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ORIGINAL ARTICLE

Prevalence and risk factors for hypoparathyroidism following total thyroidectomy in Spain: a multicentric and nation-wide retrospective analysis

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Abstract

Purpose The prevalence of postoperative hypoparathyroidism has been studied in registries and in surgical series with highly variable and imprecise results. However, the frequency of this hormonal deficiency in the clinical practice of endocrinologists is not known with accuracy. We aimed to assess the prevalence and risk factors of hypoparathyroidism in patients undergoing total thyroidectomy in Spain.

Methods We designed a retrospective, multicentre and nation-wide protocol including all patients with total thyroidectomy who were seen in the endocrinology clinic of the participant centers from January to March 2018. Prevalence of hypoparathyroidism was evaluated at discharge of surgery, 3–6 months after surgery, 12 months after surgery and at last visit. Twenty hospitals participated in the study.

Results Of 1792 patients undergoing total thyroidectomy, 866 (48.3%) developed postoperative hypoparathyroidism at discharge of surgery. Most of them recover parathyroid function over time. Prevalence of hypoparathyroidism at 3–6 months, 12 months and at last visit was 22.9%, 16.7% and 14.5%, respectively. The risk of developing definitive hypoparathyroidism was related to the presence of parathyroid tissue at histology, lymph node dissection, and two-stage thyroidectomy. Patients with thyroid cancer, with higher postoperative calcium levels and treated by expert surgical teams exhibited lower risk of developing permanent hypoparathyroidism.

Conclusions Although most patients with postsurgical hypoparathyroidism recover parathyroid function, the prevalence of permanent disease in clinical practice is non negligible (14.5%). Postoperative calcium, extent and timing of surgery, the presence of cancer, expert surgical team, and parathyroid tissue at histology are predictors of permanent hypoparathyroidism.

Keywords Thyroidectomy · Hypoparathyroidism · Hypocalcemia · Thyroid surgery · Prevalence · Risk factors

Introduction

Hypoparathyroidism is a rare endocrine disease characterized by low serum calcium (Ca) and inappropriately low or insufficient circulating parathyroid hormone (PTH) levels [1, 2]. In the Rochester Epidemiology Project, an incidence of 37 cases per 100,000 person-years was found in the period 2006–2008 [3, 4]. The majority of cases (78%) were caused by cervical surgery and only a small proportion was familial (7%) or idiopathic (6%). In the Danish Patient Registry, the prevalence was 22 per 100,000 for postoperative hypoparathyroidism and 2.3 per 100,000 for nonsurgical hypoparathyroidism [5, 6].

Postoperative hypoparathyroidism is a surgical complication that may occur after any type of neck surgery for several clinical entities, mainly thyroid and parathyroid disease, and is the result of inadvertent parathyroid tissue

The original version of this article was revised: the given and family name of Juan Carlos Galofré was corrected.

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damage during surgery, either by excision or compromise blood flow of the parathyroid glands [7, 8]. Parathyroid hypofunction that appears after cervical surgery has been studied by different authors with highly variable results, ranging from 10 to 60% [1, 9–17]. Most cases of hypoparathyroidism are transient and resolved in the first 12 months after surgery, but the available estimates on the persistence of this hormone deficiency are highly variable, from 0.12 to 12% [2, 9–16, 18–21].

It seems, therefore, that the prevalence of transient and permanent postoperative hypoparathyroidism has not been established with accuracy and the different studies show variable and inconsistent values [8]. Therefore, we designed this multicenter and nation-wide study with the objective to assess the prevalence of hypoparathyroidism during the different stages of the follow-up of these patients after total thyroidectomy for any reason. An additional objective was to analyze the surgical, pathological, and biochemical variables associated to presence of parathyroid hypofunction at discharge and its persistence in the long-term.

Methods

This study aimed to evaluate the prevalence of different forms of hypoparathyroidism in the setting of the clinical practice of Spanish endocrinologists in real life. The project received a favorable evaluation from the board of directors of the Spanish Society of Endocrinology (SEEN) and was disseminated to all members of the Thyroid Task Force of the SEEN, a working group that includes most of the endocrinologists who are experts in thyroid disease. All members had the opportunity to review the protocol and suggest modifications. After several rounds of emails and discussion sessions, a final version of the protocol was approved by the 26 investigators from 20 centers who were interested in participating. Since this is a non-intervention and exclusively retrospective analysis of data from routine clinical practice, the informed consent of the patients has not been considered necessary. Nonetheless, the study protocol was approved by the local ethical committee of the Hospital Universitario Ramón y Cajal (Madrid).

