


Late Recovery of Parathyroid Function After Total Thyroidectomy: A Case-Control Study

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ABSTRACT

The clinical characteristics of patients with postoperative hypoparathyroidism who recover parathyroid function more than 12 months after surgery have not been studied. We aimed to evaluate whether the intensity of replacement therapy with calcium and calcitriol is related to the late recovery of parathyroid function. We compared the demographic, surgical, pathological, and analytical features of two groups of patients: cases, i. e., late recovery patients (those who recover parathyroid function > 1 year after thyroidectomy, $n = 40$), and controls, i. e., patients with permanent hypoparathyroidism ($n = 260$). Replacement therapy with calcium and calcitriol was evaluated at discharge of surgery, 3–6 months, 12 months, and last visit. No significant differences were found in clinical, surgical, pathological, or analytical characteristics between cases and

controls. The proportion of cases who required treatment with calcium plus calcitriol at 12 months was significantly lower than that found in controls ($p < 0.001$). Furthermore, daily calcium and calcitriol doses in controls were significantly higher than those in cases at 3–6 months ($p = 0.014$ and $p = 0.004$, respectively) and at 12 months ($p < 0.001$ and $p = 0.043$, respectively). In several models of logistic regression analysis therapy with calcium and calcitriol at 12 months was negatively related to late recovery of parathyroid function. Although delayed recuperation of parathyroid function after total thyroidectomy is uncommon (13%), follow-up beyond 12 months is necessary in patients with postoperative hypoparathyroidism, especially in those whose needs of treatment with Ca and calcitriol are reducing over time.

Introduction

Total thyroidectomy is one of the most performed endocrine operations. Definitive or permanent postoperative hypoparathyroidism is the most common chronic complication of this procedure [1, 2]. However, the time points used to determine when postoperative hypoparathyroidism should be classified as permanent have been a matter of debate among researchers in the last years [3, 4]. Some authors consider that the 12-month after thyroidectomy criterion should be used for this definition [5–9], while others advocate that postoperative hypoparathyroidism should be considered definitive if it lasts more than 6 months [10–14]. Recent international clinical guidelines seem to support this last criterion [2, 15, 16], although some maintain the chronological criterion in 12 months [17].

Nevertheless, it has also been shown that the recovery of parathyroid function is a dynamic phenomenon and various authors have reported anecdotal cases or small groups of patients who recover thyroid function more than 6–12 months after thyroidectomy [18, 19]. These late recovery patients have been barely studied given their low frequency.

Late recovery of parathyroid function might be related to the number of parathyroid glands inadvertently injured or removed during surgery and also to the ability of the glands remaining in situ to recover their function over time [20]. In turn, this recovery of parathyroid function could be influenced by the intensity of the replacement treatment used after surgery [21]. Therefore, our objective has been to assess whether the intensity of therapy with calcium (Ca) and calcitriol during the first year after thyroidectomy is related to late recovery of parathyroid function.

Patients and Methods

Ethics approval and study design

This study was carried out by members of the Thyroid Task Force of the Spanish Society of Endocrinology (SEEN), after receiving the approval of the board of directors of the SEEN and the ethical committee of the Hospital Universitario Ramón y Cajal (Madrid). All the

details on the patients and methodology used are described in detail in a previous report [8]. Briefly, each researcher recruited all patients with total thyroidectomy who attended their outpatient clinic between January 1 and March 31, 2018. Inclusion criteria were: 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.

In every patient demographic data, details on surgical procedure, histopathological data, analytical data on Ca metabolism, and information on therapy with Ca and calcitriol were retrospectively collected. As this was a retrospective study, there was no prior programming of the frequency of visits or blood samplings. Each hospital acted according to its local protocols. All investigators retrieved clinical information at various stages, that is, at discharge from hospital after surgery, 3–6 months after surgery, 12 months after the surgery, and at last visit. Postoperative serum concentrations of Ca and parathyroid hormone (PTH) were defined as the values obtained within the first 48 hours after surgery. For the purpose of this study hypoparathyroidism at discharge was defined as the 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 [2, 17]. We defined hypoparathyroidism at 12 months and definitive hypoparathyroidism as the need for treatment with Ca or calcitriol at 12 months after surgery or at the last visit of the follow-up, respectively. In this study, we considered three intensities of treatment for hypoparathyroidism, that is, oral Ca, calcitriol, and Ca plus calcitriol, the last modality being considered as high intensity therapy. Recovery of parathyroid function was defined from a clinical point of view, that is, as the absence of the need for treatment with Ca and/or calcitriol.

Patients

Three hundred subjects out of 1792 who underwent total thyroidectomy remained hypoparathyroid at 12 months after surgery. Of these, 40 patients (13.3%) recovered parathyroid function throughout the subsequent follow-up until the last visit and were considered cases. The 260 remaining subjects with permanent hypoparathyroidism were considered as controls.

