

Risk factors for hypocalcemia after total thyroidectomy

Factores de riesgo para hipocalcemia después de una tiroidectomía total

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Abstract

Background: Hypocalcemia is a common complication of total thyroidectomy; transient hypocalcemia has been reported in up to 68% of the patients. **Materials and Methods:** Chart review of all patients undergoing total thyroidectomy from 2016 to 2020. Clinical, biochemical, and pathological information was registered. We sought correlations between the different variables and the occurrence of post-operative hypocalcemia. This is a retrospective study carried out at a tertiary care teaching hospital. **Objectives:** The aim of the study was to ascertain the incidence of hypocalcemia after thyroidectomy and to establish potential clinical and pathological risk factors for its development. **Results:** Three hundred and thirty-seven patients were included in this study (78% female), with a median age of 47 years. The majority (75%) harbored thyroid neoplasms. Post-operative hypocalcemia developed in 43 patients (12.7%). On bivariate analysis, the most significant risk factor was an intraoperative injury of the parathyroid glands (OR = 2.49, 95% CI = 1.11-5.59), followed by a surgical time > 2.5 h (OR = 2.0, 95% CI = 1.03-4.19), concomitant lymph node dissection (OR = 2.45, 95% CI = 1.2-4.9), and placement of drains (OR = 2.40, 95% CI = 1.19-4.87). Only parathyroid injury remained statistically significant on multivariable analysis. **Conclusions:** The most significant risk factor for the development of post-operative hypocalcemia after thyroidectomy is injury of the parathyroid glands, which is usually noticed by the surgeon.

Keywords: Hypocalcemia. Hypoparathyroidism. Thyroidectomy. Thyroid cancer. Parathyroid glands.

Resumen

Introducción: La hipocalcemia es una complicación común después de una tiroidectomía; la hipocalcemia transitoria ha sido reportada hasta en el 68% de los pacientes posoperados. **Materiales y Métodos:** Revisión de expedientes de pacientes a los cuales se les realizó una tiroidectomía total entre el 2016 y 2020. La información clínica, bioquímica y patológica fue recopilada. Se buscó una correlación entre las variables y el desarrollo de hipocalcemia. Es un estudio retrospectivo en un hospital escuela de atención terciaria. **Objetivos:** Determinar la incidencia de hipocalcemia pos-tiroidectomía y establecer posibles factores de riesgo clínicos y patológicos para desarrollarlo. **Resultados:** Se incluyeron 337 pacientes en este estudio (78% mujeres), con edad media de 47 años. La mayoría (75%) presentaron neoplasias tiroideas. Cuarenta y tres pacientes desarrollaron hipocalcemia (12.7%). En el análisis bivariado el factor de riesgo más importante fue la lesión de paratiroides (RM = 2.49, IC95% = 1.11-5.59), seguido por un tiempo quirúrgico > 2.5 horas (RM = 2.0, IC 95% = 1.03-4.19), disección linfática (RM = 2.45, IC95% = 1.2-4.9) y la colocación de drenajes (RM = 2.40, IC95% = 1.19-4.87). Únicamente la lesión de paratiroides mantuvo significancia en el análisis multivariado. **Conclusiones:** La lesión de paratiroides es el factor de riesgo más grande para desarrollar hipocalcemia y generalmente es identificado por el cirujano.

Palabras clave: Hipocalcemia. Hipoparatiroidismo. Tiroidectomía. Cáncer de tiroides. Glándulas paratiroides.

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Introduction

Well-differentiated thyroid carcinoma (WTC) is the most frequent endocrine malignant neoplasia. Its incidence has been rising over the past two decades, at least in part due to the widespread use of neck ultrasound¹. According to Globocan, thyroid cancer in Mexico is the 4th most common malignant tumor with 12,000 new cases diagnosed in 2018².