Subjects

All patients with total (one- or two-stage, i.e., reoperation to complete thyroidectomy) thyroidectomy who came to the Endocrinology clinic of the participant centers from 1 January to 31 March 2018 were studied. All the following criteria had to be fulfilled to be included in the study: age > 14 years at the time of thyroidectomy, availability of surgical and pathological reports, and follow-up in the same hospital for at least one year after thyroidectomy. The following were considered as exclusion criteria (any of them): absence of a surgical report, absence of histological report, time from thyroidectomy <12 months, and hypoparathyroidism of any cause known before thyroidectomy.

Study design

The following data were retrospectively collected from the clinical record of the patients: demographic data (gender, age), details on hospital (hospital volume, availability of specialized surgical team, and availability of multidisciplinary board), details on surgical procedure (date and type of surgery, complications, identification of parathyroid glands by the surgeon, and autotransplantation), histopathological data (presence or absence of parathyroid tissue in the specimen, result of thyroid pathology), analytical data on Ca metabolism (before surgery, in the immediate postoperative period, and at last visit), and information on therapy with Ca and calcitriol (at discharge from hospital after surgery, 3–6 months after surgery, 12 months after the surgery, and at last visit).

Definitions

For the purpose of assessing prevalence, comparing patients and assessing risk factors, the following definitions were established before starting this research:

Hypoparathyroidism at discharge: presence, in the immediate postoperative period, of serum Ca levels < 8.5 mg/dl with inappropriate low PTH levels (<15 pg/ml), and/or need for treatment with Ca or calcitriol at discharge from surgery [7, 22, 23].

Hypoparathyroidism at 3–6 months: need for treatment with Ca or calcitriol at 3–6 months after surgery.

Hypoparathyroidism at 12 months: need for treatment with Ca or calcitriol at 12 months after surgery.

Hypoparathyroidism at last visit (definitive hypoparathyroidism): need for treatment with Ca or calcitriol at the last visit of the follow-up.

Early recovery patients (transient hypoparathyroidism): patients with hypoparathyroidism at discharge from surgery, but absence of need for Ca and calcitriol therapy in the visit 3–6 months after surgery, i.e., patients who recover parathyroid function between discharge and the 3–6 months visit

Intermediate recovery patients (protracted hypoparathyroidism): patients with hypoparathyroidism at 3–6 months, but no need for Ca or calcitriol at 12 months after surgery, i.e., patients who recover parathyroid function between the visits at 3–6 months and 12 months.

Late recovery patients: subjects with hypoparathyroidism at 12 months and with no need for Ca for calcitriol at the last visit.

Need for calcium: Prescription of supplements of this element at any dose in association with calcitriol, or without association with calcitriol, but at high doses (more than 1000 mg/day), in order to treat hypoparathyroidism.

Serum corrected Ca: when available, we calculated serum Ca corrected by albumin or total proteins according to the following formulas: corrected Ca (mg/dl) = Ca (mg/dl) + 0.8 (4-albumin [g/dl]), or Ca/[(total proteins (g/dl)/16) + 0.55].

To estimate the *volume of the hospital*, the number of patients with total thyroidectomy seen in the endocrinology clinic during 3 months was quantified. Those with more than 100 patients were considered high volume hospitals.

Statistical analysis

For quantitative variables, results are expressed as mean ± SD for normally distributed data and as median (interquartile range) for nonparametric data. Adjustment to normal distribution was tested by the Kolmogorov test. Categorical variables are described as percentages (%). To estimate the prevalence of different types of hypoparathyroidism point estimate and 95% confidence intervals were calculated according to the formula: $CI = p_0 \pm z_\alpha(p_0 q_0/n)\uparrow 0.5$, where CI = confidence interval, p_0 = observed proportion in the sample, $z_\alpha = 1.96$, for a 95% confidence interval, $q_0 = 1 - p_0$, and n = number of studied subjects (sample size).

For comparisons of means between two groups of subjects, the Student's *t*-test was used for normally distributed data and the Mann–Whitney *U*-test was employed for nonparametric data. For ratio comparisons, the chi-squared test or Fisher's exact test was used. Several models of logistic regression analysis were used to assess the presence of hypoparathyroidism as a function of quantitative and qualitative variables. All used tests were two-sided and differences were considered significant when $P < 0.05$.

Results

Studied patients

Data from a total of 2431 patients who underwent total thyroidectomy in the 20 hospitals participating in this multicenter study were analyzed. Among them, 639 were excluded because of the following reasons: time of follow-up < 12 months in 283 patients, absence of surgical report in 245, absence of pathological report in 188, previous diagnosis of hypoparathyroidism in 1, and age < 14 years in three patients. Therefore, we studied 1792 patients (1413 women, 78.9%) aged 48.5 ± 15.0 years (range 14–85) with a median follow-up of 59 (26–106) months (Table 1). One-stage thyroidectomy was performed in 1548 subjects (86.5%), whereas 244 patients (13.6%) underwent two-stage thyroidectomy. Histopathological diagnoses were benign thyroid disease in 339 patients (18.9%) and thyroid cancer in 1453 patients (81.1%). Hundred and fifty-eight patients suffered surgical complications other than hypoparathyroidism: recurrent laryngeal nerve palsy or dysphonia in 100, bleeding in 26, seroma in 2, infection or abscess in 3, Horner's syndrome in 5, trachea or esophagus injury in 2, tracheostomy in 6 and other in 14 subjects.

