons published guidelines for postoperative PTH measurement based on four studies which combined data from 458 patients (20). They recommended that all patients have PTH measured 4 hours postoperatively. The included studies differed in the laboratory assays used for PTH level determination and so the authors defined normal levels based on the standard limits of each assay (>10, >12, >6 pg/mL, or >1.0 pmol/L). Undetectable levels were any value below the lower limit of detection (<3 pg/mL or <0.1 pmol/L), and intermediate levels were any value between the normal and undetectable ranges. The authors made the following recommendations: normal postoperative PTH levels are accurate in predicting normocalcemia and allow for early discharge without supplementation, undetectable PTH levels warrant early initiation of combination therapy with oral calcium and calcitriol and weekly monitoring of laboratory values, and patients with intermediate levels should receive calcium supplementation and should be monitored for hypocalcemia as they may require addition of calcitriol as well. These guidelines are limited by significant variability amongst

the four included studies, particularly with respect to calcium supplementation regimens and resultant rates of hypocalcemia.

Several studies have compared the accuracy of PTH levels drawn within the first 6 hours and on POD1. In a prospective cohort study of 100 patients who underwent total thyroidectomy, Sywak *et al.* (25) evaluated PTH levels at 4 and 23 hours after surgery to determine if the shorter time interval would alter the accuracy with which PTH determination could predict hypocalcemia. Using a threshold of 10 pg/mL, the sensitivity and specificity of the 4- and 23-hour interval (90% *vs.* 86% and 84% *vs.* 83%, respectively) were similar. The mean PTH levels were also similar between groups at the 2 time points (22.3 pg/mL at 4 hours and 23.2 pg/mL at 23 hours). The authors advocated for routine supplementation with calcium 1,200 mg twice daily for all patients regardless of postoperative PTH level; in addition, calcitriol 0.5 mcg twice daily was added and hospital stay was extended to 2 days for any patient with PTH <3 pg/mL. For patients with PTH between 3 and 10 pg/mL, calcitriol was added if the serum calcium level dropped below 2.0 mmol/L. This

Table 2 Unadjusted analysis of characteristics of 143 patients, by report of hypocalcemic symptoms [reprinted with permission from Cayo *et al.* (1)]

	No symptoms (n=117)	Symptoms (n=26)	Odds ratio	95% CI		P value
				Lower	Upper	
Age (years)			0.96	0.92	0.99	0.03
Mean (SD; range)	49 (14; 18–82)	41 (11; 23–64)				
0–37	26 (22%)	13 (50%)				
38–48	32 (27%)	6 (23%)				
49–56	27 (24%)	4 (15%)				
>56	32 (27%)	3 (12%)				
Postoperative calcium			0.16	0.07	0.41	<0.0001
Mean (SD; range)	8.4 (0.5; 6.9–9.6)	7.9 (0.6; 6.9–9.9)				
<8.1	27 (23%)	17 (65%)				
8.1–8.6	54 (46%)	7 (27%)				
>8.6	36 (31%)	2 (8%)				
Postoperative PTH			0.93	0.89	0.96	<0.0001
Mean (SD; range)	29.8 (17.2; 3.9–85.5)	14.6 (13.0–44.5)				
<10	16 (14%)	15 (58%)				
≥10	101 (86%)	11 (42%)				
Number of CN nodes			0.88	0.77	1.01	0.75
Mean (SD; range)	9.0 (7.4; 0–29)	8.3 (7.4; 1–26)				

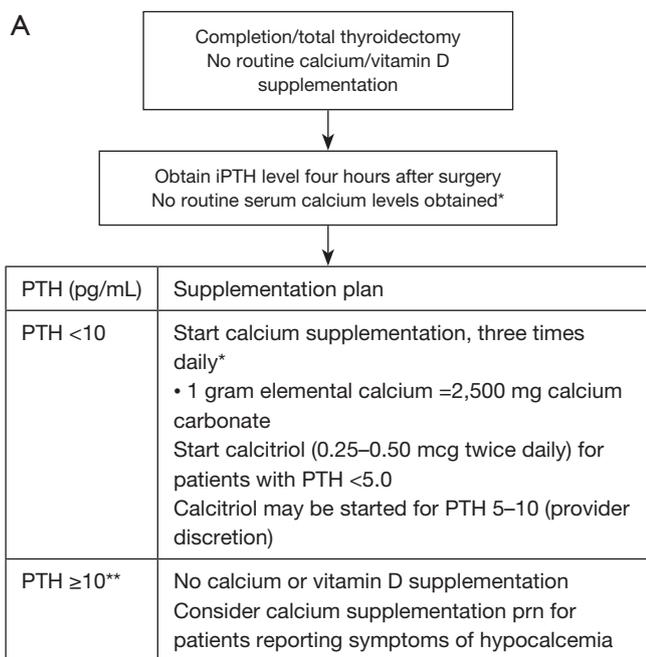
CN, central neck; PTH, parathyroid hormone.

