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ROMM
Revista de Osteoporosis y Metabolismo Mineral

Original

Predictors of early and late recovery in post-thyroidectomy transient hypoparathyroidism

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Abstract

Purpose: to analyze predictors of early, intermediate, late remission of transient hypoparathyroidism after total thyroidectomy.

Methods: we conducted a multicenter, retrospective, observational study of individuals who developed postoperative transient hypoparathyroidism.

Results: a total of 164 patients with postoperative transient hypoparathyroidism were analyzed. Thyroidectomy was performed in 56 % for benign disease and 44 % for suspected malignancy. Hypoparathyroidism remission occurred early (< 3 months) in 47 % of patients, intermediate (3-6 months) in 23.7 %, and late (> 6 months) in 29.3 %. No differences were found across 3 groups regarding preoperative PTH levels, PTH 24 hours after surgery, or the percentage of PTH decrease. However, we observed higher calcium values 24 hours after surgery, and higher serum calcium and PTH levels at the first outpatient appointment (2 weeks after discharge) in patients with early remission of hypoparathyroidism. In patients with late remission of hypoparathyroidism, a past medical history of surgery for malignancy, the presence of undetectable PTH levels, lower serum calcium levels 24 hours after surgery, and the need for IV calcium treatment were remarkable ($p < 0.05$). This group had lower PTH levels in their 1st and 2nd outpatient visits, and lower serum calcium levels on the 2nd visit ($p < 0.05$).

Conclusions: serum calcium and PTH levels measured 2 weeks after discharge can predict early recovery. Late remission was more common in patients undergoing thyroidectomy for suspected malignancy, those with undetectable PTH 24 hours after surgery, and those requiring IV calcium. Although calcium levels 24 hours after surgery could probably predict hypoparathyroidism remission time, the absence of a unique protocol to guide management at hospitalization does not allow us to draw robust conclusions.

Keywords:
Hypocalcemia.
Hypoparathyroidism.
Thyroidectomy.

Received: 01/22/2025 • Accepted: 05/18/2025

Conflict of interest: The authors declare no conflict of interest.

Artificial intelligence: The authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Mera Carreiro S, López Guerra A, Ávila Antón L, Ugalde-Abiega B, Parra Ramírez P, Martín-Fuentes M, Sánchez-Maroto García N, Humanes-Navarro AM, Huguet I. Predictors of early and late recovery in post-thyroidectomy transient hypoparathyroidism. Rev Osteoporos Metab Miner 2025;17(3): 101-106

DOI: 10.20960/RevOsteoporosMetabMiner.00077

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INTRODUCTION

Calcium homeostasis is a complex process mainly regulated by parathyroid hormone (PTH) and vitamin D, with PTH being the major regulator of calcemia (1,2). Hypoparathyroidism is a disorder of mineral metabolism characterized by hypocalcemia and absent or deficient production of PTH (3).

Surgical hypoparathyroidism occurs after inadvertent trauma, devascularization, or removal of the parathyroid glands during neck surgery. In fact, anterior neck surgery is the most common cause of acquired hypoparathyroidism, especially after bilateral thyroid surgery (4). Postoperative hypoparathyroidism can be transient or permanent. Permanent hypoparathyroidism is most commonly defined as the failure of the parathyroid gland to return to normal function 12 months after surgery (5). The ability to anticipate transient as opposed to permanent hypoparathyroidism after thyroidectomy requires further investigation. Furthermore, since transient hypoparathyroidism requires frequent biochemical monitoring for tapering or discontinuation of calcium and calcitriol due to risk of hypercalcemia and potential kidney damage, the identification of predicting remission parameters is needed to improve follow-up (6,7).

Although numerous authors have sought to predict the development of postoperative hypocalcemia with increasing accuracy, to our knowledge, parameters that predict the timing of recovery in transient hypoparathyroidism have not been studied. The objective of this retrospective, multicenter observational study was to identify predictors of early, intermediate, and late remission of hypoparathyroidism following total thyroidectomy.