Prevalence of hypoparathyroidism

Prevalence of hypoparathyroidism at different stages of the study is shown in Table 2. At discharge from thyroidectomy, we found 866 patients (48.3%) with hypoparathyroidism. Most of the patients who recovered parathyroid function did so between discharge and the visit at 3–6 months (transient hypoparathyroidism, early recovery patients, n = 455). A group of 111 subjects recovered parathyroid function after this visit and before the 12-month visit (protracted hypoparathyroidism, intermediate recovery patients). Lastly, we found a group of 40 patients who recovered parathyroid function beyond one year of follow-up (late recovery patients) (Table 2). Therefore, the prevalence of definitive (last visit) hypoparathyroidism in our cohort was 14.5%. A summary of the evolution of the parathyroid function for the entire sample is depicted in Fig. 1.

Prevalences in different subgroups of patients are shown in Table 3. Male patients showed significant lower prevalence of hypoparathyroidism at discharge than females, but not at any other stage during the follow-up. Patients treated in high volume hospitals exhibited lower prevalence of hypoparathyroidism at 3–6 months, 12 months and at last visit, in comparison with patients who were studied in low volume hospitals. We found no other significant differences of prevalence in patients classified according to age, time of follow-up or date of surgery (Table 3).

Patients with and without hypoparathyroidism

In comparison with patients with euparathyroidism, patients with hypoparathryoidism at discharge had a significantly lower age (47.7 ± 14.8 vs 49.2 ± 15.1 yr, $P < 0.05$) and lower preoperative Ca levels (9.46 ± 0.50 vs 9.55 ± 0.62 mg/dl, $P < 0.01$). In addition, in comparison with patients with normocalcemia, patients with hypoparathyroidism at discharge had a higher proportion of women, lymph node dissection, surgical complications, identification of parathyroid glands, autotransplantation, and parathyroid tissue in histology, and a lower percentage of 2-stage thyroidectomy and thyroid cancer (Fig. 2a).

When analyzing patients at last visit, we found no differences in age between patients with and without hypoparathyroidism (47.2 ± 14.8 vs 48.7 ± 15.0 yr). Postoperative corrected serum Ca was significantly lower in patients with

Table 1 Demographic, clinical and analytical features of studied patients with total thyroidectomy

	All ($n = 1792$)	Females ($n = 1413$)	Males ($n = 379$)
Age, yr	48.5 ± 15.0	48.4 ± 14.8	48.9 ± 15.6
Time of follow-up	59 (26–107)	59 (25–105)	60 (26–107)
Date of surgery			
Before 2010	612 (34.2)	481 (34.0)	131 (34.6)
2011 and after	1180 (65.8)	932 (68.0)	248 (65.4)
Hospital volume			
≤100 patients	676 (37.7)	536 (37.9)	140 (36.9)
>100 patients	1116 (62.3%)	877 (62.1)	239 (63.1)
Specialized surgical team	1548 (86.4)	1217 (86.1)	331 (87.3)
Extent of surgery			
Thyroidectomy	1054 (58.8)	869 (61.5)	185 (48.8)
Thyroidectomy and LN dissection	738 (41.2)	544 (38.5)	194 (48.9)**
Type of thyroidectomy			
1-stage	1548 (86.4)	1228 (86.9)	320 (84.4)
2-stage	244 (13.6)	185 (13.1)	59 (15.6)
Surgical complications	158 (8.8%)	118 (8.4)	40 (10.7)
Identification of parathyroid glands	1331 (74.3)	1048 (74.2)	283 (74.7)
Autotransplantation	146 (8.1)	117 (8.3)	29 (7.7)
Parathyroid tissue at histology	406 (22.7)	331 (23.5)	75 (19.9)
Thyroid histopathology			
Benign thyroid disease	339 (18.9)	282 (20.0)	57 (15.0)
Thyroid cancer	1453 (81.1)	1131 (80.0)	322 (85.0)*
Preoperative Ca (mg/dl)[a]	9.51 ± 0.54	9.50 ± 0.55	9.54 ± 0.50
Postoperative corrected Ca (mg/dl)[b]	8.38 ± 0.85	8.36 ± 0.86	8.46 ± 0.82
Postoperative PTH (pg/ml)[c]	23 (8–41.3)	23 (8–42)	24.1 (6.8–38.8)

Data are the mean ± SD or the median (interquartile range) for quantitative variables, and the number (percentage) for categorical variables

LN lymph node, *Ca* calcium, *PTH* parathyroid hormone

*$P < 0.05$; **$P < 0.001$

[a] $n = 1143$ (894 females, 249 males)

