



## Hypocalcemia after thyroidectomy: iPTH levels and iPTH decline are predictive? Retrospective cohort study<sup>☆</sup>



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### ABSTRACT

**Background:** Hypocalcemia is the most common complication of thyroid surgery. The aim of this study was to determine the early predictive factors of postoperative hypocalcemia and to analyze their efficiency.

**Methods:** We performed a retrospective study of 345 consecutive patients who underwent total thyroidectomy at the Endocrine Surgery Department (Policlinico G. Rodolico Hospital of Catania) between January 2011 and November 2013. We measured serum intact parathormone (iPTH) levels preoperatively and 4 h after surgery. The threshold values of hypocalcemia for iPTH levels and iPTH relative decline were obtained by receiver operating curves (ROC) analysis.

**Results:** The incidence of hypocalcemia was 32.2% (111 of 345 patients). Our statistical analysis revealed that hypocalcemia rate was strongly correlated with the lower iPTH values and greater iPTH decline ( $P < 0.001$ ). The threshold enabling prediction of hypocalcemia were 12,5 pg/mL for iPTH and 55,7% for relative iPTH decline. Patients with iPTH  $< 12,5$  pg/mL developed hypocalcemia in 58.6% of cases while those with iPTH  $\geq 12,5$  pg/dl in 18.8%. Among 175 patients with iPTH relative decline greater than 55,7% hypocalcemia was diagnosed in 91 cases (52%), while other 170 patients with iPTH relative decline less than 55,7% developed hypocalcemia only in 20 cases (11,7%).

**Conclusions:** The decreased iPTH levels and increased iPTH relative decline resulted to be an accurate predictive factors of postoperative hypocalcemia. The early administration of Calcium and vitamin D in the high-risk patients should be put on in order to prevent the symptoms of hypocalcemia and to reduce the costs and duration of hospitalization.

## 1. Introduction

The main life-threatening complications of thyroid surgery include damage to the recurrent laryngeal nerve (RLN) and hypoparathyroidism. To avoid or reduce the incidence of these complications, the surgeon should identify and preserve the RLN and parathyroid glands during intervention. However, the dissection of parathyroid glands can lead to their lesion or accidental removal resulting in a temporary or permanent hypoparathyroidism [1,2]. The incidence of postoperative hypocalcemia varies significantly in the literature from 1,7%–68% [1–4]. Hypocalcemia should be diagnosed early to prevent the appearance of clinical symptoms. Recently different studies have reported the reliability of serum intact parathormone (iPTH) measurements in

predicting postoperative hypocalcemia [5–8].

The aim of this study was to analyze the correlation between serum iPTH levels and total serum calcium (Ca) levels and to evaluate the accuracy of postoperative iPTH levels in predicting hypocalcemia in patients who undergo total thyroidectomy. Local ethics committee approved the study.

## 2. Materials and methods

We performed a cohort retrospective study of 345 consecutive patients who underwent total thyroidectomy at the Endocrine Surgery Department (Policlinico G. Rodolico Hospital of Catania) between January 2011 and November 2013. Surgical indications were benign

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(64%) and malignant (36%) thyroid pathology; patients affected by Graves' disease were excluded from this review. Demographic, clinical and laboratory data were obtained from hospital records.

Thyroidectomy in all patients was performed by the same team of surgeons; during the intervention we always identified and preserved the recurrent laryngeal nerves through their entire extension, without use of intraoperative neuromonitoring. Parathyroid glands were identified and accurately separated from the thyroid gland with preservation of their vascularization.

We measured iPTH levels preoperatively and 4 h after surgery. Calcemia was measured before surgery and 18 h after operation. iPTH was estimated by the CLIA method (normal range: 15–65 pg/mL). The absolute iPTH decline was defined as:  $\Delta$  PTH = preoperative iPTH - postoperative 4 h iPTH. Relative iPTH decline was defined as:  $\Delta$  PTH/pre-PTH = (preoperative iPTH - postoperative 4 h iPTH)/preoperative iPTH. Serum calcium normal values ranged from 8.4 to 10.2 mg/dl, though we considered hypocalcemia when the serum Ca concentration was < 8.0 mg/dl.

All patients with subnormal iPTH levels or patients who developed hypocalcemia received oral calcium and vitamin D supplements even if they didn't present any symptoms. Patients with hypocalcemia symptoms received intravenous infusion of calcium gluconate. (Flow Diagram).