MATERIALS AND METHODS

This retrospective analysis enrolled 164 patients older than 18 years from different hospitals in the Community of Madrid (Spain) with experience in thyroid surgery, who underwent total thyroidectomy and developed transient hypoparathyroidism. Remission of hypoparathyroidism was defined as the discontinuation of substitutive treatment and categorized as "early" (< 3 months), "intermediate" (3-6 months), or "late" (> 6 months after surgery). Indications for surgery were thyroidectomy for benign nodular disease; thyroidectomy for Graves´ disease; thyroidectomy for malignant disease; combined thyroid and parathyroid surgery; and re-intervention for thyroidectomy totalization. We included combined thyroid and parathyroid procedures as a single group, as preexisting hyperparathyroidism may alter postoperative calcium metabolism, likely through the influence of hungry bone syndrome.

We included sociodemographic and clinical data (sex, age, presence of obesity, treatment with vitamin D or thiazide). Data on the surgical procedure, changes in parathyroid function, and the management of hypoparathyroidism were reviewed. Intact PTH, alkaline phosphatase, and vitamin D were preoperatively assessed. Serum PTH and calcium levels (albumin-adjusted calcium), and phosphatemia were evaluated at 24, 48, and 72 hours, at the 1st outpatient visit after discharge, the 2nd visit after discharge, and the visit of recovery. Since several hospitals were involved in the study, there was not a unique follow-up protocol: on average the 1st follow-up visit was performed 2 weeks after discharge and the 2nd, 4-8 weeks after discharge. Visits between 4 and 8 weeks, as well as those at the time of recovery, were not systematically recorded but were conducted at the discretion of the treating physician, following the recommendations of the I International Conference on the Management of Hypoparathyroidism (3), which was the prevailing guideline at that time. We also included as treatment data the need for IV calcium or magnesium in the immediate postoperative period. Therapy at discharge included oral calcium carbonate and calcitriol, according to the physician´s clinical criteria, same as the treatment withdrawal.

The descriptive and statistical analysis was performed using the Statistical Package software for Social Sciences 24.0 (SPSS). Qualitative variables are presented with their frequency distribution. Quantitative variables are expressed as mean. Quantitative variables showing an asymmetric distribution are expressed as median. A comparison of sociodemographic, clinical, surgical, and laboratory data based on the time of remission was conducted as well. The association between qualitative variables was assessed using the chi-square test or Fisher's exact test, if > 25 % of the expected values were < 5. For quantitative variables, means were compared using a two-tailed Student's t-test or the Mann-Whitney U test if quantitative variables did not follow normal distribution.

RESULTS

A total of 164 patients were included. There were 144 women (87.8 %) and 20 men (12.2 %) with a mean age of 51 years (range 18-89), and mean vitamin D levels of 23 mg/mL and 17.7 % having received previous vitamin D treatment. A total of 5.5 % of patients were on thiazides. Most patients (72, 43.9 %) underwent a total thyroidectomy for suspected malignancy; 61 (37.2 %) patients for benign nodular disease and 21 (12 %) patients for Graves´ disease. In addition, 6 patients (3.7 %) underwent combined thyroid and parathyroid surgery, and 4 patients (2.4 %) required reoperation for completion thyroidectomy (Table I).

Table I. Patient characteristics and indications for surgery

	Early remission (n = 77)	Intermediate remission (n = 39)	Late remission (n = 48)
Patient characteristics			
Patient age at surgery, mean ± SD	54 ± 15*	46 ± 14*	50 ± 15
Sex n (%)			
Male	9 (12)	4 (10)	7 (15)
Female	68 (88)	35 (90)	41 (85)
Indication for surgery n (%)			
Malignant disease	30 (39)	13 (33)	29† (60)
Benign nodular disease	33 (43)	15 (38)	13 (27)
Graves´ disease	7 (9)	8 (21)	6 (3)
Combined thyroid and parathyroid surgery	5 (6)	1 (3)	0
Completion thyroidectomy	2 (3)	2 (5)	0

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$.