Total thyroidectomy is the treatment of choice in most cases of WTC (3). When this procedure is carried out by a high-volume surgeon, the morbidity and mortality are almost negligible³. However, thyroidectomy is not only performed by expert surgeons and in this setting the complication rate of the procedure increases considerably³. Transient post-operative hypocalcemia is perhaps the most frequent complication, occurring in 15-30% of cases, although in some series the reported incidence is over 60%⁴. Permanent hypocalcemia is considerably less frequent and its incidence ranges between 0.2% and 10%^{4,5}. The risk factors that have been associated with the development of post-operative hypocalcemia include female gender, extrathyroidal tumor invasion, parathyroid injury, central compartment lymph node dissection, and obesity⁴. We here describe and analyze the occurrence of postoperative hypocalcemia in our center, seeking to find clinical and biochemical features that could serve as prognostic markers.

Material and methods

The electronic charts of patients undergoing a total thyroidectomy between January 2016 and December 2020 at the American British Cowdray Medical Center in Mexico City were retrospectively reviewed. The study protocol was approved by our Local Scientific and Ethics Committees. Patients younger than 16 years and patients with preoperative hypocalcemia or hypoparathyroidism as well as patients with scheduled concomitant parathyroid surgery were excluded from the study. The corresponding pathology reports were also assessed looking for the presence of parathyroid tissue. Hypocalcemia was defined as a total serum calcium < 8 mg/dL or an ionized calcium < 4.0 mg/dL. In those patients with discrepant results, the normal measurement was favored.

Variables were categorized into the following three groups:

- a) Baseline variables: Gender, age, pre-operative hyper/hypothyroidism, history of neck surgery, and comorbidities.

- b) Surgical variables: Indication for surgery, operating room (OR) time, a > 200 mL intraoperative bleeding, lymph node dissection, drain placement, surgeon's yearly volume, and parathyroid identification, parathyroid gland incidental injury, and reimplantation when detected.

- c) Tumor variables: Size, histological type, stage, lymph node invasion, capsular, and vascular lymphatic or neural invasion as well as locoregional and/or distant metastasis.

Statistical analysis

Nominal and ordinal variables were described as absolute numbers and percentages; numeric variables depending on their type of distribution were expressed as means with standard deviations medians with interquartile ranges. Continuous variables were analyzed with the T student test for independent variables when a normal distribution was present and with the U of Mann-Whitney when it was not. Nominal and ordinal variables were analyzed with a χ^2 test. All the losses from baseline variables were smaller than 15% so they were all substituted. The ordinal and nominal variables were substituted by mode and the continuous variables by means or medians, depending on their distribution. Finally, the association values like odds ratio and confidence intervals and the statistical significance were obtained with χ^2 , as well as with linear and logistic regressions. $p < 0.05$ was considered statistically significant. All the information was consolidated on an unidentified spread sheet on Microsoft Excel version 2010 and the statistical analysis was done using IBM SPSS Statistics version 25.

Results

A total of 337 patients underwent a total thyroidectomy at our center over the study period. Median age was 47 years (interquartile range [IQR] = 37-69), 262 (77.7%) were women and 75 (22.2%) were men (Table 1). Preoperatively, the majority of patients had normal thyroid function tests; 43 (12.8%) had a prior diagnosis of hypothyroidism and were under levothyroxine replacement and 29 (8.6%) had evidence of hyperthyroidism (Table 1). In the majority of patients (253, 75.1%), the underlying diagnosis was WTC (Table 1). Other indications for surgery included goiter (38, 11.3%) and thyroiditis (15, 4.5%) (Table 1). Complete outcome information was available in 290 patients. Post-operative hypocalcemia was diagnosed in

38 (13.1%). Symptoms and signs of hypocalcemia ranged from perioral numbness to frankly positive Trousseau and Chvostek signs.