[b] $n = 1150$ (913 females, 237 males)

[c] $n = 746$ (590 females, 156 males)

hypoparathyroidism at last visit in comparison with euparathyroid patients (7.21 ± 0.67 vs 8.16 ± 0.79 mg/dl; $P < 0.001$). In a subgroup of 746 subjects with available postoperative PTH we also found significant differences between patients with ($n = 129$, 6.1[3.0–10.5] pg/ml) and without hypoparathyroidism ($n = 617$, 29[12.8–45.0] pg/ml; $P < 0.001$). Dosage of calcitriol at discharge was available in a subgroup of 519 patients. This dosage was slightly higher in patients with hypoparathyroidism at last visit in comparison with euparathyroid subjects at last visit (0.50 [0.50–0.75] µg/day, $n = 196$, vs. 0.50 [0.50–0.75] µg/day, $n = 323$; $P = 0.004$).

In comparison with euparathyroid subjects, patients with hypoparathyroidism at last visit showed lower proportion of subjects treated in high volume hospitals, and in centers with specialized surgical teams. The identification of parathyroid gland by the surgeon and the diagnosis of thyroid cancer were lower in patients with hypoparathyroidism at last visit. On the other hand, postsurgical complications and the presence of parathyroid tissue at pathological specimen were more frequent in the group of patients with hypoparathyroidism at last visit (Fig. 2b).

Logistic regression analysis

Several models of logistic regression analysis were performed to study the dependence of the variable hypoparathyroidism as a function of several independent variables (Tables 4 and 5). At discharge, hypoparathyroidism was negatively related to male gender, age, hospital volume, 2-stage thyroidectomy and thyroid cancer, and positively related to lymph node dissection, autotransplantation, and the identification of parathyroid tissue at histology (Table 4, model 2). When including preoperative calcium in the model this analytical variable was negatively related to hypoparathyroidism and the relationship between gender and hypoparathyroidism was lost (Table 4, model 3).

When studying at last visit, hypoparathyroidism was negatively related to specialized surgical team, identification of parathyroid glands and the presence of thyroid cancer, and positively to lymph node dissection, surgical complications, and parathyroid tissue at histology (Table 5, model 2). When including corrected postoperative Ca as independent variable, hypoparathyroidism was negatively related to specialized surgical team, cancer and postoperative Ca, and positively related to lymph node dissection, 2-stage thyroidectomy and parathyroid tissue at histology (Table 5, model 3),

Table 2 Prevalence of different types of hypoparathyroidism and recovery of parathyroid function at different stages

	n	Prevalence (%)	95% CI
Hypoparathyroidism at different stages of follow-up			
At discharge	866	48.3	46.0–50.6
At 3–6 months	411	22.9	21.1–24.9
At 12 months	300	16.7	15.1–18.5
At last visit	260	14.5	13.0–16.2
Recovery of parathyroid function			
Early recovery (transient hypoparathyroidism)	455	25.4	23.4–27.4
Intermediate recovery (protracted hypoparathyroidism)	111	6.2	5.2–7.4
Late recovery patients	40	2.2	1.6–3.0

Discussion

Our study shows that, in the setting of the clinical practice of Spanish endocrinologists, the prevalence of hypoparathyroidism at discharge after total thyroidectomy is 48%. Seventy percent of these patients (666 out of 866) had recovered parathyroid function when evaluated at last visit. These data imply that the diagnosis of permanent hypoparathyroidism should not always be considered as definitive, since recovery of parathyroid function is a dynamic process [7, 16], and a number of subjects (in our study 40 out of 300, i.e., 13%) recovered the ability to maintain normocalcemia without treatment at >12 months after surgery. This is in agreement with data by Kim et al. [24], who found that 5 out 22 [23%) patients with permanent hypoparathyroidism discontinued calcium and vitamin D therapy and with those by Villarroya-Marquina et al. [25], who found that 12 subjects of a cohort of 142 (8.5%) with protracted hypoparathyroidism (defined as hypoparathyroidism 1 month after surgery) recovered parathyroid function after 1 year.

