

ORIGINAL ARTICLE

Hypoparathyroidism following thyroidectomy: Predictive factors



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KEYWORDS

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Predictive factors;
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Histological diagnosis

Abstract

Objective: To evaluate the incidence and predictive factors for transient and permanent hypocalcemia and hypoparathyroidism following thyroidectomy.

Method: We studied all the 162 patients that underwent thyroid surgery in the ENT department of the Centro Hospitalar Vila Nova Gaia/Espinho from January 2005 to December 2014. We reviewed pre-operative, 6 h and 12 h after surgery ionized calcium and PTH levels. All patients were reviewed and evaluated according to the following criteria: gender, age, thyroid function, histologic diagnosis of the specimen, surgery extension and presence or absence of hypoparathyroidism.

Results: There were 31 (19.1%) cases of transient hypoparathyroidism and 8 (5%) of permanent hypoparathyroidism. No significant difference was found for transient hypoparathyroidism when patients were analyzed by gender. However, all cases of permanent hypoparathyroidism were observed in female individuals.

Comparing hemithyroidectomy with all other surgical procedures, we found that extension of surgery was a great predictor of transient ($p=0.0001$) and permanent ($p=0.001$) hypoparathyroidism.

Diagnosis of malignancy was a strong predictor of transient hypoparathyroidism ($p=0.002$). It was also associated with permanent hypoparathyroidism, although differences did not reach statistical significance ($p=0.096$).

Conclusion: Extension of surgery (total thyroidectomy) and diagnosis of malignancy are predictors of transient and permanent hypoparathyroidism.

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PALABRAS CLAVE

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histológico

Hipoparatiroidismo tras tiroidectomía: factores predictivos**Resumen**

Objetivo: Evaluar la incidencia y los factores predictivos de hipocalcemia transitoria y permanente e hipoparatiroidismo tras la tiroidectomía.

Método: Se estudiaron todos los pacientes sometidos a cirugía de tiroides en el Servicio de ORL del Centro Hospitalario de Vila Nova de Gaia/Espinho desde enero de 2005 a diciembre de 2014. Se revisaron los valores de calcio ionizado preoperatorio, a las 6 y a las 12 h de la intervención, y los niveles de PTH. Se revisaron y evaluaron todos los archivos de acuerdo con los siguientes criterios: sexo, edad, función tiroidea, diagnóstico histológico de la muestra, extensión de la cirugía y presencia o ausencia de hipoparatiroidismo.

Resultados: Encontramos 31 (19,1%) casos de hipoparatiroidismo transitorio y 8 (5%) de hipoparatiroidismo permanente. No se encontraron diferencias significativas en cuanto a hipoparatiroidismo transitorio cuando los pacientes fueron analizados por sexo. Sin embargo, todos los casos de hipoparatiroidismo permanente se observaron en individuos de sexo femenino. Comparando la hemitiroidectomía con el resto de los procedimientos quirúrgicos, se encontró que la extensión de la cirugía fue un gran factor predictivo de hipoparatiroidismo transitorio ($p=0,0001$) y permanente ($p=0,001$). El diagnóstico de malignidad es un fuerte factor predictivo de hipoparatiroidismo transitorio ($p=0,002$). También de hipoparatiroidismo permanente, aunque las diferencias no alcanzaron la significación estadística ($p=0,096$).

Conclusión: La extensión de la cirugía y el diagnóstico de malignidad son factores predictivos de hipoparatiroidismo transitorio y permanente.

