

# Parathyroid hormone: an early predictor of symptomatic hypocalcemia after total thyroidectomy

*Hormônio da paratireoide: um preditor precoce da hipocalcemia sintomática após a tireoidectomia total*

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## ABSTRACT

**Objective:** The purpose of this study was to evaluate if the measurement of peri-operative parathyroid hormone (PTH) is able to identify patients with increased risk of developing symptoms of hypocalcemia. **Subjects and methods:** Forty patients who underwent total thyroidectomy were studied prospectively. Ionized serum calcium and PTH were measured after induction of anesthesia, one hour (PTH1) and one day after surgery (PTH24). Patients were evaluated for symptoms of hypocalcemia and treated with calcium and vitamin D supplementation as necessary. **Results:** Symptomatic hypocalcemia developed in 16 patients. Symptomatic patients had significant lower PTH1 and greater drops in PTH levels. The selection of 12.1 ng/L as PTH1 level cutoff level divided patients with and without symptoms with 93.7% sensitivity and 91.6% specificity. The selection of 73.5% as the cutoff value for PTH decrease resulted in 91.6% sensitivity and 87.5% specificity. **Conclusion:** PTH1 levels and the drop in PTH levels are reliable predictors of developing symptomatic hypocalcemia after total thyroidectomy. *Arq Bras Endocrinol Metab.* 2012;56(3):168-72

## Keywords

Thyroid gland; PTH; hypocalcemia; thyroidectomy; parathyroid gland

## RESUMO

**Objetivo:** O objetivo deste estudo é avaliar se a medida perioperatória do hormônio da paratireoide (PTH) pode identificar os pacientes com maior risco de desenvolver sintomas de hipocalcemia. **Sujeitos e métodos:** Foram estudados quarenta pacientes submetidos à tireoidectomia total. A medida do cálcio sérico e do PTH foi feita após a indução anestésica, uma hora (PTH1) e um dia após a cirurgia. Os pacientes foram avaliados quanto à presença de sintomas de hipocalcemia e tratados com suplementação de cálcio e vitamina D quando necessário. **Resultados:** Dezesesseis pacientes apresentaram sintomas de hipocalcemia. Os pacientes sintomáticos apresentaram PTH1 significativamente menor e queda no PTH significativamente maior. Usando o valor de 12,1 ng/L como corte, conseguimos distinguir pacientes com e sem sintomas de hipocalcemia com sensibilidade de 93,7% e especificidade de 91,6%. Utilizando como corte a queda de 73,5% no valor do PTH, temos sensibilidade de 91,6% e especificidade de 87,5%. **Conclusão:** O PTH1 e a queda no PTH são bons preditores de hipocalcemia no pós-operatório de tireoidectomia total. *Arq Bras Endocrinol Metab.* 2012;56(3):168-72

## Descritores

Glândula tireoide; PTH; hipocalcemia; tireoidectomia; glândula paratireoide

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## INTRODUCTION

Thyroidectomy has been performed since 500 AD, and initially presented very high morbidity and mortality that persisted even to the time of Billroth, who in 1883 reported a 40% mortality rate in 20 thyroidectomies. This high mortality possibly reflected a lack of knowledge concerning the parathyroid glands and their influence on calcium metabolism (1). By 1912, Theodore Kocher recognized the need to preserve parathyroid glands, and had successfully performed more than 5000, mostly subtotal thyroidectomies (1-3).

Hypocalcemia, usually transient, is the most common complication following total thyroidectomy, and occurs in 10% to 50% of cases. It is the result of parathyroid gland injury and can cause great discomfort to the patient (1,4-8).

Symptoms of serum hypocalcemia may not be manifest for up to four days after surgery and can significantly lengthen hospital stay (4,9-11). Finding a simple and reliable method to predict which patients may show hypocalcemia could decrease patient discomfort, hospital stay and treatment costs associated with total thyroidectomy.

The purpose of this study is to evaluate if peri-operative measurement of parathyroid hormone (PTH) during total thyroidectomy may identify those patients with the greatest risk of developing symptoms of hypocalcemia.

## SUBJECTS AND METHODS

We developed a prospective study in the São Paulo Hospital of the Universidade Federal de São Paulo (Brazil) from January to August, 2006. Informed consent was obtained from all subjects, and the study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo. The first author was present at all surgical procedures.

Forty-four consecutive patients who underwent total thyroidectomy without simultaneous neck dissection were included. Four patients were eliminated: two had parathyroid adenomas identified during surgery, one because of problems in blood sample identification, and one because the patient was unable to adequately express herself. Therefore, information about forty patients was analyzed (37 females and 3 males).