Whatever the time point to define permanent hypoparathyroidism, we detected that the prevalence of permanent hypoparathyroidism in the real-life practice among Spanish endocrinologists is non-negligible (14.5–16.7%) and, in general, higher than that reported in most studies. In the study by Powers et al. [26], a prevalence of hypoparathyroidism of 7.6% was found in a cohort of 117,342 surgeries of the anterior cervical region. Seventy-five percent of these cases were transitory (duration ≤ 6 months) and 25% were permanent (duration < 6 months). The Spanish study by Sitges-Serra et al. [27], carried out in 442 thyroidectomized patients, showed

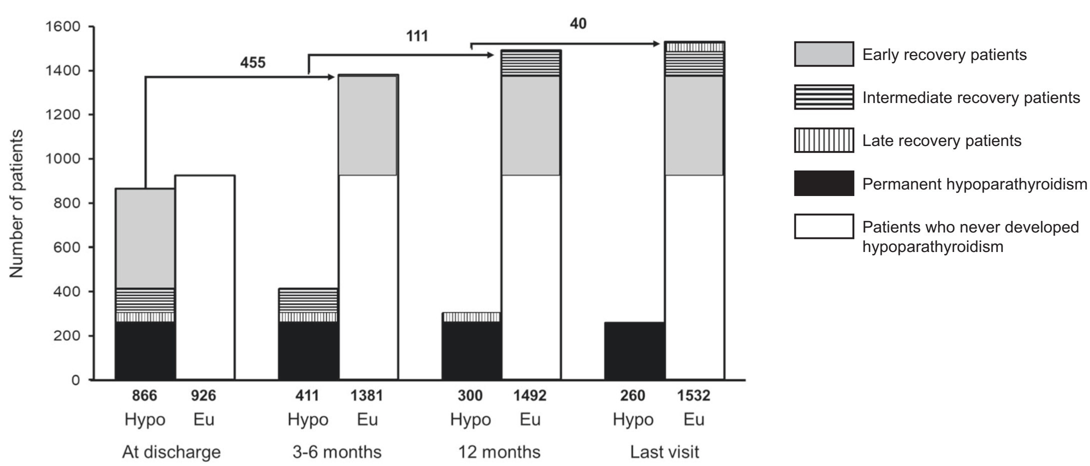

Fig. 1 Evolution of parathyroid function throughout the study period. The number of patients with hypoparathyroidism and euparathyroidism at discharge, 3–6 months, 12 months and at last visit is indicated in the abscissa axis. The number of patients who recover parathyroid function between the different stages is indicated by arrows and with different rectangles: early recovery patients (transient hypoparathyroidism, gray rectangles), intermediate recovery patients (protracted hypoparathyroidism, rectangles with horizontal lines), late recovery patients (rectangles with vertical lines). Closed rectangles indicate patients with definitive (last visit) hypoparathyroidism and open rectangles indicate patients who never developed parathyroid hypofunction

Table 3 Prevalence of hypoparathyroidism at different stages during the study in patients classified in subgroups

Group	*n*	Prevalence of hypoparathyroidism											
		At discharge			3–6 months			12 months			Last visit		
		n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Gender													
Female	1413	702	49.7	47.1–52.3	336	23.8	21.6–26.1	244	17.3	15.4–19.3	207	14.6	12.9–16.6
Male	379	164	43.3*	38.4–48.36	75	19.8	16.1–24.1	56	14.8	11.6–18.7	53	14.0	10.9–17.8
Age													
≤48 yr	910	459	50.4	47.25–53.7	214	23.5	20.9–26.4	157	17.3	14.9–19.8	138	15.2	13.0–17.6
>48 yr	879	404	46.0	42.7–49.3	195	22.2	19.6–25.1	142	16.2	13.9–18.7	121	13.8	11.7–16.2
Time follow-up													
<60 mo	911	449	49.3	46.1–52.5	218	23.9	21.3–26.8	154	16.9	14.6–19.5	134	14.7	12.6–17.2
≥60 mo	881	417	47.3	44.1–50.6	193	21.9	19.3–24.8	146	16.6	14.3–19.2	126	14.3	12.1–16.8
Date of surgery													
≤2010	612	286	46.7	42.8–50.7	130	21.2	18.2–24.7	99	16.2	13.5–19.3	89	14.5	12.0–17.6
>2010	1180	580	49.2	46.3–52.0	281	23.8	21.5–26.3	201	17.0	15.0–19.3	171	14.5	12.6–16.6
Hospital volume, *n*													
≤100 patients	676	332	49.1	45.4–52.9	178	26.3	23.2–29.8	130	19.2	16.4–22.4	114	16.9	14.2–19.9
>100 patiens	1116	534	47.8	44.9–50.8	233	20.9**	18.6–23.4	170	15.2*	13.2–17.5	146	13.1*	12.7–17.9

Data are the number and percentage (with 95% confidence interval) of patients included in each group or subgroup

*$P < 0.05$, **$P < 0.01$

postoperative transient hypocalcemia in 50.2% and permanent disease in 3.8%. In a recent meta-analysis, the median (IQR) incidence of transient and permanent post-thyroidectomy hypocalcemia was 27% (19–38) and 1% (0–3), respectively [15]. Differences with these and other studies [9–21] may be accounted for by the setting where the patients were recruited, i.e., in the endocrinology clinics where it is foreseeable that gather patients with greater complications after thyroidectomy and with greater needs for prolonged follow-up. Other reasons for the discrepancy of data among studies lies in lack of homogeneous definition, variety of laboratory ranges for normocalcemia, different case mix and sample sizes of studies, and short of incomplete follow-up of patients [28].