Statistical analysis

For quantitative variables, results are expressed as mean \pm SD for normally distributed data and as median (interquartile range, IQR) for nonparametric data. Adjustment to normal distribution was tested by the Kolmogorov test. Categorical variables are described as ratios or percentages. For comparisons of means between two groups of patients, the Student's *t*-test was used for normally distributed data, and the Mann–Whitney U-test was used for nonparametric data. For ratio comparisons, the chi-square test or Fisher's exact test was used. Several models of logistic regression analysis were used to assess the late recovery of parathyroid function as a function of quantitative and qualitative variables. Since not all the variables were available in all the patients, we have indicated both in the text and tables, the sample size of each variable. All used tests were two-sided and differences were considered significant when $p < 0.05$.

Results

The group of late recovery patients consisted of 37 women and 3 men, aged 49.5 ± 14.1 years, and with a median follow-up of 60.5 (32.3–90.0) months. Demographic, surgical, pathological, and laboratory characteristics of these patients are shown in ► **Table 1**.

When we compared this group with patients with permanent hypoparathyroidism, no significant differences were found in any of the analyzed parameters. Although our study did not evaluate the time of functional recovery in each of the late recovery patients, data in ► **Table 1** show that the time of follow-up was similar in cases and controls [60.5 (32.3–90.0) vs. 58 (28.5–109.5) months, $p = 0.590$].

► **Table 2** and ► **Fig. 1** summarize the intensity of treatments used in the two groups throughout the study. At 12 months the proportion of patients requiring Ca and calcitriol was higher in patients with permanent hypoparathyroidism (71.2%) compared to late recovery patients (37.5%; $p < 0.001$). In addition, patients with permanent hypoparathyroidism required doses of oral elemental Ca and calcitriol significantly higher than those in late recovery patients at 3–6 months ($p = 0.014$ and $p = 0.004$, respectively) and at 12 months after thyroidectomy ($p < 0.001$ and $p = 0.043$, respectively) (► **Table 2**).

We analyzed the proportions of subjects who required zero doses of Ca and calcitriol in the two groups. As can be seen in ► **Table 3**, the proportion of late recovery patients who required zero-dose of calcitriol was found to be significantly higher than that found in patients with permanent hypoparathyroidism both at 3–6 months and at 12 months. We did not find significant differences

► **Table 1** Demographic, surgical, pathological, and analytical features of the two groups of studied patients.

	Late recovery patients (n = 40)		Patients with permanent hypoparathyroidism (n = 260)		p
	n	Value	n	Value	
Demographic features					
Gender (female)	40	37 (92.5)	260	207 (79.6)	0.052
Age (years)	40	49.5 \pm 14.1	259	47.2 \pm 14.8	0.366
Time of follow-up (months)	40	60.5 (32.3–90.0)	260	58 (28.5–109.5)	0.590
Surgical features					
Specialized surgical team	40	35 (90.0)	260	198 (76.2)	0.063
Lymph node dissection	40	15 (37.5)	260	134 (51.5)	0.126
2-stage thyroidectomy	40	2 (5.0)	260	26 (10.0)	0.396
Surgical complications	40	3 (7.5)	260	34 (13.1)	0.441
Identification of parathyroid glands	40	30 (75.0)	260	170 (65.4)	0.281
Autotransplantation	40	4 (10.0)	260	26 (10.0)	1.000
Pathological features					
Parathyroid tissue at histology	39	11 (28.2)	259	87 (33.5)	0.586
Thyroid cancer	40	33 (82.5)	260	190 (73.1)	0.246
Analytical features					
Preoperative Ca (mg/dl)	28	9.42 \pm 0.53	149	9.47 \pm 0.58	0.717
Postoperative Ca (mg/dl)	30	7.73 \pm 0.81	188	7.59 \pm 0.72	0.376
Postoperative PTH (pg/ml)	14	4.9 (2.5–33.6)	129	6.1 (3.0–10.5)	0.643
Undetectable PTH	14	1 (7.1)	129	10 (7.8)	1.000

Data are the number of patients (percentage), mean \pm SD for normally distributed data and median (interquartile range) for nonparametric data. Ca: Calcium; PTH: Parathyroid hormone.

► **Table 2** Distribution of the treatment modalities used for hypoparathyroidism throughout the study period in the groups of studied patients.

