

ORIGINAL ARTICLE

Posthemithyroidectomy hypothyroidism. Prevalence and predictive markers. Comparison between patients with euthyroid and hyperthyroid nodular goitre



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KEYWORDS

Hemithyroidectomy;
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Abstract

Background and objective: Posthemithyroidectomy hypothyroidism (PHH) is a relatively common complication (22%–30%) for which we have no published information from our country. The objective of the study is to determine the prevalence of PHH and evaluate its predictive markers by comparing patients who had euthyroidism with those who had hyperthyroidism before hemithyroidectomy.

Patients and method: Retrospective observational cross-sectional study on 106 patients, 88 euthyroid before hemithyroidectomy and 18 hyperthyroid.

Results: Prevalence of PHH in euthyroid patients 42% (89.2% subclinical hypothyroidism; 10.8% manifest hypothyroidism) and in hyperthyroid patients 50% (77.8% subclinical hypothyroidism; 22.2% manifest hypothyroidism). Predictive markers in euthyroid patients: preoperative thyrotropin ≥ 2.2 mIU/L (OR: 4.278, 95% CI: 1.689–10.833; sensitivity: 54.1%, 95% CI: 38%–70.1%; specificity: 78.4%, 95% CI: 67.1%–89.7%), age ≥ 50 years (OR: 3.509, 95% CI: 1.438–8.563; sensitivity: 64.9%, 95% CI: 49.5%–80.3%; specificity: 64.7%, 95% CI: 51.6%–77.8%) and percentage of remainder lobe $\leq 19.6\%$ (OR: 1.024, 95% CI: 1.002–1.046; sensitivity: 70.2%, 95% CI: 55.5%–84.9%; specificity: 48.6%, 95% CI: 34.9%–62.3%). Predictive marker in hyperthyroid patients: weight >70 kg (OR: 28, 95% CI: 2.067–379.247; sensitivity: 88.9%, 95% CI: 68.4%–100%; specificity: 88.9%, 95% CI: 68.4%–100%).

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PALABRAS CLAVE

Hemitiroidectomía;
Hipotiroidismo;
Hipotiroidismo
postoperatorio

Conclusions: This is the first study in our country that demonstrates a prevalence of PHH above the average in euthyroid patients, which is slightly higher and more intense in hyperthyroid patients, and that recognizes the classic predictive markers in euthyroid patients but highlights a novel predictive marker in hyperthyroid patients, useful to assess a different risk of PHH when indicating hemithyroidectomy and to establish closer control of postoperative hormonal evolution.

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Hipotiroidismo posthemitiroidectomía. Prevalencia y marcadores predictivos. Comparación entre pacientes con bocio nodular eutiroides e hipertiroides

Resumen

Antecedentes y objetivo: El hipotiroidismo posthemitiroidectomía (HPH) es una complicación relativamente frecuente (22%–30%) de la que no tenemos información publicada de nuestro país. El objetivo del estudio es determinar la prevalencia del HPH y evaluar sus marcadores predictivos comparando los pacientes eutiroides con los que tuvieron hipertiroidismo antes de la hemitiroidectomía.

Pacientes y método: Estudio retrospectivo observacional transversal sobre 106 pacientes, 88 eutiroides antes de la hemitiroidectomía y 18 hipertiroides.

Resultados: Prevalencia de HPH en los pacientes eutiroides 42% (89,2% hipotiroidismo subclínico; 10,8% hipotiroidismo manifiesto) y en los hipertiroides 50% (77,8% hipotiroidismo subclínico; 22,2% hipotiroidismo manifiesto). Marcadores predictivos en los pacientes eutiroides: tirotrópica preoperatoria $\geq 2,2$ mUI/L (OR: 4,278, IC al 95%: 1,689–10,833; sensibilidad: 54,1%, IC al 95%: 38%–70,1%; especificidad: 78,4%, IC al 95%: 67,1%–89,7%), edad ≥ 50 años (OR: 3,509, IC al 95%: 1,438–8,563; sensibilidad: 64,9%, IC al 95%: 49,5%–80,3%; especificidad: 64,7%, IC al 95%: 51,6%–77,8%) y porcentaje del lóbulo remanente $\leq 19,6\%$ (OR: 1,024, IC al 95%: 1,002–1,046; sensibilidad: 70,2%, IC al 95%: 55,5%–84,9%; especificidad: 48,6%, IC al 95%: 34,9%–62,3%). Marcador predictivo en los pacientes hipertiroides: peso >70 kg (OR: 28, IC al 95%: 2,067–379,247; sensibilidad: 88,9%, IC al 95%: 68,4%–100%; especificidad: 88,9%, IC al 95%: 68,4%–100%).

Conclusiones: Es el primer estudio en nuestro país que demuestra una prevalencia del HPH por encima de la media en los pacientes eutiroides, que resulta ligeramente superior y más intenso en los hipertiroides, y que reconoce los clásicos marcadores predictivos en los pacientes eutiroides pero destaca un marcador predictivo novedoso en los pacientes hipertiroides, útil para valorar un riesgo diferente de HPH al indicar la hemitiroidectomía y para establecer un control más estrecho de la evolución hormonal postoperatoria.