Table 2 compares the characteristics of the patients who developed post-operative hypocalcemia with those who remained normocalcemic. A pre-operative diagnosis of hypothyroidism was more commonly present among patients who did not develop post-operative hypocalcemia (13.4% vs. 0%, $p = 0.018$). Post-operative hypocalcemia developed in 32 of the 219 patients with a diagnosis of thyroid cancer (14.6%), in two of the 31 patients with multinodular goiter (6.4%), and in two of the 15 patients with thyroiditis (13.3%); the difference in the rates of hypocalcemia among patients with these three different diagnostic categories did not reach statistical significance. Lymph node invasion and dissection as well as surgical time > 2.5 h were significantly more common among patients who became hypocalcemic after surgery. Parathyroid gland injury was significantly more frequent in patients who developed hypocalcemia than in those who remained normocalcemic, as was the need to leave a drain after surgery.

On bivariate analysis, pre-operative hypothyroidism, intraoperative parathyroid gland injury, and the need to leave a drain were all significantly associated with the development of post-operative hypocalcemia (Fig. 1). However, on multivariate analysis, only documented parathyroid injury remained significantly associated with the development of post-operative hypocalcemia (OR = 3.68, 95% CI = 1.65-8.21, $p = 0.001$) (Fig. 2). Table 3 shows a side-by-side comparison between the bivariate and the multivariate analysis.

Discussion

Parathyroid gland injury with the consequent post-operative hypocalcemia due to primary hypoparathyroidism (PHPT) is without a doubt, one of the most frequent complications of thyroid surgery, particularly of total thyroidectomy^{3,4}. In a recently published meta-analysis, comprising 115 observational studies, the median rates of transient and permanent hypocalcemia were 27% (IQR = 19-38) and 1% (IQR = 0-3), respectively⁶. Post-operative hypocalcemia even when transient could hamper an appropriate surgical recovery and may prolong hospitalization⁴. Several risk factors have been variably associated with the occurrence of this complication, including concomitant central neck dissection specially when performed by

Table 1. Baseline characteristics of the cohort

	n	%
Median age (IQR)	47	(37-69)
Female gender	262	77.7
Hypothyroidism	43	12.8
Hyperthyroidism	29	8.6
Underlying diagnosis		
Thyroid cancer	253	75.1
Goiter	38	11.3
Thyroiditis	15	4.5
Other	31	9.2

IQR: interquartile range.

Table 2. Univariate analysis of clinical and surgical features of patients who developed post-operative hypocalcemia and those who did not

n (%)	Hypocalcemia 37 (12.7%)	Normocalcemia 253 (87.3%)	p
Age > 60	8 (21.6)	60 (23.7)	0.770
Female gender	24 (64.8)	199 (78.6)	0.063
Pre-operative hypothyroidism	0	34 (13.4)	0.018
Pre-operative hyperthyroidism	4 (10.8)	21 (8.3)	0.611
Underlying diagnosis			
Thyroid carcinoma	32 (86.4)	187 (74)	0.33
Goiter	2 (5.4)	29 (11.4)	0.33
Lymph node invasion	15 (40.5)	54 (21.3)	0.01
Lymph node dissection	16 (43.2)	60 (23.7)	0.01
Surgical time > 2.5 h	18 (48.6)	79 (31.2)	0.03
Estimated blood loss > 200 mL	2 (5.4)	12 (4.7)	0.861
Parathyroid gland identification	35 (94.6)	238 (94)	0.891
Parathyroid gland reimplantation	1 (2.7)	18 (7.1)	0.311
Parathyroid gland injury	16 (43.2)	58 (23)	0.008
Drain placement	17 (46)	66 (26)	0.008

In bold: p statistically significant.

a low volume surgeon, an underlying diagnosis of thyroid cancer or Graves' disease, a lengthy surgical procedure particularly when accompanied by a > 200 mL intraoperative bleeding, as well as the lack of identification and/or inadvertent injury of parathyroid glands⁶.