Statistical analysis was performed using the Statistica version 10.0 and R software. Comparisons of data were obtained by Student-t and chi-squared tests. Results were considered statistically significant when  $p < 0,05$ . To identify the cut-off values for iPTH levels and iPTH decline and to analyze their diagnostic accuracy in predicting postoperative hypocalcemia we used the receiver operating characteristic (ROC) curve and we measured the area under the curve (AUC). The manuscript is compliant with the STROCSS criteria [9].

**Table 1**

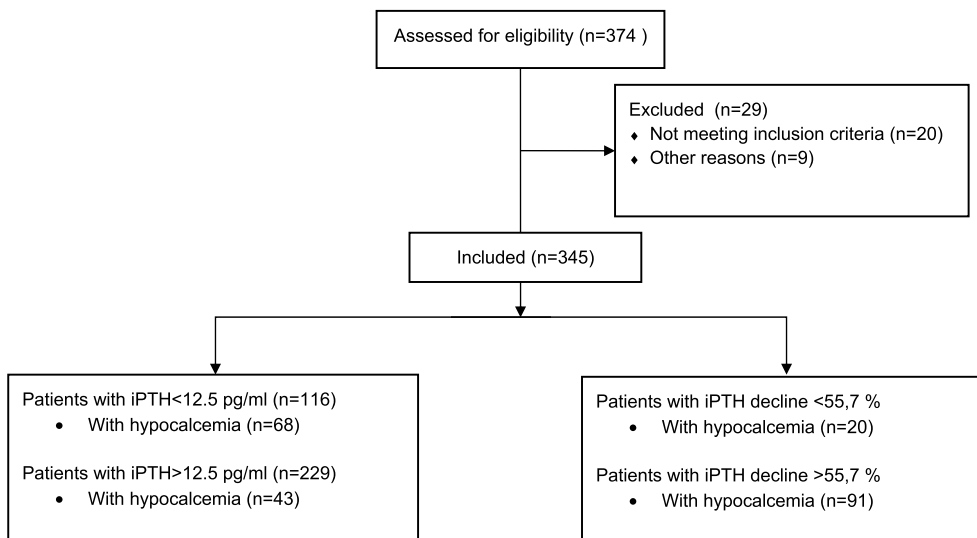
Mean preoperative and postoperative iPTH levels and iPTH relative decline in hypocalcemic and normocalcemic patients.

	All patients n = 345	Hypocalcemic n = 111	Normocalcemic n = 234	P
Mean preoperative PTH level,ng/L	51,2	51,5	50,9	< 0.001
Mean postoperative PTH level,ng/L	25,1	13,9	30,4	< 0.001
Mean PTH relative variation,%	49,1	70,9	38,7	< 0.001

developed postoperative hypocalcemia had a significant lower postoperative iPTH levels (mean iPTH = 13,9 pg/mL) than normocalcemic patients (mean iPTH = 30,4 pg/mL) and a significantly greater iPTH relative decline (70,9%). **Table 1.**

ROC analysis was performed. **Fig. 1** shows the ROC curves corresponding to postoperative 4 h iPTH level and relative iPTH decline. From this analysis we obtained the optimal thresholds enabling prediction of hypocalcemia for iPTH (12,5 pg/mL) and relative iPTH decline (55,7%).

Sensitivity, specificity, and positive and negative predictive values for iPTH with a threshold of 12,5 pg/mL were 61% (95% confidence interval [95%CI] 51,5–70,4), 79,5% (95% CI 73,7–84,5), 58,6% (95% CI 49,1–67,7) and 81,2% (95% CI 75,6–86,1). The curve had an area under the curve (AUC) of 0.77 (SE = 0.05, 95% CI = 0.72–0.81,  $P < 0.0001$ ). Patients with iPTH levels < 12,5 pg/mL developed hypocalcemia in 58.6% (68 of 116 patients) of cases while those with  $iPTH \geq 12,5$  pg/mL had hypocalcemia only in 18.8% (43 of 229 pa-



**3. Results**

The 345 patients included 267 females (77%) and 78 males (23%), the mean age was 51,2 years old (ranging from 11 to 85 years). Hypocalcemia, as defined by Ca levels lower than 8.0 mg/dl at 18 h after surgery, was observed in 111 (32.2%) of 345 patients. Of 111 patients with hypocalcemia, 70 (63.0%) patients were symptomatic and 41 (37.0%) were asymptomatic. In the majority of the cases hypocalcemia was transient, only two patients (0.005%) showed permanent hypocalcemia (evaluated 6 months after total thyroidectomy).