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Introduction

Hemithyroidectomy is a widely performed surgical procedure to treat symptomatic benign nodular goiter, for definitive diagnosis in cases of nodular goiter with intermediate cytology (Bethesda III and Bethesda IV), and some cases of thyroid cancer with a low risk of recurrence.¹ Compared with total thyroidectomy, hemithyroidectomy has the advantage of reducing surgical complications such as compressive cervical hematoma, recurrent laryngeal nerve paralysis, and postoperative hypoparathyroidism, and in some cases, it also avoids postoperative hypothyroidism. In fact, post-hemithyroidectomy hypothyroidism (PHH) is the most common complication associated with this surgical intervention, so knowing its prevalence and predictive

markers allows for providing personalized information on the likelihood of its occurrence in a patient and establishing the most appropriate postoperative follow-up plan.^{2,3}

PHH in patients with nodular goiter in a euthyroid functional state before surgery has been widely studied. Its mean prevalence is 22% up to 30% when the follow-up period exceeds 2 years. PHH usually runs subclinical and appears mainly at the 1-year follow-up. It is more common in women, older ages, obese patients, those with higher preoperative thyrotropin (TSH) values and lower free thyroxine (T4I) values, cases with iodine deficiency, multinodular goiter, thyroiditis in the excised lobe, positivity for antithyroid peroxidase antibodies, in patients undergoing right-sided hemithyroidectomy, as well as in those with smaller thyroid remnants.^{2,4–15}

Most patients with nodular goiter are euthyroid and very few are hyperthyroid. In cases of hyperthyroidism due to unilateral toxic thyroid nodules, treatment is diversified among radioiodine, percutaneous treatments, and surgery.^{3,16,17} Except for studies aimed at highlighting hemithyroidectomy as a rapid solution for hyperthyroidism or describing immediate surgical complications, there are very few evaluations of PHH in series of patients operated on for toxic nodular goiter. In these cases, it could be assumed that treatment with hemithyroidectomy would result in a higher rate of PHH vs patients with euthyroid nodular goiter, as the extranodular parenchyma is atrophied due to prolonged functional inactivity.¹⁷⁻¹⁹ However, postoperative hormonal evolution has been scarcely studied, reporting a prevalence of PHH in patients operated on for toxic thyroid nodules from 0% up to 65.2%,^{16,20-25} indicative of significant imprecision. Furthermore, no predictive factors for this PHH have ever been reported.¹⁶ As far as we know, no study has specifically compared the occurrence of PHH in patients with preoperative euthyroidism and hyperthyroidism.

The objective of this study was to determine the prevalence of PHH and evaluate the possible predictive markers of its occurrence, comparing patients with hyperthyroidism with those who were euthyroid before hemithyroidectomy.

Material and methods

This is a retrospective observational study of consecutive cases based on the routine clinical practice of a hospital center. Adults older than 18 years undergoing hemithyroidectomy (excision of 1 thyroid lobe and half of the thyroid isthmus) for nodular goiter from January 2015 through September 2021 were included. Postoperative follow-up was, at least, 24 months in all cases. Patients with past medical histories that could change the spontaneous occurrence of PHH, such as previous cervical radiotherapy, radioiodine treatment, thyroid surgery, autoimmune hyperthyroidism, hypothyroidism, or thyroid hormone treatment, as well as all patients with thyroid carcinomas found in histopathological studies were excluded. The study was approved by *Fundació Assistencial Mútua de Terrassa* Clinical Research Ethics Committee.

The variables collected from the patients' health history were: patient age and sex, weight and height at the time of surgery, preoperative ultrasound volume of thyroid lobes, presence of single or multiple thyroid nodules > 10 mm in the remaining lobe, the largest ultrasound diameter of the main nodule in the excised lobe, preoperative plasma values of TSH, T4l and positivity of antithyroid peroxidase and antithyroglobulin antibodies, preoperative diagnosis of thyroid disease (unilateral or bilateral single or multiple nodular goiter, toxic or normofunctional), whether patients received preoperative antithyroid drug treatment, hemithyroidectomy location (right or left), the histopathological diagnosis of lesions in the resected specimen (nodular hyperplasia or follicular adenoma) and the concomitant presence of lymphocytic thyroiditis, postoperative TSH and T4l values, whether the patient received postoperative thyroid hormone treatment and the reason why²⁶ (subclinical hypothyroidism with TSH > 10 mIU/L, symptomatic hypothyroidism with TSH < 10 mIU/L, pro-

gressive subclinical hypothyroidism, overt hypothyroidism, desire for pregnancy or pregnancy, desire to maintain TSH within normal ranges, growth of other nodules), and the follow-up period.

Patients were categorized as euthyroid or hyperthyroid before hemithyroidectomy based on their functional status. The criterion for considering hyperthyroidism was a repeated TSH value < 0.1 mIU/L, subclinical when the serum T4l concentration was normal, or overt in the presence of a concomitant supranormal T4l value (>1.61 ng/dL).²⁶ Hyperthyroidism was attributed to the nodular lesions included in the hemithyroidectomy through a preoperative technetium 99 m scan, which showed that these lesions were hyperactive with concurrent hypoactivity in the contralateral thyroid lobe. All hyperthyroid patients received antithyroid drugs until hemithyroidectomy to achieve and maintain euthyroidism or subclinical hyperthyroidism. Patients considered euthyroid had preoperative TSH and values within normal ranges. Patients with intermediate TSH values (between 0.1 mIU/L and 0.35 mIU/L) were not included.