Hypoparathyroidism remission was early in 47 % of patients, intermediate in 23.7 % and late in 29.3 %. Although no sex-related differences were observed, age-related differences at the time of surgery were identified in the early (p = 0.02) and intermediate (p = 0.021) groups compared with the remaining patients. There were no differences in clinical parameters such as obesity, presence of low vitamin D, serum alkaline phosphatase, or previous treatment with vitamin D or thiazides before surgery. In our study, malignant disease was associated with late recovery (p = 0.003). Regarding biochemical parameters, no differences were found across the 3 groups regarding preoperative PTH values (55 pg/mL, 52 pg/mL, and 53 pg/mL); PTH 24 hours after surgery (10 pg/mL, 9 pg/mL, and 9.5 pg/mL), or the median percentage of PTH decrease (82 %, 80.5 %, and 83 %).

As shown in table II; patients from the early remission hypoparathyroidism group had significantly higher serum calcium levels 24 hours after surgery (8.4 mg/dL, p = 0.001), and only a small proportion of patients had undetectable PTH 24 hours after surgery (6.6 %, p = 0.020) vs other patients. In this group, only 9.2 % (p = 0.000) of patients required IV calcium and 0 % required magnesium. In addition, at the 1st visit, these patients had mean calcium levels of 9.3 mg/dL (p = 0.010) and median PTH levels of 20 pg/mL (p = 0.039), indicating early resolution of hypoparathyroidism and allowing discontinuation of calcium and calcitriol treatment.

In contrast, in patients with late resolution of hypoparathyroidism, calcium levels were < 7.9 mg/dL (p = 0.000) 24 hours after surgery; and 25 % of these patients had undetectable PTH (p = 0.003). In the postoperative period, 43.8 % (p = 0.000) of patients required IV calcium and 6.3 % magnesium. Calcium levels were lower, especially at the 2nd visit (8.8 mg/dL, p = 0.019), and PTH levels were lower at the 1st visit (12 pg/mL, p = 0.000) remaining lower in the 2nd visit (21 pg/mL, p = 0.014). Regarding surgical parameters, 60.4 % of patients in late remission (p = 0.012) underwent total thyroidectomy for malignant disease. After a median 11 months the remission of hypoparathyroidism occurred.

Due to several missing values, phosphorus levels were not analyzed.

Receiver operating characteristic (ROC) curve analysis showed that the only parameter with an adequate area under the curve (AUC) was serum calcium at 24 hours after surgery. The AUC for detecting early hypoparathyroidism remission using 24-hour postoperative serum calcium was 0.645, with the best cutoff value of 8.22 mg/dL (sensitivity, 56 %; specificity, 32 %; positive predictive value, 0.6) (Fig. 1).

DISCUSSION

Hypoparathyroidism is the most common complication of thyroidectomy. Its frequency, if transient, can reach up to 46 %, and, if permanent, up to 3 % in literature (8,9). Early prediction of postoperative hypocalcemia is critical to initiate treatment and avoid potentially life-threatening complications; however,

Table II. Serum PTH, calcium, alkaline phosphatase, vitamin D levels and postoperative treatment

	Early remission (n = 77)	Intermediate remission (n = 39)	Late remission (n = 48)
PTH levels			
Preoperative (pg/mL)	55 (44-75)	52 (40-68)	53 (45-65)
Postoperative (pg/mL)	10 (5-12)	9 (7-12)	9.5 (5-13)
Median % of PTH decrease	82 (77-92)	80.5 (75-90)	85 (80-91)
Patients with undetectable postoperative PTH (%)	5 (6.6)*	4 (10.8)	12 (25)†
1st visit (pg/mL)	20 (12-34)*	19 (15-34)	12 (8-18)‡
2nd visit (pg/mL)	31.5 (20-48)	31.5 (18-41)	21 (12-34)*
Alcaline phosphatase (U/L)	74.4 (63-88)*	71 (56-78)	68.1 (42-76)*
Vitamin D (pg/mL)	23 (14-30)	19 (16-25)	27.5 (20-36)
Calcemia (mg/dL)			
24 after surgery	8.4 ± 0.8†	8.1 ± 0.7	7.9 ± 0.6‡
48 after surgery	8.1 ± 0.9	8.2 ± 0.7	8.2 ± 0.6
72 after surgery	8.3 ± 0.8	8.6± 0.8	8.3 ± 0.7
1st visit	9.3 ± 0.7*	9.1± 0.4	9.3 ± 0.5
2nd visit	9.2 ± 0.9	9.2± 0.4	8.8 ± 1.2*
Treatment			
Treatment with IV Ca (%)	7 (9.2)‡	9 (23.1)	21 (43.8)‡
Treatment with Mg (%)	0 (0)	2 (5.1)	3 (6.3)