study was limited by a lack of any post-discharge follow up data on rates of hypocalcemia and ongoing need for supplementation. Nonetheless, the authors concluded that postoperative PTH levels drawn at 4 and 23 hours after surgery were equivalent, and the earlier time point could lead to earlier initiation of supplementation and hospital discharge.

Lombardi *et al.* (24) used serial measurements of calcium and PTH levels to determine the most accurate time point after thyroidectomy. They collected samples preoperatively, at skin closure, 2, 4, 6, 24, and 48 hours after surgery in 53 patients after total or completion thyroidectomy. Hypocalcemia, which they defined as serum calcium <8.0 mg/dL, was noted in 16 (30%) patients, all of whom received supplementation. A standard supplementation schedule of oral calcium 1 g 3 times daily and calcitriol 0.5 mcg twice daily was given to any hypocalcemic patient regardless of symptoms. PTH levels were in the normal range for all normocalcemic patients. The 4- and 6-hour time points were most predictive of developing

hypocalcemia (sensitivity 94%, specificity 100%) for a PTH level of <10 pg/mL. The authors concluded that a single PTH measurement at 4 hours was the most useful as it was most accurate in predicting hypocalcemia while allowing early initiation of therapy if needed or early discharge in patients at low risk.

To validate the 4-hour time point, the same authors followed their original study with a large prospective study (10). They evaluated 523 patients after thyroidectomy and found that 199 patients (38%) developed postoperative hypocalcemia (defined as a serum calcium <8.0 mg/dL). They used the same PTH threshold of 10 pg/mL as this provided the highest accuracy for predicting hypocalcemia in their previous study; however, for this cohort, the sensitivity (65%), specificity (90%), and accuracy (80%) were all considerably lower than their previous study. Of the 199 hypocalcemic patients, 70 (35%) had a normal PTH level. For the entire cohort, this coincided with a false-negative rate of 13.4% of patients who were hypocalcemic with a normal PTH level. The authors concluded that this



*, Serum calcium levels may be drawn at discretion of provider or for persistent and/or severe symptoms; **, if PTH ≥10 on any subsequent draw, discontinue calcium supplementation, unless symptomatic. Symptomatic patients will be evaluated on a case-by-case basis.

B After hospital discharge:

If patients call with symptoms of hypocalcemia:

- If postoperative PTH <10:
 - May increase calcium supplementation (frequency and/or dosage)
 - If not on calcitriol: start calcitriol (0.25–0.50 mcg PO BID)
 - If on calcitriol: increase dose by 0.25 mcg PO BID
- If postoperative PTH ≥10: may consider calcium supplementation, as needed

** Labs (calcium, PTH) to be obtained at provider discretion

Postoperative office visit:

PTH <10: obtain serum calcium, iPTH, and 25-OH vitamin D at visit

PTH ≥10: routine labs not indicated, unless patient reports symptoms of hypocalcemia

Postop PTH	PTH at visit	Plan
<10	<5	Continue supplementation. Repeat labs in 2 weeks
	5–10	Wean supplementation
	≥10	Wean supplementation

Figure 2 Algorithm for postoperative inpatient (A) and outpatient (B) management with calcium supplementation following completion/total thyroidectomy. PTH, parathyroid hormone; BID, twice per day.

false-negative rate was too high to use a 4-hour PTH level of >10 pg/mL as a justification for early discharge. They therefore recommended serial calcium monitoring and routine supplementation.

A study by Graff *et al.* (7) similarly investigated the role for an early postoperative 1-hour PTH level in the development of hypocalcemia (defined as <7.5 mg/dL) in 69 patients. With a threshold PTH value of 14 pg/mL, the sensitivity was 100% and specificity was 83% of predicting hypocalcemia in this cohort of patients. The addition of a serum calcium level at 6 hours improved the specificity to 88% without changing the sensitivity. They therefore concluded that patients with an immediate postoperative PTH level >14 pg/mL and serum calcium >8.0 mg/dL at 6 hours were safe for early discharge without supplementation. If these conditions were not met, the authors recommended additional calcium monitoring and inpatient management.