Total volume (TV) of the 2 thyroid lobes was calculated using the ellipsoid volume formula ($\text{height} \times \text{width} \times \text{depth} \times \pi/6$) from measurements taken in the last preoperative ultrasound. The remaining lobe volume (RV) was adjusted for the body surface area (BSA) of each subject according to Mosteller's criterion²⁷ using the following formula: adjusted remaining volume (ARV) = RV/BSA. The percentage of the remaining lobe volume (PRV) was calculated as $\text{PRV} = (\text{RV}/\text{TV}) \times 100$.

The main evaluation variable was the prevalence of patients with PHH, defined as the sum of patients who maintained, at least, 2 TSH values above the upper limit of normal (4.2 mIU/L) and who did not spontaneously recover at the follow-up and those who received indefinite levothyroxine replacement therapy after any supranormal TSH value.^{7,15} Hypothyroidism was considered subclinical when the concomitant T4l value was normal and overt when it was decreased (<1.12 ng/dL).²⁶

Secondary evaluation variables were possible predictive markers associated with the occurrence of PHH and differences in PHH prevalence and predictive markers between patients with hyperthyroidism and euthyroidism before hemithyroidectomy.

The TSH and T4l values were determined by electrochemiluminescent immunoassay (normal values: 0.27–4.20 mIU/L and 0.84–1.61 ng/dL, respectively), while antithyroid peroxidase and antithyroglobulin antibodies were determined by electrochemiluminescence (negative < 9 IU/mL and <60 IU/mL, respectively).

A descriptive analysis of the collected variables was performed. Univariate analysis of differences between continuous and categorical variables was analyzed using the Student *t*-test or the Mann-Whitney U test, the relationship between categorical variables and the chi-square test or Fisher's F test, and the relationship between quantitative variables and Pearson's or Spearman's correlation coefficient. To investigate the independence of predictive variables of PHH, stepwise forward binary logistic regression analysis was performed, including as independent variables those with statistical significance in the univariate analysis. Collinearity of independent variables with statistical significance was analyzed by examining the linear correlation

between them. Predictive validity of the logistic regression model was studied by evaluating calibration and discrimination with the Hosmer-Lemeshow test and area under the ROC curve constructed with the predicted probability from the model, respectively. Internal reproducibility was verified by generating 1000 samples with bootstrapping. Cutoffs were obtained from binary logistic regression performed with each significant variable. ROC curves were generated to determine sensitivity and specificity in predicting PHH. Statistical significance was set at $P < .05$ (2-tailed). Statistical analysis was performed with IBM SPSS 25.0 software (IBM Corp., Armonk, NY, United States).

Results

A total of 106 patients were included, 81 (76.4%) women and 25 (23.6%) men, with a mean age of 50.6 ± 13.9 years. Eighteen of them (17%) had hyperthyroidism while the rest—88 (83%)—remained euthyroid before hemithyroidectomy. The inter-group comparison of variables before the appearance of PHH is shown in Table 1.

The prevalence of PHH was 42% in the euthyroid group vs 50% in the hyperthyroid group. The distribution of variables related to PHH in each group is shown in Table 2.

Predictive markers of PHH in each patient group are shown in Table 3. In the euthyroid group, the variables that tuned out to be predictive in the univariate analysis were age, RV, ARV, PRV, preoperative TSH, and hemithyroidectomy laterality. A significant correlation was found between preoperative TSH and RV ($r = -0.342$; $P = .001$) and ARV ($r = -0.379$; $P < .001$), as well as between age and TV ($r = 0.251$; $P = .021$). A significant relationship was also observed between hemithyroidectomy laterality and RV (right vs left: 4.1 ± 1.8 vs 6.5 ± 3.6 cm³; $P < .001$), ARV (right vs left: 2.3 ± 1 vs 3.6 ± 1.8 cm³; $P < .001$), and PRV (right vs left: 22.4 ± 15.3 vs 34.2 ± 18.9 ; $P = .002$). In the hyperthyroid group, predictive variables turned out to be age, weight, and BMI, and men were significantly heavier (80.9 ± 7.6 vs 66.3 ± 7.4 kg; $P = .001$) and slightly older age (59.2 ± 6.7 vs 52.3 ± 8.2 years; $P = .09$).

Table 4 shows the logistic regression analysis with variables independently associated with PHH. In the preoperative euthyroid group, the model predicted a total of 79.8% of PHH cases vs 83.3% in the hyperthyroid group. In both cases, when analyzing the calibration of the predictive logistic regression model, it was confirmed that the predicted probability matched the observed one: for the euthyroid group: chi-square = 5.060, $P = .751$; for the hyperthyroid group: chi-square = 5.434, $P = .607$. Similarly, when analyzing discrimination, it was observed that the predictive model distinguished well between patients in whom PHH occurred and those in whom it did not: for the euthyroid group: area under the ROC curve: 0.819, 95%CI, 0.728–0.911; for the hyperthyroid group: area under the ROC curve: 0.901, 95%CI, 0.734–1. *Linear correlation data between variables independently associated with PHH in the logistic regression model of euthyroid patients—ruling out their collinearity—and data verifying the internal reproducibility of logistic regression in both euthyroid and hyperthyroid patients, are shown in a supplementary file (Appendix A).*

Table 5 shows data on the ROC curves for variables with predictive power for PHH obtained in logistic regression analysis, as well as characteristics associated with the cut-offs for each.