In our cohort, female patients experienced transient, although not permanent, hypoparathyroidism more frequently than men, as reported by others [14]. Contrary to some previous studies [29, 30] we did not find significant relationship between permanent hypoparathyroidism and age or gender of patients. Lower hospital volume has been identified as predictor of transient hypocalcemia [31]. Our multivariable analysis agrees with this idea, since we identified hospital volume as a negative predictor of hypoparathyroidism at discharge, although it had no impact in permanent hypoparathyroidism.

Identification of fewer than two parathyroid glands at surgery was a predictor of permanent hypoparathyroidism in the meta-analysis by Edafe et al. [15]. Lorente-Poch et al. reported that the number of parathyroid gland remaining in situ is a predictor of parathyroid function recovery [32]. Accordingly, we found a negative relationship between the surgical identification of parathyroid glands and the risk of permanent hypoparathyroidism that was lost when introducing serum Ca in the model, although unfortunately we could not quantify the number of parathyroid gland remaining in situ in our cohort. As reported by others [13, 16], we also found a significant relationship between the presence of parathyroid gland in the specimen, i.e., inadvertent removal of parathyroid gland, and the development of permanent hypoparathyroidism.

The relationship between parathyroid autotransplantation and the development of hypoparathyroidism is controversial. Some authors have found that autografting is related with postoperative hypocalcemia [13, 19, 20, 27, 33–35] but, in the long-term, it may prevent permanent hypoparathyroidism [36–38]. We found that parathyroid autografting was a risk factor for hypoparathyroidism at discharge, but it was neutral on permanent parathyroid hypofunction. This is in agreement with other studies showing that parathyroid autotransplantation does not warrant the recovery of parathyroid function [13, 15, 19, 27, 32, 39–41].

Rates of hypoparathyroidism have been described to be higher after more extensive surgical procedures [9, 13, 14, 17, 27, 29, 42–44], and in patients with lymph node dissection [32], which is probably due to more