Carr *et al.* (9) compared the predictive value of PTH levels on POD1 and at 4 hours in 77 patients after total or

completion thyroidectomy as a follow up to their previous study (1). PTH levels were drawn at 4 hours and on POD1 and all patients with PTH <10 pg/mL on POD1 were discharged with supplementation (*Figure 2A*). Of the 77 patients, 21 (27%) received supplementation; 18 had PTH <10 pg/mL at both time points and 9 of them (50%) reported having symptoms. Of the remaining 3 patients, 2 had PTH >10 pg/mL at both time points, but received supplementation because of the development of symptoms in 1 patient and a low serum calcium (7.3 mg/dL) in the other. The remaining patient had an initial PTH <10 pg/mL and POD1 PTH >10 pg/mL, but did develop symptoms. Of note, two patients with a 4-hour PTH 5–10 pg/mL had a POD1 PTH ≥10 pg/mL and were not discharged on supplementation; these patients were asymptomatic and did not require supplementation postoperatively. Comparing the 4-hour data to the POD1 data, the sensitivity (98% *vs.* 98%), specificity (90% *vs.* 86%), positive predictive value (96% *vs.* 95%), and negative predictive value (95% *vs.* 95%) were similar in their accuracy of predicting hypocalcemia

Table 3 Predictive value of 4-hour PTH vs. POD1 PTH for patients not requiring supplementation [reprinted with permission from Carr *et al.* (9)]

	Patients with PTH <10 pg/mL [%]	Patients with PTH ≥10 pg/mL [%]	Median PTH (pg/mL: range)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Four-hour PTH	20 [26]	57 [74]	21.1 (2.3–97.1)	98	90	96	95
POD1 PTH	18 [23]	59 [77]	23.2 (2.4–61.3)	98	86	95	95

PTH, parathyroid hormone; POD1, postoperative day 1.

(Table 3). Based on these data, the authors developed a protocol for calcium and calcitriol supplementation after completion/total thyroidectomy; patients with a 4-hour PTH >10 pg/mL do not receive calcium supplementation. Patients with a PTH <10 pg/mL are started on calcium carbonate; calcitriol is added when the PTH is <5 pg/mL and/or at the surgeon's discretion (Figure 2B).

Intraoperative PTH (IOPTH) measurement

With the increasing use of IOPTH monitoring in parathyroid surgery, several investigators have evaluated its role in predicting postoperative hypocalcemia after thyroid surgery. This was first examined by Richards *et al.* (26) with a prospective evaluation of 30 patients who had a total thyroidectomy. IOPTH levels were obtained, and postoperative serum calcium levels were drawn at 6 hours and again on POD1. Overall, 10 (33%) patients developed symptomatic hypocalcemia and 5 required IV calcium for tetany; this included 8 patients who had IOPTH levels <10 pg/mL. A threshold of 10 pg/mL had a sensitivity and specificity of 80% and 100%, respectively, for the development of symptomatic hypocalcemia. The authors concluded that IOPTH can be used to accurately predict postoperative hypocalcemia.

Other studies followed validating these results. Lang *et al.* (13) prospectively evaluated 117 patients that underwent total or completion thyroidectomy. Using a cutoff of 1.0 pmol/L (equal to 9.4 pg/mL), an IOPTH level obtained 5–10 minutes after skin closure was 82% sensitive and 95% specific for developing symptomatic or biochemical hypocalcemia (defined as Ca <1.9 mmol/L or 7.6 mg/dL). Patients with either symptomatic hypocalcemia or serum calcium level <1.9 mmol/L were supplemented with 500–1,500 mg oral calcium daily with the addition of calcitriol 0.25 mcg twice daily for persistent hypocalcemia. With an IOPTH threshold of 9 pg/mL, another prospective study (6) of 100 patients demonstrated similar results. IOPTH levels were drawn 20 minutes after

thyroidectomy with the patient still anesthetized. A routine supplementation schedule was given for biochemical hypocalcemia (defined as <8 mg/dL) consisting of oral calcium. With the development of hypocalcemia symptoms, patients received IV calcium gluconate and/or vitamin D in addition to oral calcium. IOPTH was 91% sensitive and 83% specific for predicting symptomatic hypocalcemia. There were only 2 of 64 (3%) patients with PTH >9 pg/mL that became symptomatic and required supplemental calcium. Both were treated successfully as outpatients and neither required addition of calcitriol. Both of these studies concluded that IOPTH was accurate in predicting hypocalcemia with an acceptably low false negative rate, and it can be used to facilitate same-day discharge in patients with IOPTH levels above the threshold. In patients with IOPTH below the threshold level, serial calcium monitoring and an additional inpatient hospital day are warranted for closer monitoring.