Of the preoperative iPTH estimates, all patients had normal levels of iPTH range from 14 to 105 pg/mL, with a mean value of 51.5 pg/mL. Postoperative measurements of iPTH revealed that the patients who

tients) of cases. These results are strongly significant ( $P < 0.001$ ). **Table 2.**

Sensitivity, specificity, and positive and negative predictive values for the relative iPTH decline with a threshold of 55,7% were 82,0% (95% CI 73,6–88,6), 64,1% (95% CI 57,6–70,2), 52,0% (95% CI 44,3–59,6) and 88,2% (95% CI 82,4–92,7). The curve had an AUC of 0.78 (SE = 0.05, 95% CI = 0.73–0.82,  $P < 0.0001$ ). Among 175 patients with iPTH relative decline greater than 55,7% hypocalcemia was diagnosed in 91 cases (52%), while other 170 patients with iPTH relative decline less than 55,7% developed hypocalcemia only in 20 cases (11,7%). **Table 3.**

Hospital stay was significantly longer in symptomatic patients

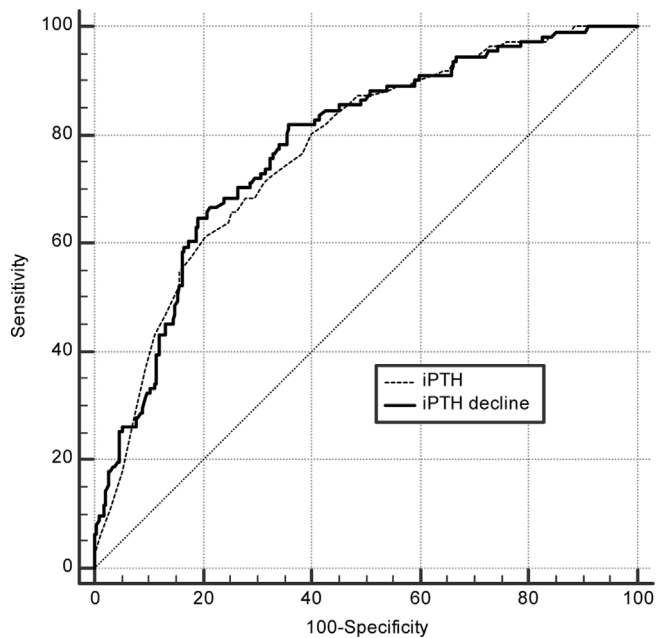


Fig. 1. ROC analysis of postoperative 4 h iPTH and iPTH relative decline in predicting postoperative hypocalcemia.

(mean hospital stay 3,4 days; range 2–7 days) compared with those asymptomatic (mean stay 2,2; range 2–3 days), ( $p < 0.001$ ).

#### 4. Discussion

Despite the accurate identification and preservation of parathyroid glands during thyroidectomy, postoperative hypocalcemia remains the most common complication after thyroid surgery. It frequently occurs due to the failure of parathyroid glands resulting in low PTH production and consequent reduction of serum calcium levels[10–11].

Hypocalcemia is often asymptomatic, though it can present with different symptoms such as paresthesia, perioral or digital tingling, muscle cramps or tetany. When severe it can manifest with life threatening cardiovascular events including heart blocks, hypocalcemic cardiomyopathy, and requires intravenous therapy to relieve the symptoms[12–13].

The functioning insufficiency of parathyroid tissue is caused by

Table 2

Accuracy of postoperative iPTH level in predicting postoperative hypocalcemia.

	Patients with iPTH < 12,5 pg/mL	Patients with iPTH $\geq$ 12,5 pg/mL
Number of patients (total: 345)	116	229
Mean postoperative Ca level (mg/dl)	7.8	8.4
Hypocalcemia rate	68 (58,6%)	43 (18,8%)
P value iPTH vs Ca levels	$p < 0,001$	$p < 0,001$

Table 3

Accuracy of postoperative iPTH relative decline in predicting postoperative hypocalcemia.