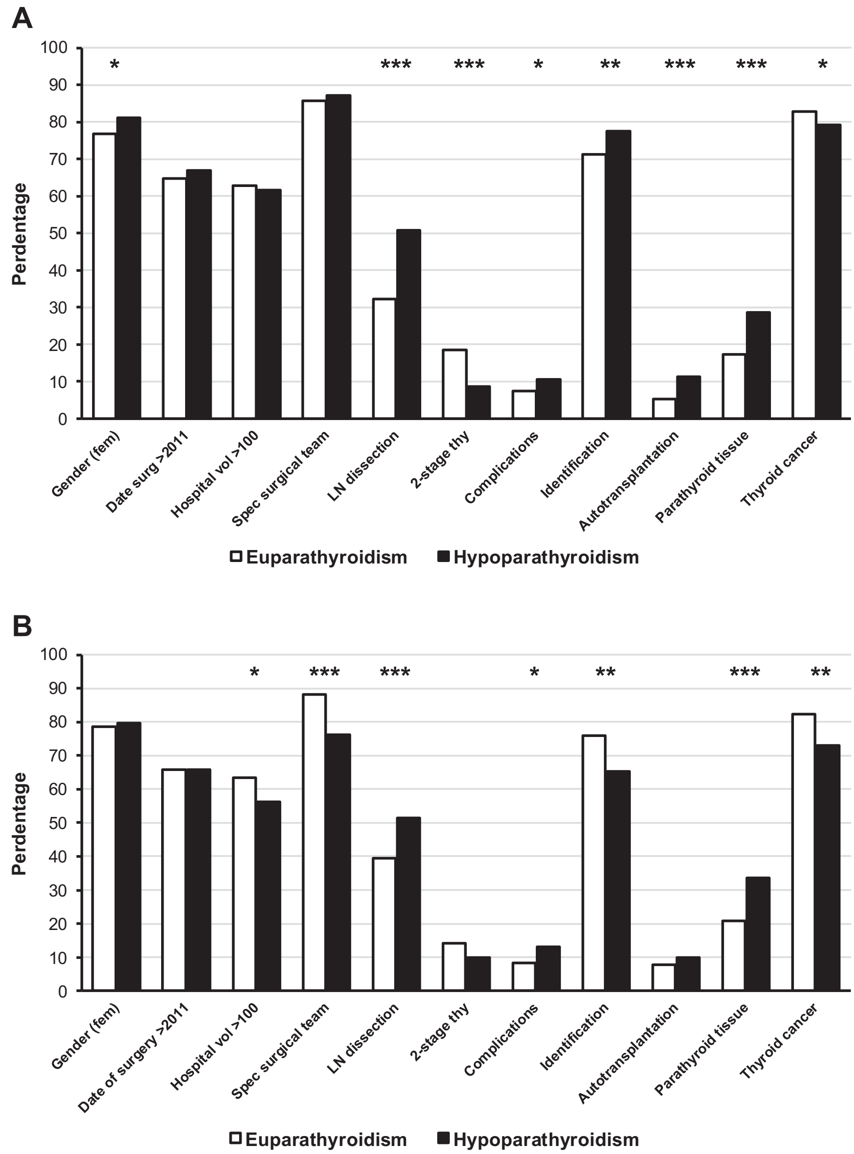

Fig. 2 Clinical features of patients classified according to the presence (closed rectangles) or absence (open rectangles) of hypoparathyroidism at discharge (**a**) and at last visit (**b**). Abscissa scale: different clinical characteristics. Ordinate scale: percentage of patients in each group. $*P<0.05$; $**P<0.01$; $***P<0.001$

ischemic injury to parathyroids. According to our multivariate analysis, node dissection has an impact in hypoparathyroidism at the two studied times (first and last visit). In addition, we found that two-stage thyroidectomy, that is, reoperation to complete thyroidectomy, increased the risk of permanent hypoparathyroidism. In agreement with these findings, surgery for recurrent goiter and reoperation for bleeding have been related to transient hypocalcemia, and reoperation for bleeding and heavier thyroid specimens were identified as predictors of permanent hypocalcemia [15].

Thyroid cancer has been reported to be associated with higher rates of postoperative hypocalcemia [14]. By contrast, Villarroya-Marquina et al. [25] found that the presence of thyroid cancer was the only significant clinical variable associated with parathyroid function recuperation after 6 months. In our study the presence of thyroid cancer was negatively associated with hypoparathyroidism both at discharge and at last visit. This could be explained, at least in part, by the fact that cancer patients are operated by more experienced surgeons, and also by the fact that the follow-up of most of patients with benign thyroid disease and without hypoparathyroidism is performed by the general practitioner and not by the specialist in Endocrinology and, therefore, not included in our survey. As previously reported [13, 29], our data suggest that the expertise of the surgical team is related to recovery of parathyroid function.

In accordance with previous reports [15], we identified preoperative Ca as a predictive factor for transient hypocalcemia. More importantly, permanent hypoparathyroidism has been associated to postoperative Ca [29, 45]. In fact, low Ca level 24 h after surgery was a significant

Table 4 Results of three models of logistic regression to study the influence of several covariates on the presence of hypoparathyroidism at discharge

	Model 1			Model 2			Model 3		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Gender, male	**0.76**	**0.60–0.95**	**0.018**	**0.69**	**0.54–0.88**	**0.003**	0.83	0.61–1.13	0.243
Age, yr	**0.992**	**0.986–0.998**	**0.012**	0.99	0.98–1.00	0.109	0.99	0.98–1.00	0.367
Date of surgery, >2011	1.13	0.92–1.39	0.232	0.91	0.73–1.14	0.425	1.04	0.78–1.41	0.777
Hospital volume, *n*	**0.997**	**0.996–0.999**	**0.000**	**0.996**	**0.995–0.998**	**0.000**	**0.996**	**0.994–0.998**	**0.000**
Specialized surgical team	1.19	0.90–1.58	0.218	0.96	0.70–1.30	0.776	0.86	0.53–1.40	0.542
Lymph node dissection				**2.34**	**1.86–2.96**	**0.000**	**2.39**	**1.77–3.22**	**0.000**
2-stage thyroidectomy				**0.53**	**0.39–0.73**	**0.000**	**0.36**	**0.23–0.56**	**0.000**
Surgical complications				1.32	0.93–1.87	0.124	1.18	0.77–1.80	0.442
Identification of parathyroid glands				1.27	0.98–1.63	0.067	1.11	0.80–1.54	0.535
Autotransplantation				**1.99**	**1.35–2.91**	**0.000**	**1.83**	**1.04–3.22**	**0.035**
Parathyroid tissue at histology				**1.63**	**1.28–2.09**	**0.000**	**1.88**	**1.38–2.55**	**0.000**
Thyroid cancer				**0.56**	**0.43–0.74**	**0.000**	**0.61**	**0.43–0.88**	**0.007**
Preoperative Ca, mg/dl							**0.63**	**0.49–0.80**	**0.000**

Model 1: Demographic features and hospital data are included as independent variables ($n = 1789$)

Model 2: In addition to the above, surgical and histopathological variables are included ($n = 1764$)

Model 3: Analytical data (preoperative serum calcium) is added to those variables included in model 2 ($n = 1127$)

OR odds ratio, *CI* confidence interval

Bold values indicate statistically significant values

Table 5 Results of three models of logistic regression to study the influence of several covariates on the presence of hypoparathyroidism at last visit