Relative decline in perioperative PTH value

While a single PTH measurement postoperatively has been demonstrated to be an accurate predictor of postoperative hypocalcemia at multiple different time points, a PTH decline perioperatively has also been described as a method to predict postoperative hypocalcemia. A systematic review published in 2007 (27) included nine studies with a total of 457 patients that documented the PTH decrease from a level drawn preoperatively to a level drawn at various time points within the first 6 hours after surgery. They evaluated the data in 3 different groups, IOPTH, PTH level drawn at 1–2 hours, and PTH level at 6 hours, and assessed the accuracy with which these different levels could predict hypocalcemia. The definition of hypocalcemia differed for each study and varied from <7.2 to <8.4 mg/dL with or without symptoms. The authors found that the greatest accuracy was determined using the trend to 6 hours, followed by 1–2 hours, and finally intraoperatively with receiver operating characteristic (ROC) area under the

curve (AUC) measurements. For this study, the AUCs were 0.97 for the 6-hour group, 0.94 for the 1–2-hour group, and 0.86 for the intraoperative group, with significant differences between the intraoperative group and each of the postoperative groups ($P=0.021$ for the 1–2-hour group and $P=0.002$ for the 6-hour group), but not between the two postoperative groups. The authors concluded that all 3 time trends offer an accurate predictor of postoperative hypocalcemia, with the 1–2- and 6-hour determination being the most predictive. Moreover, a greater percent decrease in PTH level correlated with a higher positive predictive value. Based on these data, the authors recommended obtaining preoperative as well as postoperative PTH levels 1–6 hours after thyroidectomy in order to determine a PTH trend, which can be used to guide early calcium supplementation for a larger decline in PTH levels (>90%) and safe early discharge for smaller declines (<50%). The patients that have a decline in the 50–90% range warrant additional calcium monitoring.

A prospective study (3) evaluated the relative decline of PTH 2 hours post-thyroidectomy in a cohort of 75 patients. The relative decline was 72% for hypocalcemic (defined as PTH <8 mg/dL) patients and 44% for patients who remained normocalcemic. A cutoff of 62% decline had the highest accuracy with 100% sensitivity and specificity. The authors recommended oral calcium supplementation for any hypocalcemic patient, or for a patient who is normocalcemic on POD1 with a relative decline in PTH level >62% as this group was at high risk for progression to hypocalcemia. This group did not need additional inpatient monitoring and was safely discharged home on POD1.

Several studies compared the trend in PTH levels to a single intraoperative or postoperative value and demonstrated similar accuracy between the two groups. A study (8) of 90 patients undergoing thyroidectomy with preoperative and IOPTH measurement compared the sensitivity and specificity of a single IOPTH value of 11.3 pg/mL, a PTH decline of 75%, and a combination of the two. Though all tests had high accuracy, the addition of PTH decline to a single IOPTH level did not improve the accuracy of predicting hypocalcemia with a sensitivity of 92% and specificity of 97% for both tests. A similar study of 137 patients (14) used an interval of 4 hours and compared a single 4-hour value to the trend at 4 hours. Both the single value and the trend were highly sensitive and specific for predicting hypocalcemia with a PTH threshold of 19.4 pg/mL and a PTH decline of 69%. The relative decline had a trend toward improved accuracy but this did not reach statistical

significance. A prospective study of 160 patients extended the trend until the first postoperative day (11). The accuracy of both the POD1 PTH with threshold 9.6 pg/mL and a negative trend of 69% was similar, and the combination of the two values again did not improve accuracy. Taken together, these studies demonstrate similar accuracy for a single PTH level and a trend of preoperative to postoperative PTH values. This suggests that the additional laboratory values only increase cost and discomfort to the patient without any perceived benefit and may therefore be unnecessary.

Summary

PTH assessment is an accurate predictor of developing postoperative hypocalcemia after total thyroidectomy. Given significant variation in study designs, the optimal timing of this measurement cannot be determined. However, obtaining PTH measurement within 4 hours of surgery is an accurate predictor for the development of hypocalcemia and can guide selective calcium and calcitriol supplementation in high-risk individuals while allowing for the possibility of same-day discharge in low-risk individuals without the need for supplementation or further monitoring in the absence of symptoms.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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