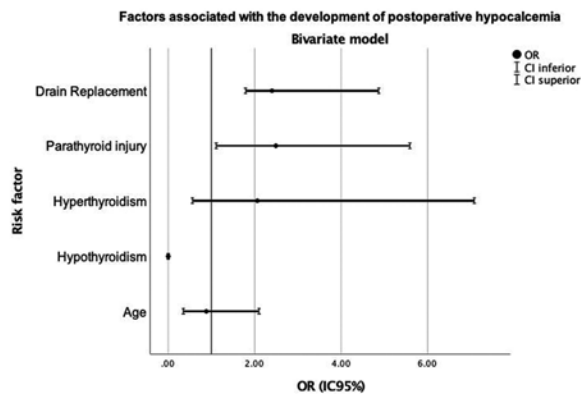


Figure 1. Bivariate model.

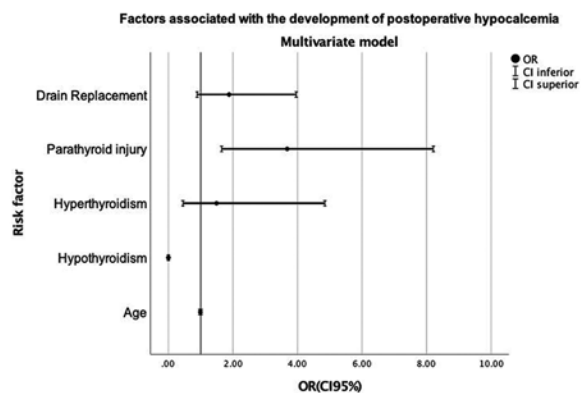


Figure 2. Multivariate model.

Table 3. Bivariate and multivariate analysis of factors associated with the development of postoperative hypocalcemia

	Bivariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age	0.88	0.35-2.10	0.779	0.99	0.97-1.02	0.692
Hypothyroidism	0	0	0.018	0	0	0.008
Hyperthyroidism	2.06	0.56-7.08	0.611	1.49	0.45-4.85	0.507
Parathyroid injury	2.49	1.11-5.59	0.008	3.68	1.65-8.21	0.001
Drain placement	2.4	1.79-4.87	0.008	1.88	0.89-3.96	0.097

CI: confidence interval.

The incidence of post-operative hypocalcemia in our cohort was unexpectedly low (12.7%) despite the fact that over 75% of our patients had an underlying diagnosis of thyroid cancer and that more than 25% had also been subjected to the central neck dissection.

Although post-operative hypocalcemia tended to be more frequent among our patients with a thyroid malignancy, this did not reach statistical significance, likely because of the relatively small number of patients with a non-malignant underlying diagnosis included in the study. In contrast to other series whereby over half of the patients who develop post-operative hypocalcemia do so asymptotically^{7,8}, all of the hypocalcemic patients in our cohort had at least paresthesias appearing 8-12 h after the surgical event. Female gender and old age have both been associated with an increased risk of post-operative hypocalcemia⁶. Almost 80% of the patients in our cohort were women, and post-operative hypocalcemia tended to be more frequent in women than in men; however, this did not reach statistical significance.

It is controversial to what extent does the identification (and preservation?) of parathyroid glands during surgery impacts the probability of developing post-operative hypocalcemia. Some authors claim that the lack of identification of parathyroid glands is associated with transient^{9,10} as well as with permanent¹¹ hypocalcemia, irrespective of the underlying diagnosis, and the extent of thyroidectomy. Conversely, other studies have found that identifying the parathyroid glands during surgery is by itself associated with a greater likelihood of post-operative hypocalcemia¹². In our study, neither the identification nor the reimplantation of parathyroid glands was significantly associated with the development of hypocalcemia. Yet, we did find that parathyroid gland injury, be it inadvertent (i.e., parathyroid glands found in the pathology specimen) or advertent, significantly predicted the development of postoperative hypocalcemia in both, bivariate and multivariate analyses. Intuitively, thyroidectomies performed by large volume surgeons should have a lower rate of complications, including the development of post-operative hypocalcemia^{6,13}. Our study was not designed to address this issue, since the majority of our patients were operated by large volume surgeons.