Discussion

PHH remains a topic of interest as new reports on this complication continue to emerge^{7,10–15} to clarify its true prevalence, which has been considered underestimated, as well as to better understand its risk factors. The goal is to have a better clinical perspective before performing hemithyroidectomy, as one of the main objectives of preserving half of the gland is for the remaining hemithyroid to be a sufficient endogenous source of thyroxine.^{7,9} More than 50 studies with patients with functionally euthyroid nodular goiter have focused on evaluating the prevalence of PHH and associated factors.⁷ Conversely, patients undergoing hemithyroidectomy for nodular goiter with hyperthyroidism are scarce, and few series on their postoperative hormonal progression have been published to this date, which are usually 20 years old. Due to the functional difference between the 2 groups, their study should be considered separately. As far as we know, not a single series has ever been published in the Spanish literature on PHH, nor explicitly comparing cases of preoperative hyperthyroidism and euthyroidism.

In our study, we found a prevalence of PHH of 42% in euthyroid patients, mainly subclinical and early, as almost all cases occurred within the first 6 months of follow-up, as previously described.^{5,7,14,15} Although this figure is higher than the mean 22%–30% from previously published series it still falls within the wide range of 10.9% up to 48.8%.^{5,7,9} Our prevalence is likely magnified because we had a considerable number of patients with mild hypothyroidism (TSH > 4.2 mIU/L and >10 mIU/L) who were on thyroxine shortly after surgery (mean, 8 weeks) due to interpreted symptoms, without allowing for spontaneous resolution. This figure of patients treated with thyroxine relative to the total number of cases in the euthyroid group was around 33% (29/88), one of the highest within the ranges reported by the existing literature, which ranges from 10.9% up to 48.8%.^{9,11,28}

The prevalence of PHH in patients with preoperative hyperthyroidism was 50%, also predominantly subclinical and early. Although this figure is slightly higher than the one found in patients with euthyroidism prior to hemithyroidectomy, it is not statistically significant. We expected such a figure or higher, considering that the extranodular parenchyma might be hypotrophic and, therefore, functionally impaired due to prolonged prior inactivity,^{17–19} as evidenced in our case by the almost statistically significant lower PRV of these patients (Table 1). Therefore, the patients' postoperative functional recovery should be considered slightly lower than the one reached by previously euthyroid patients. Moreover, in these cases, PHH requires thyroxine treatment earlier vs euthyroid patients, in part because PHH occurred slightly earlier as all cases were reported before the 6-month mark, and was a little more intense as it had a slightly higher prevalence of overt hypothyroidism, which supports closer postoperative monitoring of these patients.

Table 1 Comparison of preoperative variables for PHH onset in hemithyroidectomized patients based on preoperative euthyroid or hyperthyroid status.

	Preoperative euthyroid patients	Preoperative hyperthyroid patients	P-value
Number of cases, n (%)	88 (83)	18 (17)	–
Sex			ns
Women, n (%)	69 (78.4)	12 (66.7)	
Men, n (%)	19 (21.6)	6 (33.3)	
Age (mean $\pm$ SD, years)	49.7 $\pm$ 14.8	54.6 $\pm$ 8.2	ns
TV (mean $\pm$ SD, cm ³)	23.8 $\pm$ 27.1	19.2 $\pm$ 10.3	ns
RV (mean $\pm$ SD, cm ³)	5.35 $\pm$ 3.09	5.91 $\pm$ 5.1	ns
ARV (mean $\pm$ SD, cm ³)	2.98 $\pm$ 1.66	3.24 $\pm$ 2.74	ns
PRV (mean $\pm$ SD, %)	28.44 $\pm$ 18.19	22.15 $\pm$ 11.38	.07
Largest diameter of the main nodule removed (mean $\pm$ SD, mm)	37.18 $\pm$ 16.53	37.89 $\pm$ 10.39	ns
Nodules > 1 cm in the remaining thyroid lobe, n (%)	5 (5.7)	2 (11.1)	ns
Preoperative TSH (mean $\pm$ SD, mIU/L)	1.83 $\pm$ 0.99	2.02 $\pm$ 2.83	ns
Preoperative T4l (mean $\pm$ SD, ng/dL)	1.13 $\pm$ 0.18	1.02 $\pm$ 0.34	ns
Antithyroid peroxidase antibodies, n (%)	2 (2.3)	2 (11.1)	ns
Antithyroglobulin antibodies, n (%)	1 (1.1)	2 (11.1)	ns
Hemithyroidectomy location			ns
Right, n (%)	43 (48.8)	9 (50)	
Left, n (%)	45 (51.2)	9 (50)	
Histopathological diagnoses			ns
Nodular hyperplasia, n (%)	70 (79.5)	13 (72.2)	
Adenoma, n (%)	18 (20.5)	5 (27.8)	
Lymphocytic thyroiditis, n (%)	11 (12.5)	2 (11.1)	ns

PRV, percentage of the remaining thyroid lobe volume relative to the total thyroid volume; TSH, thyrotropin; T4l, free thyroxine; TV, volume of the excised thyroid lobe; RV, volume of the remaining thyroid lobe; ARV: volume of the remaining thyroid lobe adjusted for body surface area.