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Introduction

Thyroid gland is known for being part of the ENT surgeon work field. In our Center, Centro Hospitalar Vila Nova de Gaia/Espinho, with different surgical indications, several patients undergo thyroidectomy. It is one of the most frequently performed operations worldwide with an incidence of complications that, although not frequent, can be disabling.¹ Injury of the recurrent laryngeal nerve, which can result in dysphonia and dyspnea, is the most frequently reported complication, while metabolic complications related to thyroid function and calcium levels (Ca)¹⁻³ are often underestimated even though of major importance. The latter is actually the most common complication.¹

Hypocalcemia is defined as deficiency of calcium concentration in blood stream (normal = 8.5–10.5 mg/dl).^{1,2} It can be temporary or permanent and can take place with or without associated symptoms. Complaints appear more often about 24–48 h after surgery and there is no direct correlation between their timing and the severity of the clinical status or ionized calcium levels.³

Classic symptoms are neuromuscular, such as perioral, hands or feet numbness, myalgia or lethargy.^{1,2} However, it is not rare to observe tachycardia, irritability and bronchospasm/laryngospasm. QT prolongation and arrhythmia can occur and may result, in extreme cases, in death.¹

45% of serum Ca is free or ionized, and this is its active form, 50% bounded to proteins and 5% attached to other organic complexes.² Calcium homeostasis is complex and fundamentally regulated by parathyroid hormone

(PTH), vitamin D and Calcitonin.^{3,4} PTH is the major agent of calcemia regulation. It is synthesized and secreted by the parathyroid glands in a rate inversely proportional to the concentration of calcium ion. It operates in the kidney promoting bone reabsorption, phosphorus excretion and synthesis of Vitamin D,¹⁻³ increasing Ca blood levels.^{5,6} Small variations in calcemia change PTH secretion within minutes.^{5,6}

It should be noted that hypocalcemia is multifactorial and may be also caused by hemodilution, hypoalbuminemia, variations in concentration of phosphate and magnesium and blood pH.¹ Thus, a reduction in total serum calcium does not necessarily mean a reduction in ionic calcium and may, therefore, not be associated with clinical manifestations.⁷⁻⁹

Anatomical relationships between parathyroid and thyroid glands explain why post-thyroidectomy hypoparathyroidism relates to the following factors^{1,6}:

1. accidental removal of parathyroid glands;
2. handling of parathyroids;
3. ischemia due to injury of parathyroids' delicate blood supply. Even when one or more parathyroid glands are preserved, the whole anatomical territory suffers variations of oxygenation and irrigation during surgery and in the postoperative period.

Either way, PTH will drop with metabolic and clinical consequences. In addition, hypomagnesemia, hyperphosphatemia and metabolic alkalosis may also arise.¹⁰⁻¹²

Thus, many authors advocate Ca ion dosing 6 h, 12 h and 24 h after surgery^{10,11} and Ca replacement, when

necessary, started with oral calcium or, in cases of severe hypocalcemia, with administration of intravenous calcium gluconate. Hypoparathyroidism confirmation is laboratorial, with hypocalcemia associated with subnormal or undetectable PTH levels. However, the decrease in Ca levels may not be sudden.

Our study analyzes retrospectively patient's characteristics, such as gender and age, thyroidectomy's extension and its histologic diagnosis, aiming to see if these factors were predictive of hypoparathyroidism after surgery, in order to anticipate and promptly correct this complication.

Materials and methods

We studied all patients that underwent thyroid surgery in the ENT department of the Centro Hospitalar Vila Nova Gaia/Espinho from January 2005 to December 2014. 176 patients were analyzed and 14 patients, which had thyroidectomy performed in the context of pharyngolaryngectomy, were excluded.

We reviewed all 162 and evaluated according to the following criteria:

1. Gender (male or female)
2. Age
3. Thyroid function. We classified patients as euthyroid, hypothyroid and hyperthyroid by assessing TSH levels (0.27–4.2 μ UI/mL), T4 levels (0.93–1.7 ng/dL) and free T3 levels (0.27–4.2 ng/dL). We classified as euthyroid the patients that had a normal thyroid function, assessed by free T4 and TSH within the normal levels. Patients with high TSH levels and low T4 levels were considered hypothyroids, as were the ones with subclinical hypothyroidism – with elevated TSH levels and normal T4 – and the ones medicated with levothyroxine. We considered hyperthyroids the ones with low TSH levels and high T4 levels, but also those with low TSH levels and normal T4 levels (subclinical patients) and those taking antithyroid drugs.
4. Histologic diagnosis of the specimen, which was categorized into malignant (papillary carcinoma, follicular carcinoma, medullary carcinoma and Hurthle cells carcinoma), and benign (adenoma, follicular hyperplasia, thyroiditis and colloid nodule).
5. Surgery extension was divided into total thyroidectomy with or without neck dissection, hemithyroidectomy and completion thyroidectomy with or without neck dissection (in patients who had previously undergone partial thyroidectomy or subtotal thyroidectomy, regardless of the time elapsed between both interventions). We did not subdivide side in Hemithyroidectomy subjects or in neck dissections.
6. Presence or absence of hypoparathyroidism. Transient hypoparathyroidism was defined as a decrease of serum ionized calcium (reference range: 8.5–10.5 mg/dL) with subnormal values of PTH (15–65 pg/mL) that persisted less than six months. Permanent hypoparathyroidism was diagnosed after 6 months.

We reviewed pre-operative ionized calcium and PTH levels. Whenever they were not available, levels taken in the

immediate post-operative period were considered as a baseline value. They were repeated 6 h and 12 h after surgery and every day during hospitalization. Whenever calcium blood levels were low, Calcium gluconate was administered intravenously at a dose of 94 mg/ml. If Ca levels were still low by the time the patient was discharged, Endocrinology's collaboration was requested and, until then, 1 mg of calcium id was administered orally.

The descriptive and statistical analysis was performed using the *Statistical Package software package for Social Sciences (SPSS) version 21*. The analysis of the relationship of categorical variables was performed using contingency tables and Chi square test/Fisher test. As strength of association measures we used the relative risk (RR) and percentage of attributable risk (PRA). We considered as statistically significant p values <0.05.

Results

Of the 162 patients included 138 (85.2%) were females and 24 (14.8%) were males. Ages varied between 20 and 88 years, with a median age of 53 years old and 25% older than 61 years.

138 patients were euthyroid (85.2%), 19 hypothyroid (11.7%) and 5 hyperthyroid (3.1%).

There were 31 cases of transient hypoparathyroidism (19.1%) and 8 of permanent hypoparathyroidism (5%), meaning that about 26% of the transient hypoparathyroid patients evolved to permanent hypoparathyroidism, which is comparable with other series.^{10,11,13,14}

We studied our patients according to age and divided them into two groups: older and younger than 50 years (Table 1).

No significant difference was found for transient hypoparathyroidism when patients were analyzed by gender, since it occurred in 18.8% of women and in 20% of men. However, all cases of permanent hypoparathyroidism were observed in female individuals.

According to pre-operative thyroid function, 4 of the 19 hypothyroid patients (19.6%) and 27 of the 138 euthyroid patients (21%) developed transient hypoparathyroidism, which did not happen in any of the hyperthyroid patients. We found permanent hypoparathyroidism in 4.3% of the euthyroid patients and in 10.5% of the hypothyroid cases.

Hemithyroidectomy was the most commonly performed surgery (94 patients, 58%), as seen in Table 1.

Considering extension of the surgical procedure, of the 31 individuals that developed transient hypoparathyroidism, 12 underwent total thyroidectomy (Table 1). It is remarkable that 5% of the hemithyroidectomized patients had transient hypoparathyroidism. Nevertheless, none of these cases maintained permanent hypoparathyroidism.

We found permanent hypoparathyroidism less often in patients who underwent neck dissection, compared to isolated complete thyroidectomy and to isolated completion thyroidectomy (Table 1).

Comparing hemithyroidectomy with all other surgical procedures, since all of them implied total excision of the thyroid gland, we found that extension of surgery was a great predictor of transient ($p=0.0001$) and permanent ($p=0.001$) hypoparathyroidism.