Ionized calcium and PTH levels were measured before the operation (induction of anesthesia – Ca<sup>0</sup>/PTH<sup>0</sup>), one hour after the surgery (in the recovery

room – Ca<sup>1</sup>/PTH<sup>1</sup>) and on the day following surgery (Ca<sup>24</sup>/PTH<sup>24</sup>). Vitamin D levels were also determined. Ionized calcium measurements were carried out in an AVL 9180 – Eletrolyte Analyzer, and PTH measurements in Roche Elecsys 1010, which provides results in approximately 10 minutes. The normal values for ionized calcium are 1.24-1.41 mmol/L and PTH 15-65 ng/L. Vitamin D levels were determined by radioimmunoassay with Dia Sorin kit, and the measurement was carried out using Wallac 1277 Gammamaster gamma counter. The normal levels for vitamin D are 30-60 ng/mL.

Patients were monitored for postoperative symptoms of hypocalcemia: development of perioral or fingertip paresthesias or numbness, muscle cramping, tetany, or positive Chvostek's or Trousseau's sign. Patients were divided in two groups – those with and those without symptoms, and comparisons were made between the two groups.

Symptomatic patients were treated with calcium and vitamin D supplementation and discharged when signs and symptoms were controlled. After discharge, patients were instructed to call the researchers if they developed any symptoms of hypocalcemia. All patients were evaluated in the 7<sup>th</sup> and 13<sup>th</sup> postoperative day, and then, every three months.

Statistical analyses were made with SPSS 13.0 for Windows, LEAD Technologies, Inc. The groups were compared using a Person's X<sup>2</sup> and Student's *t* test. Differences were considered significant when *p* < 0.05.

## RESULTS

Sixteen of forty (40%) total thyroidectomy patients developed symptoms of hypocalcemia. Thirty four patients were discharged on the first postoperative day, five on the second, and the patient who experienced the greatest drop in PTH levels (92%) and the lowest PTH concentration (5 ng/L) one hour after the surgery was hospitalized for five days.

All patients were discharged without symptoms or signs of hypocalcemia. Eight patients became symptomatic on the first postoperative day, six on the second, and two only on the third postoperative day. Patients were followed up for at least 10 months (10-18 months), and only one patient (2.5%) needed calcium supplementation six months after surgery. No patient needed to be readmitted to the hospital after discharge, and there were no surgical complications.

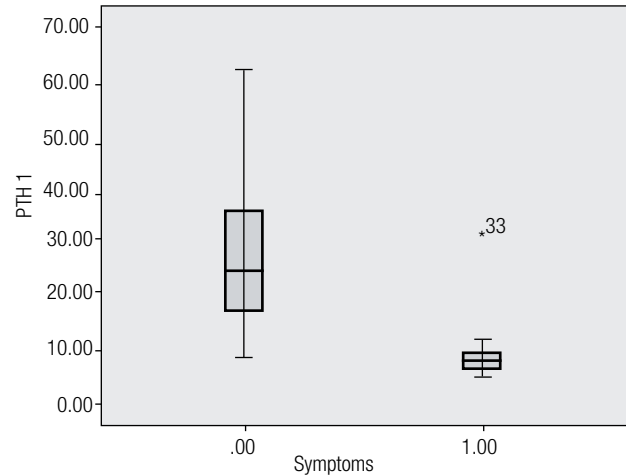
Mean age of symptomatic patients was  $53.6 \pm 16.5$  years, and for patients without symptoms  $50.1 \pm 14.7$  years ( $p = 0.48$ ). Four parathyroid glands were identified in 19 patients, three in 16 patients, two parathyroid glands in three patients, and only one parathyroid was identified in two patients. The number of parathyroid glands identified was not statistically different between symptomatic and asymptomatic patients ( $p = 0.46$ ). Ten patients needed parathyroid transplantation (one parathyroid in nine patients, and two parathyroids in one patient). Among those patients who needed parathyroid transplantation, six (60%) became symptomatic, and in the group that did not need parathyroid transplantation, 10 patients (33%) became symptomatic. This difference, however, was not significant ( $p = 0.136$ ). Vitamin D levels were also similar in the symptomatic and asymptomatic groups ( $21.6 \pm 8.2$  ng/mL and  $23.9 \pm 7.4$  ng/mL,  $p = 0.88$ ). Six patients showed hyperthyroidism in the preoperative period, and two (33%) of them developed symptoms of hypocalcemia.