Patients undergoing thyroidectomy for diffuse toxic goiter or Graves' disease appear to have an elevated risk of post-operative hypocalcemia¹¹. More recently, one of the few prospective studies evaluating post-operative hypocalcemia after thyroidectomy found that thyrotoxicosis diagnosed < 10 years before surgery was significantly associated with hypocalcemia⁸. Of the 29 hyperthyroid patients included in our cohort, only four developed post-operative hypocalcemia. Interestingly, however, none of the 43 patients with hypothyroidism

became hypocalcemic after surgery and in the multivariate analysis, hypothyroidism was negatively associated with post-operative hypocalcemia.

Our study has several limitations such as its retrospective nature, the lack of a uniform surgical procedure due to the fact that it reflects the combined experience of several low volume and a few large volume surgeons, and perhaps more importantly, the lack of long-term follow-up. Despite these weaknesses, the present report takes place in a real-life setting and thus, our data are undoubtedly representative of what occurs in day-to-day life.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest regarding this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for

analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

References

1. Sanabria A, Kowalski LP, Shah JP, Nixon IJ, Angelos P, Williams MD, et al. Growing incidence of thyroid carcinoma in recent years: factors underlying overdiagnosis. *Head Neck*. 2018;40:855-66.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
3. Schlumberger M, Leboulleux S. Current practice in patients with differentiated thyroid cancer. *Nat Rev Endocrinol*. 2021;17:176-88.
4. Stack BC Jr., Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, et al. American association of clinical endocrinologists and American college of endocrinology disease state clinical review: postoperative hypoparathyroidism—definitions and management. *Endocr Pract*. 2015;21:674-85.
5. Edeife O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. *Br J Surg*. 2014;101:307-20.
6. Lemaire FX, Debruyne F, Delaere P, Poorten VV. Parathyroid function in the early postoperative period after thyroidectomy. *Acta Otorhinolaryngol Belg*. 2001;55:187-98.
7. Eismontas V, Slepavicius A, Janusonis V, Zeromskas P, Beisa V, Strupas K, et al. Predictors of postoperative hypocalcemia occurring after a total thyroidectomy: results of prospective multicenter study. *BMC Surg*. 2018;18:55.
8. Bergenfelz A, Jansson S, Kristoffersson A, Mårtensson H, Reihner E, Wallin G, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbecks Arch Surg*. 2008;393:667-73.
9. León-Ballesteros GP, Velázquez-Fernández D, Hernández-Calderón FJ, Bonilla-Ramírez C, Pérez-Soto RH, Pantoja JP, et al. Hypoparathyroidism after total thyroidectomy: importance of the intraoperative management of the parathyroid glands. *World J Surg*. 2019;43:1728-35.
10. Thomusch O, Machens A, Sekulla C, Ukkat J, Brauckhoff M, Dralle H. The impact of surgical technique on postoperative hypoparathyroidism in bilateral thyroid surgery: a multivariate analysis of 5846 consecutive patients. *Surgery*. 2003;133:180-5.
11. Lindblom P, Westerdahl J, Bergenfelz A. Low parathyroid hormone levels after thyroid surgery: a feasible predictor of hypocalcemia. *Surgery*. 2002;131:515-20.
12. Falch C, Hornig J, Senne M, Braun M, Konigsrainer A, Kirschniak A, et al. Factors predicting hypocalcemia after total thyroidectomy—a retrospective cohort analysis. *Int J Surg*. 2018;55:46-50.
13. Welch KC, McHenry CR. Total thyroidectomy: is morbidity higher for graves' disease than nontoxic goiter? *J Surg Res*. 2011;170:96-9.