Table 1 Frequency of each surgery and its relation to the outcome of transient and permanent hypoparathyroidism.

Surgery extension	Frequency (%)	Hypoparathyroidism	
		Transient	Permanent
TT	34 (21%)	12 (35.3%)	5 (14.7%)
TT + ND	12 (7.4%)	6 (50%)	1 (8.3%)
HT	94 (58%)	5 (5.3%)	0
Completion thyroidectomy	20 (12.3%)	7 (35%)	2 (10%)
Completion thyroidectomy + ND	2 (1.3%)	1 (50%)	0
Total	162 (19.2%)	31 (19.2%)	8 (4.9%)

TT: total thyroidectomy; ND: neck dissection; HT: hemithyroidectomy.

In [Table 2](#) the histological diagnosis of surgical specimens are shown, as well as their respective frequency of hypoparathyroidism. 76% (123 patients) had benign thyroid disease, 20% were diagnosed with papillary carcinoma and the remaining histologies were less relevant.

We compared hypoparathyroidism with the surgical specimen histological diagnosis. It was more frequent in patients with histological diagnosis of papillary carcinoma (39.3% transient and 12.1% permanent). In the presence of benign thyroid disease the percentage of transient and permanent hypothyroidism was lower ([Table 2](#)). We studied the statistical significance of these results dividing our patients in two groups: benign and malignant thyroid disease. Malignant diagnosis was a strong predictor of transient hypoparathyroidism ($p=0.002$). As to permanent hypoparathyroidism, although statistical significance was not so high ($p=0.096$), it suggests that malignancy is an important risk factor for permanent hypothyroidism.

4 out of the 19 hypothyroid patients developed transient hypoparathyroidism (21%), as did 27 of the 138 euthyroid patients (19.6%). None of the hyperthyroid patients developed transient hypoparathyroidism. We verified definitive hypoparathyroidism in 4.3% of the euthyroid patients and in 10.5% of the hypothyroid patients ([Table 3](#)).

Discussion

Hypocalcaemia is the most common complication of thyroidectomy. Its frequency, if transient, can reach up to 50%, and, if permanent, up to 4%.^{13,14} Moreover, studies demonstrate a decrease in PTH of 83% in total thyroidectomies 1 h after surgery.¹⁵ This highlights the great susceptibility of parathyroid glands to surgical trauma.

Demeester-Mirkine et al. define hypoparathyroidism as a complex and multifactorial phenomenon for which the reduction of parathyroid function seems to be the main contributor.² Hypoparathyroidism can take place even when parathyroids are preserved and some studies suggest that systematic search during surgery is a risk factor for transient hypocalcemia.¹⁶ The authors prefer not look for them but, once they come across on the surgical field, to try to spare them, and have no experience on reimplant.

In most studies, female gender has no effect on calcium homeostasis after thyroid surgery.¹⁷⁻¹⁹ However, all our 8 patients with permanent hypocalcemia were women, which

was also found in a minority of studies.^{18,20} On one hand, we could wonder about gender's influence on definitive hypocalcaemia but, on the other hand, we must keep in mind that 85% of our sample were females, making it impossible to obtain p values.

The literature²¹⁻²³ describes no influence of age on calcium levels after thyroid surgery. We got to the same conclusion.

Most papers point a greater likelihood of post-surgical hypocalcaemia in untreated hyperthyroid patients.^{20,14} This is explained by the fact that thyroid hormone increases bone turnover rate, primarily increasing fecal and urinary calcium excretion and phosphorus absorption.²⁰ That induces osteoarthritis which will, on the post-operative period following total thyroidectomy, lead to "hungry bone" syndrome.^{21,14} This was not verified in our series, in which 21% of hypothyroid patients, 19.6% of euthyroid patients and none of hyperthyroid patients developed transient hypoparathyroidism.