In the group that did not develop symptoms, mean values were:  $56.6 \pm 24.4$  ng/L for PTH0,  $27.7 \pm 14.5$  ng/L for PTH1,  $26.8 \pm 11.4$  ng/L for PTH24,  $1.23 \pm 0.7$  mmol/L for Ca0,  $1.21 \pm 0.7$  mmol/L for Ca1, and  $1.15 \pm 0.6$  mmol/L for Ca24. In those who developed symptoms, mean values were:  $56.1 \pm 18.5$  ng/L for PTH0,  $9.5 \pm 6.5$  ng/L for PTH1,  $8.0 \pm 3.4$  ng/L for PTH24,  $1.21 \pm 0.5$  mmol/L for Ca0,  $1.17 \pm 0.5$  mmol/L for Ca1 and  $1.05 \pm 0.5$  mmol/L for Ca24. Ca0, PTH0 and Ca1 were similar between symptomatic and asymptomatic groups ( $p = 0.47$ ,  $p = 0.94$ , and  $p = 0.07$  respectively). Patients in the symptomatic group had PTH1 significantly lower than patients in the asymptomatic group ( $p < 0.001$ ) (Figure 1). PTH24 and Ca24 were also statistically different between symptomatic and asymptomatic patients ( $p < 0.001$ ). Thirty eight patients (95%) had ionized calcium levels below normal range in the first postoperative day, and the other two had ionized calcium levels in the lower limit of the reference range (1.24 mmol/L).

PTH drop (difference between PTH1 and PTH0) was greater in the symptomatic group ( $82.2 \pm 8.8\%$  vs.  $47.4 \pm 6.4\%$ ,  $p < 0.001$ ) compared to the group of patients without symptoms (Figure 2).

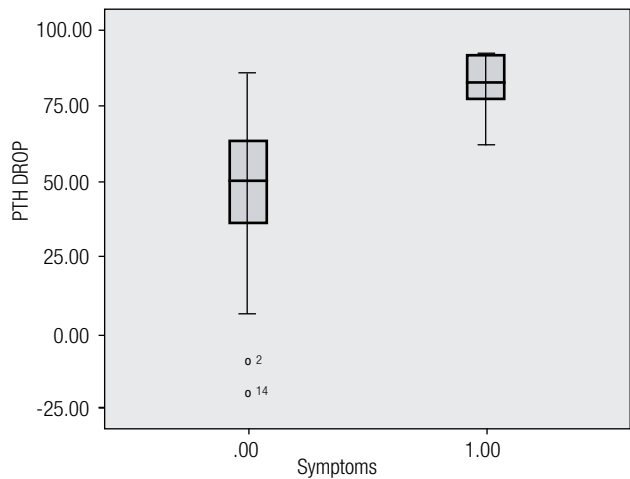
PTH1 value below 12.1 ng/L predicted which patient had a greater chance of developing symptoms of hypocalcemia with 93.7% sensitivity and 91.6% specificity. PTH drop of 73.5% also effectively predicted symptoms of hypocalcemia among patients who underwent

total thyroidectomy with 91.6% sensitivity and 87.5% specificity. The Roc curves show that both PTH1 value and PTH drop are reliable predictors of symptoms of hypocalcemia. Using 12.1 ng/L as PTH1 cutoff value, the area under the curve is 0.927 (Figure 3), and using 73.5% as PTH drop cutoff value, the area under the curve is 0.896 (Figure 4).



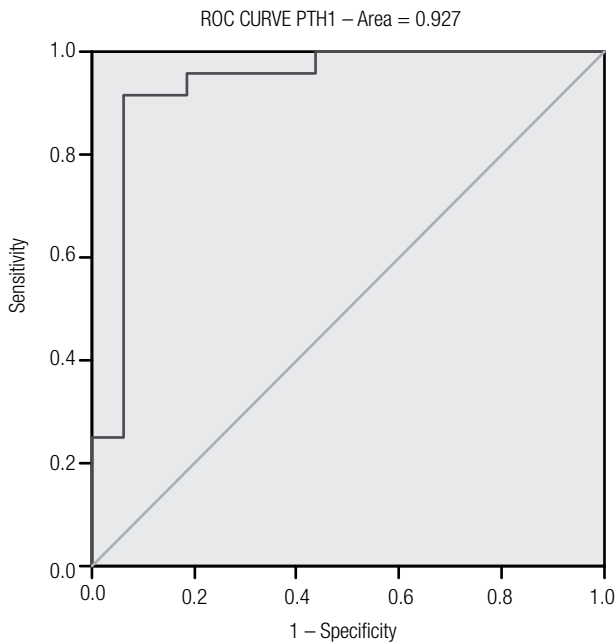
0.0: patients without symptoms; 1.00: patients with symptoms.