The prevalence of PHH in hyperthyroid patients is difficult to frame in the literature. A bibliographic review of PHH in cases of toxic nodular goiter shows many studies not specifically aimed at evaluating this objective, presenting methodological limitations that make it difficult to draw definitive conclusions. After excluding series of cases with diffuse and nodular hyperthyroidism without differentiating results, other series in which thyroidectomies are more or less extensive than a hemithyroidectomy as they apply or combine nodulectomies and subtotal thyroidectomies, series with a significant number of patients previously on radioiodine, or series of patients with insufficient hormonal characterization, approximate conclusions on PHH in hyperthyroid patients can only be drawn from a few studies and with a small number of patients. Series in which an approximation to the prevalence of PHH in patients with hyperfunctioning nodular goiter can be seen are shown in Table 6. As observed, the volume of patients is reduced as toxic nodular goiter is a rare entity, and in recent years, the advent of minimally invasive treatment techniques has diminished the prominence of surgical treatment. In the series by Bramson et al. from 1979,²⁰ only 2.8% of 1228 thyroid surgical procedures were performed on toxic adenomas. In the series of Berglund et al. from 1991,²² 35 out of 309 cases of thyrotoxicosis selected for study were toxic adenomas, and only 10 underwent surgery. In the series of Gurleyik et al. from 2005²⁵ of 202 nodular goiter surgical procedures, only 7.4% were toxic adenomas.

In the group of preoperative euthyroid patients, we found, as previously described in the literature,^{5,7,9,11–15} that higher preoperative TSH concentrations, older age, and lower PRV were independent predictive markers of the occurrence of PHH. Simply put, preoperative TSH > 2.2 mIU/L or age older than 50 years confers a high OR for PHH. These data can provide useful information for the patient's final functional outcome and the professional who has to make a decision between hemithyroidectomy or total thyroidectomy, and are also helpful for planning closer postoperative follow-ups in higher-risk cases. The significant effect on the univariate analysis of remaining lobe volume and hemithyroidectomy laterality was lost in logistic regression analysis as these variables were related to preoperative TSH. Other occasionally described predictors such as lower preoperative T4l concentrations and the presence of lymphocytic thyroiditis in the resected hemithyroid, scarcely represented in this series, did not make statistically significant differences.

In patients with preoperative hyperthyroidism, the only independent predictive marker associated with PHH was higher subject weight. Specifically, weight > 70 kg resulted in a 28-fold higher OR for PHH. This is a novel predictive marker. Only the study by Yano et al. from 2011¹⁶ analyzed the presence of predictive markers for PHH in patients with preoperative hyperthyroidism, but none these markers

Table 2 Characteristics of PHH according to preoperative euthyroid or hyperthyroid status.

	Preoperative euthyroid patients	Preoperative hyperthyroid patients	P-value
Total No. of cases, n (%)	88 (83)	18 (17)	–
No. of hypothyroid patients, n (%)	37 (42)	9 (50)	ns
Hypothyroidism intensity			
Subclinical, n (%)	33 (89.2)	7 (77.8)	ns
Overt, n (%)	4 (10.8)	2 (22.2)	
Hypothyroidism onset time			
Within the first 6 months, n (%)	34 (91.9)	9 (100)	ns
Between 6 and 12 months, n (%)	2 (5.4)	0 (0)	
Between 12 and 24 months, n (%)	0 (0)	0 (0)	
After 24 months, n (%)	1 (2.7)	0 (0)	
Treatment of hypothyroid patients			
On levothyroxine, n (%)	8 (21.6)	4 (44.4)	ns
Off levothyroxine, n (%)	29 (78.4)	5 (55.6)	
Reason for levothyroxine treatment			ns
TSH 4.2–10 mU/L with symptoms, n (%)	12 (41.4)	3 (60)	
SH with TSH > 10 mU/L, n (%)	5 (17.2)	0 (0)	
Progressive SH, n (%)	7 (24.1)	0 (0)	
Overt hypothyroidism, n (%)	4 (13.8)	2 (40)	
Desire for pregnancy, n (%)	0 (0)	0 (0)	
Desire to maintain normal TSH, n (%)	0 (0)	0 (0)	
Growth of thyroid nodules, n (%)	1 (3.5)	0 (0)	
Time to start levothyroxine treatment (mean $\pm$ SD, months)	8.1 $\pm$ 8.2	2.4 $\pm$ 1.7	< .01
Follow-up time (mean $\pm$ SD, months)	54.2 $\pm$ 22.7	52.6 $\pm$ 25.7	ns

SD, standard deviation; SH, subclinical hypothyroidism; TSH, thyrotropin.

were found in any of patients. Only the presence of antithyroglobulin antibodies and a previous history of antithyroid drug treatment were studied. As a possible hypothesis, we could think that heavier patient weight requires greater thyroid hormone needs that the remaining hemithyroid in preoperative hyperthyroidism patients cannot meet. Age and male sex lost their influence as predictive markers in the logistic regression analysis as these variables were associated with weight, so heavier subjects were predominantly men with slightly older. In these patients, the preoperative TSH level was influenced by antithyroid drug treatment and, therefore, did not reflect spontaneous hormone secretion, unlike in euthyroid patients. Additionally, RV, ARV, and PRV were influenced by preoperative hyperthyroidism,^{17–19} which could change the influence of these variables on PHH occurrence and age due to its recognized relationship with glandular functional reserve.⁷