	Model 1			Model 2			Model 3		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Gender, male	0.96	0.69–1.33	0.806	0.96	0.68–1.35	0.819	0.78	0.48–1.27	0.320
Age, yr	0.993	0.984–1.002	0.126	0.994	0.985–1.004	0.067	1.00	0.99–1.01	0.953
Date of surgery, >2011	1.19	0.89–1.60	0.224	1.07	0.78–1.46	0.365	1.27	0.81–1.97	0.297
Hospital volume, *n*	0.998	0.996–1.000	0.077	0.998	0.996–1.001	0.133	0.998	0.995–1.002	0.316
Specialized surgical team	**0.43**	**0.31–0.61**	**0.000**	**0.46**	**0.32–0.67**	**0.000**	**0.53**	**0.30–0.94**	**0.029**
Lymph node dissection				**2.15**	**1.52–3.06**	**0.000**	**2.07**	**1.29–3.32**	**0.002**
2-stage thyroidectomy				0.83	0.52–1.32	0.427	**2.16**	**1.20–3.88**	**0.010**
Surgical complications				**1.58**	**1.03–2.42**	**0.036**	1.55	0.87–2.78	0.138
Identification of parathyroid glands				**0.63**	**0.45–0.88**	**0.007**	0.66	0.41–1.06	0.084
Autotransplantation				1.50	0.94–2.42	0.092	0.71	0.37–1.34	0.285
Parathyroid tissue at histology				**1.93**	**1.42–2.63**	**0.000**	**1.84**	**1.24–2.74**	**0.003**
Thyroid cancer				**0.36**	**0.25–0.53**	**0.000**	**0.42**	**0.25–0.71**	**0.001**
Postoperative corrected Ca, mg/dl							**0.22**	**0.17–0.28**	**0.000**

Model 1: Demographic features and hospital data are included as independent variables ($n = 1789$)

Model 2: In addition to the above, surgical and histopathological variables are included ($n = 1764$)

Model 3: Analytical data (postoperative serum calcium) is added to those variables included in model 2 ($n = 1134$)

OR odds ratio, *CI* confidence interval

Bold values indicate statistically significant values

predictor of permanent hypoparathyroidism in previous studies [15, 45]. In the analysis by Sitges-Serra et al. [46], late recovery of parathyroid function was related to higher serum Ca 1 month after surgery. Our data also show that postoperative Ca (24–48 h) is significantly related to the development of permanent hypoparathyroidism. PTH levels after thyroidectomy have been related to recovery of parathyroid function [27, 33, 38, 45–47]. Our results, in a subgroup of 746 patients with available data, also indicate that low postoperative PTH is associated with permanent hypoparathyroidism. Furthermore, higher dosage of postoperative calcitriol was also related to permanent hypoparathyroidism in a subgroup of our patients. Taken together these data suggest that patients with better parathyroid function, i.e., higher values of Ca and PTH, and less need of calcitriol, in the immediate postoperative period retain a greater ability to recover normality in parathyroid function in the long-term.

Our study has been carried out exclusively in the framework of endocrinology clinics in hospitals that have surgeons and endocrinologists who are experts in thyroid disease and, therefore, results cannot be extrapolated to other settings. Although we have harmonized diagnostic criteria, the different participating centers have used different laboratory procedures to measure Ca and PTH. As reported in other studies [48], we defined recovery of parathyroid function by clinical criteria, that is, as cessation of Ca and calcitriol supplementation, without analytical measurement of PTH levels. Unfortunately, our study did not allow us to quantify the number of parathyroid glands identified by surgeon and the number of glands remaining in situ, factors that are of crucial importance in maintaining Ca homeostasis. We did not register information neither on body mass index or clinical symptoms during in the postoperative period. Thus, we cannot relate these parameters with the development of parathyroid hypofunction. On the other side, we could not study other analytical parameters such as 25-hydroxyvitamin D or magnesium. Another limitation is due to the fact that when we introduced a quantitative variable in our logistic regression model (preoperative or postoperative Ca) the sample size was significantly reduced. Main strengths of our study are the high sample size, its multicentric nature, including high and low volume hospitals, with surgical teams with different degrees of expertise, and the use of multivariate analysis to adjust for potential confounders. This study also reflects the practice in real-life, with no potential bias in the outcome as far as surgical teams report mainly their good results.

Our data emphasizes that frequency of permanent hypoparathyroidism among patients with thyroidectomy who attend endocrinology clinics in Spain is not negligible (about 15%). This implies a noteworthy burden of care with lifelong medical supervision and continuous therapy that must be taken into account by health authorities and physicians who treat patients undergoing thyroid surgery, i.e., general practitioners, endocrinologists, and surgeons. Among the risk factors for the development of permanent hypoparathyroidism are not only the expertise of the surgical team, but also the extent and timing of surgery, the presence of parathyroid tissue in surgical specimen and the low postoperative levels of Ca and PTH. The presence of thyroid cancer is associated to lower frequency of permanent hypoparathyroidism.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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