**Figure 1.** PTH 1 hour after the surgery.

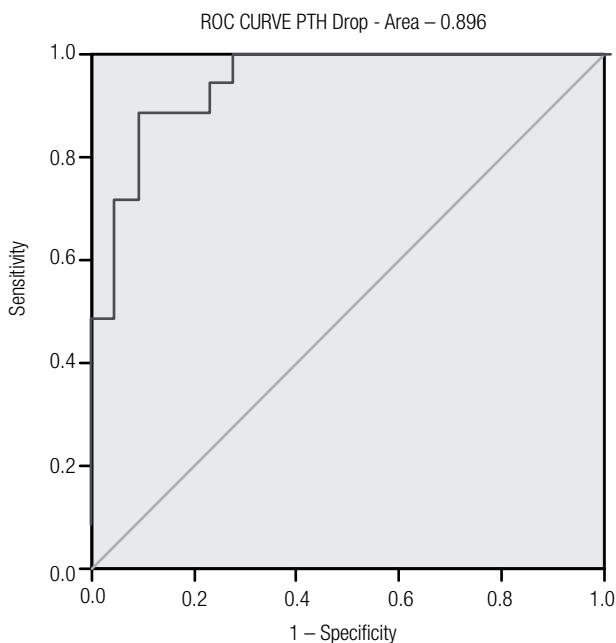


0.00: patients without symptoms; 1.00: patients with symptoms.

**Figure 2.** PTH drop (difference between PTH at induction and PTH one hour after surgery).



**Figure 3.** Roc curve with TH1 cutoff value of 12.1 ng/L.



**Figure 4.** Roc curve with cutoff value of 73.5% for PTH drop.

## DISCUSSION

Hypocalcemia is the most frequent complication of total thyroidectomy. Some physicians prescribe supplementation of calcium and vitamin D to all total thyroidectomy patients, while others obtain serial calcium

determinations to try to predict which patients will develop hypocalcemia. Neither strategy seems to be cost-effective, the former because all patients are exposed to side effects of calcium but less than half actually need the supplementation, and the latter because it can delay discharge and subject the patient to the discomfort of multiple venipunctures. Some protocols based on calcium slope are useful (12-14), but still require serial measurements, postpone treatment and may prolong hospital stay. It is still difficult to predict whether a patient has a greater risk of developing hypocalcemia based only on calcium levels or surgical events (15,16).

The success of rapid PTH determinations in parathyroid surgery led some investigators to evaluate its usefulness to predict hypocalcemia following thyroid surgery. Lam and Kerr found that all patients with PTH value less than 8 pg/mL measured one hour after the surgery became hypocalcemic, and all patients with PTH level greater than 9 pg/mL did not (17). Higgins and cols. demonstrated that 64% of those patients who subsequently required calcium supplementation had a decrease in PTH levels greater than 75% from baseline 20 minutes after surgery, and 74% of those who did not need calcium supplementation demonstrated a decrease of less than 75% from baseline (18). For Lombardi and cols., PTH less than 10 pg/mL measured four or six hours after surgery predicted hypocalcemia with an overall accuracy of 98% (19). Pattou and cols. reported that a postoperative PTH level of 12 pg/mL or less was a good predictor of hypocalcemia, but did not state how long after surgery PTH values were obtained (20). A group of Australian surgeons found that normal postoperative PTH levels accurately predicted normocalcemia after total thyroidectomy, and the optimal time to make the measurement was four hours after the surgery (21).

Almost all studies define hypocalcemia as either low serum calcium or development of symptoms of hypocalcemia (9,11,15-19,21-26). We used only the symptoms of hypocalcemia because we believe that mixing two parameters (biochemical hypocalcemia and symptomatic hypocalcemia) can introduce a bias. Postoperative serum calcium level can take up to four days to reach its lowest value (20) and, like Richards and cols., we also found that almost all patients have calcium levels below reference range after total thyroidectomy (27). Furthermore, the speed of decrease in calcium levels appears to be more important than the absolute value itself (4,20).

Similar to other studies, we did not find a relationship between patient demographic characteristics and development of hypocalcemia (15,18-20,27-29), and although several authors have reported a relationship between hyperthyroidism and hypocalcemia (1,7,28), our study (like those of Lombardi and cols. (29), Higgins and cols. (18) and Scurry and cols. (15) did not observe this relationship. Additionally, we found no relationship with the number of parathyroid glands identified or transplanted, which is in agreement with other authors (18,19,30).

## CONCLUSION

Serum PTH determinations one hour after total thyroidectomy and the decrease in PTH levels from the preoperative baseline are safe and reliable predictors of symptomatic hypocalcemia. A single measurement one hour after surgery is slightly more accurate and more cost-effective, since only one measurement is required.

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