The study has several limitations we should take into consideration. First, it was conducted in a single hospital center, which could lead to selection bias. The sample size of hyperthyroid patients is relatively small, intermediate compared to other studies (Table 6), which may have resulted in a lower statistical power to detect differences in the population. The follow-up period, although prolonged, could be insufficient to detect all cases of PHH occurrence. We did not

evaluate patients' iodine intake, which could have affected TSH levels. PHH follow-up and replacement therapy criteria among different professionals varied as there are no clinical practice guidelines on this matter.¹⁵ Postoperative hormonal analysis timing was not homogeneous, leading to different detection times of PHH and different hormone levels due to post-hemithyroidectomy dynamics.⁷ Finally, patients who started thyroxine treatment a few weeks after surgery had elevated TSH values and maintained treatment indefinitely, which is why they were counted as hypothyroid without considering the possibility of spontaneous hypothyroidism remission, a limitation that also commonly occurs in other studies.^{5,7,14,15}

In conclusion, we were able to quantify, for the first time in Spain, a prevalence of PHH around 42% in euthyroid patients and 50% in hyperthyroid patients. PHH in hyperthyroid patients is slightly more common and intense and requires earlier treatment vs euthyroid cases. Preoperative TSH level, age, and PRV were independent predictive markers of PHH in the euthyroid group, while patient weight was the only predictive marker in the hyperthyroid group. In the routine clinical practice, it is advisable to differentiate the effect of various predictive factors when considering if a patient will have PHH or need closer follow-up when they are euthyroid or hyperthyroid before surgery.

Table 3 Predictive markers of PHH based on preoperative euthyroid or hyperthyroid status.

	Preoperative euthyroid patients			Preoperative hyperthyroid patients		
	Euthyroid final state	Hypothyroid final state	<i>P</i> -value	Euthyroid final state	Hypothyroid final state	<i>P</i> -value
No. of cases, <i>n</i> (%)	51 (58)	37 (42)	—	9 (50)	9 (50)	—
Gender	ns	0.066	ns			
Women, <i>n</i> (%)	42 (82.3)	27 (72.9)		8 (88.9)	4 (44.4)	
Men, <i>n</i> (%)	9 (17.7)	10 (27.1)		1 (11.1)	5 (55.6)	
Age (mean $\pm$ SD, years)	46 $\pm$ 15.7	54.9 $\pm$ 11.8	< .01	49.3 $\pm$ 6.8	59.9 $\pm$ 5.9	< .003
Weight (mean $\pm$ SD, kg)	71.4 $\pm$ 14.8	74.5 $\pm$ 15.6	ns	64.1 $\pm$ 4.7	78.1 $\pm$ 9.4	< .001
BMI (mean $\pm$ SD, kg/m ²)	27.02 $\pm$ 5.00	27.90 $\pm$ 6.11	ns	24.99 $\pm$ 1.88	28.07 $\pm$ 1.61	.002
TV (mean $\pm$ SD, cm ³)	19.4 $\pm$ 18.3	29.3 $\pm$ 34.7	ns	14.9 $\pm$ 6.9	22.9 $\pm$ 11.7	ns
RV (mean $\pm$ SD, cm ³)	6.2 $\pm$ 3.6	4.2 $\pm$ 1.8	< .001	6.6 $\pm$ 5.8	5.2 $\pm$ 4.6	ns
ARV (mean $\pm$ SD, cm ³)	3.5 $\pm$ 1.8	2.3 $\pm$ 1.0	< .001	3.8 $\pm$ 3.2	2.7 $\pm$ 2.3	ns
PRV (mean $\pm$ SD, %)	32.5 $\pm$ 18.2	23.2 $\pm$ 17.1	< .05	27.5 $\pm$ 13.8	17.3 $\pm$ 6.1	.08
Largest diameter of removed nodule (mean $\pm$ SD, mm)	36.6 $\pm$ 16.6	38 $\pm$ 16.5	ns	35.5 $\pm$ 11.7	40.2 $\pm$ 8.9	ns
Nodules > 1 cm in the remaining thyroid lobe, <i>n</i> (%)	7 (13.7)	1 (2.7)	ns	0 (0)	2 (22.2)	ns
Preoperative TSH (mean $\pm$ SD, mUI/L)	1.50 $\pm$ 0.83	2.28 $\pm$ 1.03	< .001	1.59 $\pm$ 1.28	2.44 $\pm$ 3.87	ns
Preoperative T4l (mean $\pm$ SD, ng/dl)	1.16 $\pm$ 0.19	1.11 $\pm$ 0.16	ns	0.93 $\pm$ 0.22	1.10 $\pm$ 0.43	ns
Hemithyroidectomy	< 0.05	ns				
Right, <i>n</i> (%)	20 (39.2)	23 (62.2)		4 (44.4)	5 (55.6)	
Left, <i>n</i> (%)	31 (60.8)	14 (37.8)		5 (55.6)	4 (44.4)	
Histopathological diagnoses	ns	ns				
Nodular hyperplasia, <i>n</i> (%)	38 (74.5)	32 (86.5)		8 (88.9)	5 (55.6)	
Adenoma, <i>n</i> (%)	13 (25.5)	5 (13.5)		1 (11.1)	4 (44.4)	
Lymphocytic thyroiditis, <i>n</i> (%)	5 (9.8)	6 (16.2)	ns	0 (0)	2 (22.2)	ns
Follow-up time (mean $\pm$ SD, months)	52.2 $\pm$ 24.12	56.9 $\pm$ 20.5	ns	59 $\pm$ 29.9	46.2 $\pm$ 20.4	ns

BMI, body mass index; PRV, percentage of the remaining thyroid lobe volume relative to the total thyroid volume; TSH, thyrotropin; T4l, free thyroxine; TV, volume of the excised thyroid lobe; RV, volume of the remaining thyroid lobe; ARV, volume of the remaining thyroid lobe adjusted for body surface area.