**p < 0.05, †p < 0.01, ‡p < 0.001. Data are expressed as mean ± SD or median (IQR) range depending on the type or the data distribution.*

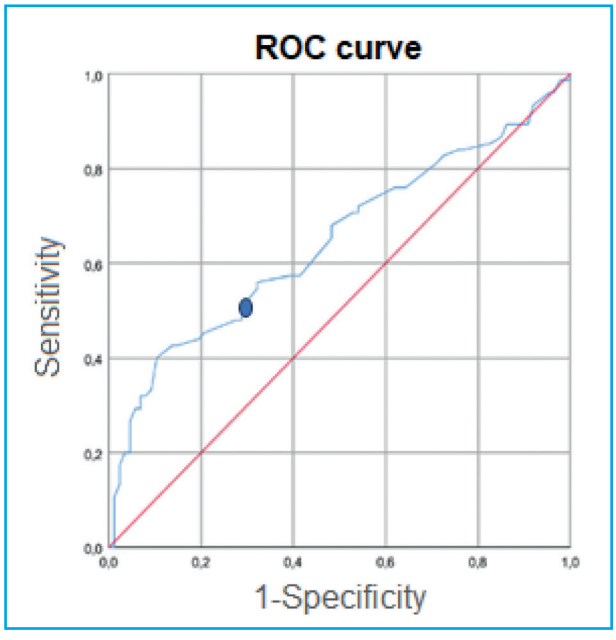

Figure 1. Receiver operating characteristic (ROC) curve analysis, serum calcium levels at 24 hours.

this treatment must be closely monitored since resolution of hypoparathyroidism should be accompanied by a discontinuation of calcium and calcitriol to prevent hypercalcemia (10).

Type and extent of surgery, operative technique, surgeon expertise and cause of disease contribute to the risk of surgical hypoparathyroidism (11-13) and probably to the length of the recovery period. In our study, patients who underwent total thyroidectomy for malignant disease more frequently experienced later remission compared with those who underwent thyroidectomy for other causes, possibly due to a more aggressive surgical approach. Because of the multicentric design of the study, we could not compare surgeon expertise as a predictor of time of remission.

PTH has been shown to be a useful tool in predicting postoperative hypoparathyroidism. Since calcium trends often require sampling over a period of 12 to 24 hours or longer, PTH seems to be a more reliable parameter (12). Although several studies have attempted to validate different PTH thresholds and combinations of PTH and calcium, results have not been consistent (14-18).

The percentage decrease in PTH levels has also been evaluated as a predictor of hypocalcemia. In our series, the median decrease in PTH was of 84.9 %, which is similar to the decline reported by other authors in patients developing hypoparathyroidism. According to clinical practice guidelines (19) postoperative PTH can be used to predict patients who will not develop permanent postoperative hypoparathyroidism. The development of permanent hypoparathyroidism is unlikely when PTH values exceed 10 pg/mL within 12 to 24 hours after surgery; thus, long-term treatment with active vitamin D and calcium supplements beyond the recommended daily allowance is generally unnecessary. Furthermore, according to Yao et al. (20) 3-64 % of patients with PTH values < 10 pg/mL 12-24 hours after surgery may still recover from temporary hypoparathyroidism. In our study the mean levels of PTH 24 h after surgery were 9 pg/mL, while the median levels were 11 pg/mL, thus supporting guidelines assertion. Although we evaluated these parameters as predictors of time of recovery, we did not find significant differences between preoperative PTH, PTH 24 hours after surgery or in the percentage of PTH decrease. Although the use of different PTH assays across centers could explain the lack of significance, it should not affect the percentage of decrease. We found that higher levels of PTH and calcium in the 1st visit (2 weeks after surgery) could predict early remission of hypoparathyroidism while lower PTH levels were associated with late remission. Regarding serum calcium levels at 24, 48 and 72 hours, the absence of a unique protocol to guide management at hospitalization could have influenced these levels, mainly at 48 and 72 hours and, in some cases, at 24 hours. Our results suggest that serum calcium levels 24 hours after surgery could probably predict hypoparathyroidism remission time, since ROC analysis suggested that calcium levels > 8.2 mg/dL 24 hours after surgery are associated with early remission of hypoparathyroidism. In addition, although were found differences between early and late groups, we cannot draw robust conclusions on this regard.