The higher prevalence of hypoparathyroidism in hypothyroid patients in our series was unique. A possible explanation could be our very small group of hyperthyroid patients (5), of which 2 were subclinical and 3 were already treated for one year, and also a small but four times greater group of hypothyroid patients (19).

We found that the extent of the surgical procedure was directly related to the incidence of transitory and permanent hypoparathyroidism, which also is reported in other series^{6,10,22,23}. We highlight the fact that the transient form can take place in less extensive surgery as hemithyroidectomy.^{22,23} In fact, surgical vascular manipulation compromises parathyroid's function until blood flow is re-established through collateral vessels. Total thyroidectomy and completion thyroidectomy had the same outcome regarding to permanent hypoparathyroidism. However, aside from ours, few other studies showed that neck dissection nearly doubled the likelihood of transient hypoparathyroidism when associated to either completion thyroidectomy or total thyroidectomy.

In completion thyroidectomy, there are further risks associated with scar tissue and distortion of the surgical area, especially when the second intervention takes place more than one month after the first. The risk of iatrogenic injury is 10 times higher during re-intervention.^{23,14}

Most studies agree that, when histological diagnosis is malignant, transient hypocalcemia takes place in

Table 2 Histologic diagnosis of the specimen and its frequency related to the presence of transient and permanent hypoparathyroidism.

Histologic diagnosis of the specimen	Frequency (%)	Hypoparathyroidism	
		Transient	Permanent
Adenoma/follicular hyperplasia/thyroiditis/colloid nodule	123 (76%)	17 (13.8%)	4 (3.2%)
Papillary carcinoma	33 (20%)	13 (39.3%)	4 (12.1%)
Follicular carcinoma	4 (2.5%)	0	0
Medullary carcinoma	1 (0.75%)	1 (100%)	0
<i>Hurthle</i> cells carcinoma	1 (0.75%)	0	0
Total	162 (100%)	31 (19.1%)	8 (4.9%)

Table 3 Thyroid's function before surgery and its relation to the post surgery outcome of transient and permanent hypoparathyroidism.

Thyroid's function before surgery	Frequency (%)	Hypoparathyroidism	
		Transient	Permanent
Euthyroid	138 (85.2%)	12 (8.7%)	6 (4.3%)
Hyperthyroid	5 (3.1%)	0	0
Hypothyroid	19 (11.7%)	4 (21%)	2 (10.5%)
Total	162 (85.2%)	31 (19.2%)	8 (4.9%)

13.6–19.3% of cases^{16,17,14} or even up to 75%,^{21,23} while permanent hypoparathyroidism is found in 3.3–5.8%.^{17,19,14} Malignancy is considered the main predictor for both complications.

Our results confirmed this statement. Papillary carcinoma was associated with higher incidence of both transient and permanent hypocalcemia, which is probably due to the extent of surgery, including total thyroidectomy or early completion, with or without neck dissection. In the presence of malignancy, thyroid and its neighboring territory's anatomy may also increase surgical difficulty.

In the future, we intend to study a larger sample of patients in order to be more conclusive about the influence of pre-operative thyroid function on post-thyroidectomy hypoparathyroidism, and also enlighten the importance of female gender on permanent hypoparathyroidism. We also aim to study both phosphate and magnesium ions postoperatively given their major importance in calcium metabolism.

Since we found that some hemithyroidectomy patients can also develop transient hypoparathyroidism, we consider that it is wise to always evaluate post-operative calcemia.

Conclusion

Histological diagnosis of malignant disease, especially papillary carcinoma, and the extent of surgical procedure are predictors of permanent and temporary hypoparathyroidism. The latter is the most important risk factor for both complications and neck dissection assumes the higher importance in prediction of the transient form of hypoparathyroidism. A higher pool of patients will be necessary to clarify whether a deficient thyroid function

or female gender are also risk factors for these surgical complications.

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Conflict of interests

The authors declare to have no conflict of interests.

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