Table 4 Variables independently associated with PHH onset in the binary logistic regression model based on preoperative euthyroid or hyperthyroid status.

Independent significant variables	Coefficient	P-value	Odds ratio	95% confidence interval
<i>Preoperative euthyroid patients</i>				
Preoperative TSH (mIU/L)	1.055	.001	2.872	1.553–5.312
Age (years)	0.057	.004	1.058	1.018–1.100
PRV (%)	−0.035	.027	0.965	0.936–0.996
Constant	−4.099	.002	–	–
<i>Preoperative hyperthyroid patients</i>				
Weight (kg)	0.258	.022	1.294	1.038–1.613
Constant	−18.126	.021	–	–

Table 5 Variables with predictive power for PHH and characteristics associated with cutoffs based on preoperative euthyroid or hyperthyroid status^a.

Variable	Area Under Curve (95%CI)	Cutoff	PHH Probability (1)	Odds ratio (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)
<i>Preoperative euthyroid patients</i>						
Preoperative TSH (mIU/L)	0.727 (0.622–0.832)	≥ 2.2	29.8% vs 64.5%	4.278 (1.689–10.833)	54.1% (38%–70.1%)	78.4% (67.1%–89.7%)
Age (years)	0.671 (0.560–0.783)	≥ 50	27.2% vs 56.8%	3.509 (1.438–8.563)	64.9% (49.5%–80.3%)	64.7% (51.6%–77.8%)
PRV (%)	0.655 (0.536–0.774)	≤ 19.6	56.2 vs 36.5	1.024 (1.002–1.046)	70.2% (55.5%–84.9%)	48.6% (34.9%–62.3%)
Preoperative TSH and Age	0.785 (0.689–0.880)	≥ 2.2, ≥ 50	35.1% vs 78.6%	6.769 (1.732–26.451)	54.1% (38%–70.1%)	78.4% (67.1%–89.7%)
Preoperative TSH, age, and PRV	0.819 (0.728–0.911)	≥ 2.2, ≥ 50, ≤ 19.6	36.7 vs 88.9	13.793 (1.641–115.905)	62.2% (46.6%–77.8%)	80.9% (70.1%–91.7%)
<i>Preoperative hyperthyroid patients</i>						
Weight (kg)	0.901 (0.734–1)	≥ 70	20% vs 87.5%	28 (2.067–379.247)	88.9% (68.4%–100%)	88.9% (68.4%–100%)

^a Chances of PHH based on the variable value being below or above the cutoff. In the case of 2 or more grouped variables, it represents the chances of being above all cutoffs vs being below any or all of them.

Table 6 Prevalence of PHH in series of patients with toxic thyroid nodules undergoing surgery.

Author (Year)	Patients	Surgical technique	PHH prevalence, n (%)	Follow-up time, mean (range)
Branson et al. (1979) ²⁰	35 toxic thyroid nodules	Hemithyroidectomy	5 (14.3)	6.3 ± 3.9 (0.5–15) years
Eyre-Brook and Talbot (1982) ²¹	55 toxic thyroid nodules	Lobectomy	4 (7.3)	6 years
Berglund et al. (1991) ²²	10 toxic thyroid nodules	6 hemithyroidectomies, 4 enucleations	0 (0) ^a	120 (36–168) months
O'Brien et al. (1992) ²³	9 toxic thyroid nodules	6 subtotal lobectomies and 3 bilateral subtotal thyroidectomies	2 (22)	9 months
David et al. (1995) ²⁴	31 solitary hot thyroid nodules, 19 hyperthyroid	23 partial thyroidectomies, 8 total thyroidectomies	15 (65.2)	3 years

Table 6 (Continued)

Author (Year)	Patients	Surgical technique	PHH prevalence, n (%)	Follow-up time, mean (range)
Gurleyik et al. (2005) ²⁵	13 toxic thyroid nodules	Lobectomy with isthmectomy	0 (0)	6 months
Yano et al., 2011 ¹⁶	72 toxic thyroid nodules	Lobectomy	6 (8)	35 ± 3 months
Present series	18 toxic thyroid nodules	Hemithyroidectomy	9 (50)	52.6 ± 25.7 months

^a 2 cases were excluded for having received immediate postoperative thyroxine replacement therapy.

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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.

Authors' contributions

Each author has materially contributed to the research and preparation of the article. Specifically:

Luis García Pascual: study conception and design, data acquisition and analysis, interpretation of results, drafting of the manuscript, and approval of the final version.

Andreu Simó-Servat, Carlos Puig-Jové, and Lluís García-González: study conception and design, interpretation of results, critical revision, and approval of the final version.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.endien.2024.05.003>.