Moreover, we tried to analyze phosphorus levels, but there were considerable missing values, so results turned out biased. Phosphate has gained interest in the evaluation of PTH function, not only for distinguishing hungry bone disease from hypocalcemia due to hypoparathyroidism in the early postoperative period (21) but also as an indicator of the severity of PTH deficiency. In a study of patients with PTH levels < 10 pg/mL on the first postoperative day, serum phosphorus concentration was identified as an independent factor influencing recovery of PTH to normal levels within the first week after surgery (22). Since fibroblast growth factor 23 (FGF23) was not available in routine biochemical test in several hospitals, this value was not considered in this study. As far as we know, only 1 study has ever evaluated FGF23 in postoperative hypoparathyroidism. In this study, the authors found a significant positive correlation between serum phosphate and FGF23 levels. Serum FGF23 was elevated in patients with hypoparathyroidism and hyperphosphatemia and normalized along with normalized phosphate levels after recovery of parathyroid function. The peak level of phosphate always preceded that of FGF23 by several days, suggesting that elevated phosphate is a primary stimulus for FGF23 release (23), which could explain the fact that phosphate changes appear to be slower than that of serum calcium, whose change is rapidly corrected within minutes.

The strength of this study lies in the multicenter recruitment of patients, the number of enrolled patients and the point that it represents real clinical practice involving 2nd and 3rd-level hospitals (Table III). Furthermore, since our study is focused on transient hypoparathyroidism, we believe that our conclusions could bring understanding to the recovery process of parathyroid function. On the other hand, a limitation of our study is that evaluating a more homogeneous population might have yielded more precise data; however, our goal was to provide a broader perspective that encompasses different clinical settings. We did not consider either the effect that the treatment with Iodine-131 had in patients treated due to malignant disease, which could be of interest since it has been described a prolonged recovery of parathyroid function of patients with thyroid cancer and treatment with Iodine-131 treatment after surgery (24). Additionally, we did not include data on lymph nodes dissection, which influences the extent of surgery.

In conclusion, the definition of permanent hypoparathyroidism remains controversial. Since in most cases, parathyroid dysfunction after thyroidectomy resolves a few months after surgery, several authors consider that if parathyroid disfunction persists over 6 months (3), hypoparathyroidism should be considered as permanent. In our study almost 70 % of the patients had remission of hypoparathyroidism within the first 6 months (early 47 %, intermediate 23.7 %) but after that period, a significant percentage of patients recovered the parathyroid function (29.3 %), supporting the recommendation of the II International Workshop for the Evaluation and Management of Hypoparathyroidism (19) to diagnose permanent hypoparathyroidism if the condition persists > 12 months after surgery.

Table III. No. of patients included per hospital

Medical center	No. of patients included *n*; (%)
Hospital Universitario Clínico San Carlos	32 (23)
Hospital General Universitario Gregorio Marañón	39 (27)
Hospita Universitario La Paz	18 (12)
Hospital Universitario Ramón y Cajal	27 (18)
Hospital Universitario Santa Cristina	15 (10)
Hospital Universitario Infanta Leonor	15 (10)

CONCLUSIONS

Two weeks after discharge, serum calcium and PTH levels can predict early recovery. Late remission was more common in individuals undergoing thyroidectomy for suspected malignancy, those with undetectable PTH 24 hours after surgery, and those requiring IV calcium.

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