	Patients with iPTH decline < 55,7%	Patients with iPTH decline $\geq$ 55,7%
Number of patients (total: 345)	170	175
Mean postoperative Ca level (mg/dl)	8.5	7.9
Hypocalcemia rate	20 (11,7%)	91 (52%)
P value iPTH decline vs Ca levels	$p < 0,001$	$p < 0,001$

inadvertent removal of parathyroid glands or their damage during surgical manipulations such as devascularization, thermal or mechanical trauma, restraint of venous function [14,15]. Graves' disease, retrosternal goiter, central neck dissection, re-interventions, thyroid malignancies and parathyroid autotransplantation have all been shown to increase the risk of postoperative hypocalcemia [16–18].

The early monitoring of calcium levels in postoperative period is very important in the prevention of symptomatic hypocalcemia. However it was demonstrated that the appearance of postoperative hypocalcemia can be delayed up to 12–24 h after surgery. Delay in the diagnosis can lead to the retard in treatment and prolongation of hospitalization [6]. Different studies have revealed the correlation between the decrease of serum iPTH levels and Calcium levels [19–22]. Intact PTH is characterized by a short half-life of 1–4 min [23], thus its decrease may be detected previously in the early postoperative period.

Lombardi et al. reported that iPTH levels < 10 pg/mL at 4 and 6 h after thyroidectomy accurately predict the appearance of postoperative hypocalcemia and necessity of pharmacological therapy [6]. Carr et al. confirm that iPTH level of 10 pg/mL or less measured 4 h after surgery is an accurate predictor of postoperative hypocalcemia which allows the earlier identification of patients who need supplementary treatment with calcium and vitamin D [7]. Other studies suggested that a single measurement of iPTH levels 1 h after thyroid surgery is a strong predictor of postoperative hypocalcemia[24–25]. Nevertheless, in several studies decrease in serum iPTH levels seemed not to be predictive of postoperative hypocalcemia[26–27].

Recently some authors studied the role of iPTH decline in order to find a more accurate predictive factor of hypocalcemia. Lecerf et al. reported that the iPTH decline (iPTH decline > 68.5%) is more precise than the single measurement of postoperative iPTH levels and allows earlier identification of patients at a high risk of hypocalcemia[28]. Seo et al. suggested that iPTH level of < 10.42 pg/mL and decrease of > 70% of PTH levels 1 h after surgery were the reliable predictive factors of postoperative hypocalcemia[29].

In our review we observed that mean postoperative iPTH level and iPTH relative decline were predictive factors of postoperative hypocalcemia. By using the ROC analysis we found that both tests yield the same overall diagnostic performance. Consequently, the calculation of iPTH relative decline could be avoided, and only a single measurement of iPTH at 4 h after surgery may be used like a predictive factor of hypocalcemia. We found that a level of iPTH < 12,5 pg/mL correctly identify the patients at high risk of postoperative hypocalcemia, though the level of iPTH  $\geq$  12,5 pg/mL does not exclude absolutely the appearance of hypocalcemia. In our series of patients the rate of hypocalcemia with a level of iPTH  $\geq$  12,5 pg/mL was 18.8%. Therefore, the monitoring of Ca levels in the postoperative period is recommended in all patients. Ca and vitamin D supplementation should be placed on in the high-risk patients, in the patients with the serum Ca concentration < 8.0 mg/dl and in the patients with symptomatic hypocalcemia.

#### 5. Conclusions

In this study we analyzed the predictive value of iPTH levels and iPTH relative decline and we found that a level of iPTH < 12,5 pg/mL and iPTH relative decline  $\geq$  55,7% correctly predict the patients at high risk of postoperative hypocalcemia. The authors suggest that early administration of Calcium and vitamin D in these patients should be indicated in order to prevent the symptoms of hypocalcemia and to reduce the costs and duration of hospitalization.

#### Ethical approval

No ethical approval was required.

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## Author contribution

Cannizzaro MA: study design.  
 Okatyeva V: data analysis, writing.  
 Lo Bianco S: data analysis, writing.  
 Caruso V: data collections.  
 Buffone A: study design.

## Conflicts of interest

The authors declare that they have no conflict of interest.

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## Guarantor

Cannizzaro Matteo Angelo.

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