References

- Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26:1–133.
- Ahn D, Sohn JH, Jeon JH. Hypothyroidism following hemithyroidectomy: incidence, risk factors, and clinical characteristics. *J Clin Endocrinol Metab*. 2016;101:1429–36.
- Menegaux F, Baud G, Chereau N, Christou N, Deguelte S, Frey S, et al. SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules: surgical treatment. *Ann Endocrinol*. 2022;83:415–22.
- Stoll SJ, Pitt SC, Liu J, Schaefer S, Sippel RS, Chen H. Thyroid hormone replacement after thyroid lobectomy. *Surgery*. 2009;146:554–60.
- Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JWA, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. *J Clin Endocrinol Metab*. 2012;97:2243–55.
- Park S, Jeon MJ, Song E, Oh HS, Kim M, Kwon H, et al. Clinical features of early and late postoperative hypothyroidism after lobectomy. *J Clin Endocrinol Metab*. 2017;102:1317–24.
- Li Z, Qiu Y, Fei Y, Xing Z, Zhu J, Su A. Prevalence of and risk factors for hypothyroidism after hemithyroidectomy: a systematic review and meta-analysis. *Endocrine*. 2020;70:243–55.
- Cho MJ, Yu HW, Kim W, Kim YK, Choi S II, Kim SJ, et al. Comparison of the incidence of postoperative hypothyroidism in patients undergoing conventional thyroid lobectomy and pyramid-and-isthmus-preserving lobectomy. *Int J Endocrinol*. 2021;2021:8162307.
- Kandil E, Krishnan B, Noureldine SI, Yao L, Tufano RP. Hemithyroidectomy: a meta-analysis of postoperative need for hormone replacement and complications. *ORL*. 2013;75:6–17.
- Buehler LA, Madhun NZ, Baena J, Nasr C, Scharpf J, Zhou K. Hormonal outcomes following hemithyroidectomy. *Otolaryngol Head Neck Surg*. 2021;164:1011–8.
- Lee SJ, Song CM, Ji YB, Choi YY, Sohn YS, Park JH, et al. Risk factors for hypothyroidism and thyroid hormone replacement after hemithyroidectomy in papillary thyroid carcinoma. *Laryngoscope*. 2021;131:2223–31.
- Chaabouni MA, Sellami M, Jameleddine E, Kharrat R, Thabet W, Mnejja M, et al. Predictive factors for hypothyroidism after hemithyroidectomy. *F1000Research*. 2022;11:1355.
- Abraham CR, Ata A, Stain SC, Khalaf ZM, Hazimeh Y. Time to hypothyroidism following hemithyroidectomy. *Cureus*. 2022;14:e32837.
- Cao Z, Liu R, Wu M, Xu X, Liu Z. Risk factors for thyroid hormone replacement therapy after hemithyroidectomy and development of a predictive nomogram. *Endocrine*. 2022;76:85–94.
- Prévo J, Potard G, Thuillier P, Roudaut N, Le Pennec R, Leclère JM, et al. Risk factors for hypothyroidism following hemithyroidectomy. *Ann Endocrinol*. 2023;84:739–45.
- Yano Y, Sugino K, Akaishi J, Urano T, Okuwa K, Shibuya H, et al. Treatment of autonomously functioning thyroid nodules at a single institution: radioiodine therapy, surgery, and ethanol injection therapy. *Ann Nucl Med*. 2011;25:749–54.
- Ferrari C, Reschini E, Paracchi A. Treatment of the autonomous thyroid nodule: a review. *Eur J Endocrinol*. 1996;135:383–90.
- Horst W, Rösler H, Schneider C, Labhart A. 306 cases of toxic adenoma: clinical aspects, findings in radioiodine diagnostics, radiochromatography and histology; results of 131I and surgical treatment. *J Nucl Med*. 1967;8:515–28.

19. Hamburguer JI. The autonomously functioning thyroid nodule: Goetsch's disease. *Endocrin Rev.* 1987;8:439–47.
20. Bransom CJ, Talbot CH, Henry L, Elemenoglou J. Solitary toxic adenoma of the thyroid gland. *Br J Surg.* 1979;66:590–5.
21. Eyre-Brook IA, Talbot CH. The treatment of autonomous functioning thyroid nodules. *Br J Surg.* 1982;69:577–9.
22. Berglund J, Christensen SB, Dymling JF, Hallengren B. The incidence of recurrence and hypothyroidism following treatment with antithyroid drugs, surgery or radioiodine in all patients with thyrotoxicosis in Malmö during the period 1970-1974. *J Int Med.* 1991;229:435–42.
23. O'Brien T, Gharib H, Suman VJ, van Heerden JA. Treatment of toxic solitary nodules: surgery versus radioactive iodine. *Surgery.* 1992;112:1166–70.
24. David E, Rosen IB, Bain J, James J, Kirsh JC. Management of the hot thyroid nodule. *Am J Surg.* 1995;170:481–3.
25. Gurleik E, Pehlivan M, Gokpinar I. Surgery is the procedura of choice for the treatment of patients with toxic adenoma in an endemic goitre área. *Acta Chirurgica Belgica.* 2005;105:373–7.
26. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev.* 2008;29:76–131.
27. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med.* 1987;317:1098.
28. Barranco H, Fazendin J, Lindeman B, Chen H, Ramonell KM. Thyroid hormone replacement following lobectomy: long-term institutional analysis 15 years after surgery. *Surgery.* 2023;173:189–92.