	Late recovery patients (n = 40)		Patients with permanent hypoparathyroidism (n = 260)		p *
	n	Value	n	Value	
At discharge					
Treatment	40		260		0.290
Oral Ca		7 (17.5)		53 (20.4)	
Calcitriol		1 (2.5)		1 (0.4)	
Ca and calcitriol		32 (80.0)		206 (79.2)	
Dose of oral Ca (g/day)	36	3.0 (2.0–3.0)	246	3.0 (2.0–3.0)	0.479
Dose of calcitriol (µg/day)	33	0.50 (0.25–0.50)	196	0.50 (0.50–1.75)	0.063
At 3–6 months					
Treatment	40		260		0.093
Oral Ca		13 (32.5)		49 (18.8)	
Calcitriol		3 (7.5)		13 (5.0)	
Ca and calcitriol		24 (60.0)		198 (76.2)	
Dose of oral Ca (g/day)	34	1.5 (1.0–2.5)	231	2.0 (1.5–3.0)	0.014
Dose of calcitriol (µg/day)	26	0.25 (0.25–0.50)	200	0.50 (0.25–0.50)	0.004
At 12 months					
Treatment	40		260		<0.001
Oral Ca		18 (45.0)		52 (20.0)	
Calcitriol		7 (17.5)		23 (8.8)	
Ca and calcitriol		15 (37.5)		185 (71.2)	
Dose of oral Ca (g/day)	32	1.0 (1.0–1.5)	226	1.5 (1.0–3.0)	<0.001
Dose of calcitriol (g/day)	20	0.43 (0.25–0.50)	195	0.50 (0.25–0.50)	0.043
At last visit					
Treatment	40		260		
Oral Ca		0		51 (19.6)	
Calcitriol		0		28 (10.8)	
Ca and calcitriol		0		181 (69.6)	
Dose of oral Ca (g/day)		–	225	1.5 (1.0–2.5)	
Dose of calcitriol (g/day)		–	204	0.50 (0.25–0.50)	

Data are the number of patients (percentage) in the variable that represents the treatment modality, and the median (interquartile range) for nonparametric data (doses of oral elemental Ca and calcitriol). The medians (interquartile range) of the doses of oral Ca and calcitriol have been calculated only in patients with available information on these values, excluding patients who required zero doses of Ca or calcitriol. The sample size for each of these parameters is indicated in the column headed by n. Ca: Calcium. * Statistical significance compared to the group of late recovery patients.

between both groups of patients with regard to the percentages of patients requiring zero-dose of oral Ca (► **Table 3**).

Several models of logistic regression analysis were performed to study the dependence of the variable late recovery of parathyroid function as a function of several independent variables, including therapeutic, demographic, surgical, and pathological variables (► **Table 4**). Results showed that the need for high intensity therapy at 12 months (Ca and calcitriol) was negatively and significantly related to late recovery of parathyroid function both in the univariate analysis and in different multivariate models. We also found

that late recovery was negatively associated to lymph node dissection ($p = 0.015$) and positively associated to the presence of thyroid cancer ($p = 0.005$) (► **Table 4**, model 5).

Discussion

This study was performed to characterize a group of 40 out of 300 patients (13.3%) with hypoparathyroidism 12 months after thyroidectomy who were able to recuperate parathyroid function after this time, that is, that behaved as late recovery patients. Our data

► **Table 3** Proportion of subjects who required zero doses of oral calcium and calcitriol in the two groups.

	Patients requiring zero-dose of oral Ca (%)		Patients requiring zero-dose of calcitriol (%)	
	Late recovery patients (n = 40)	Patients with permanent hypoparathyroidism (n = 260)	Late recovery patients (n = 40)	Patients with permanent hypoparathyroidism (n = 260)
At discharge	2.5	0.4	7.5	20.4
At 3–6 months	7.5	5.0	32.5*	18.0
At 12 months	17.5	8.8	45.0**	20.0

* $p=0.047$; ** $p<0.001$.

► **Table 4** Results of five models of logistic regression to study the influence of high intensity therapy (Ca and calcitriol) at 12 months on the development of late recovery of parathyroid function.

Model	Independent variables included in the model	n	Significant variables in the model	OR	95% CI	p
1	HIT 12 mo (univariate)	300	HIT 12 mo	0.24	0.12–0.49	<0.001
2	HIT 12 mo and therapeutic features	300	HIT 12 mo	0.20	0.08–0.48	<0.001
3	HIT 12 mo, therapeutic and demographic features	299	HIT 12 mo	0.21	0.09–0.52	0.001
4	HIT 12 mo, therapeutic, demographic and surgical features	299	HIT 12 mo	0.24	0.10–0.59	0.002
5	HIT 12 mo, therapeutic, demographic, surgical and pathological features	297	HIT 12 mo	0.21	0.08–0.55	0.002
			Lymph node dissection	0.33	0.13–0.80	0.015
			Thyroid cancer	4.80	1.60–14.46	0.005

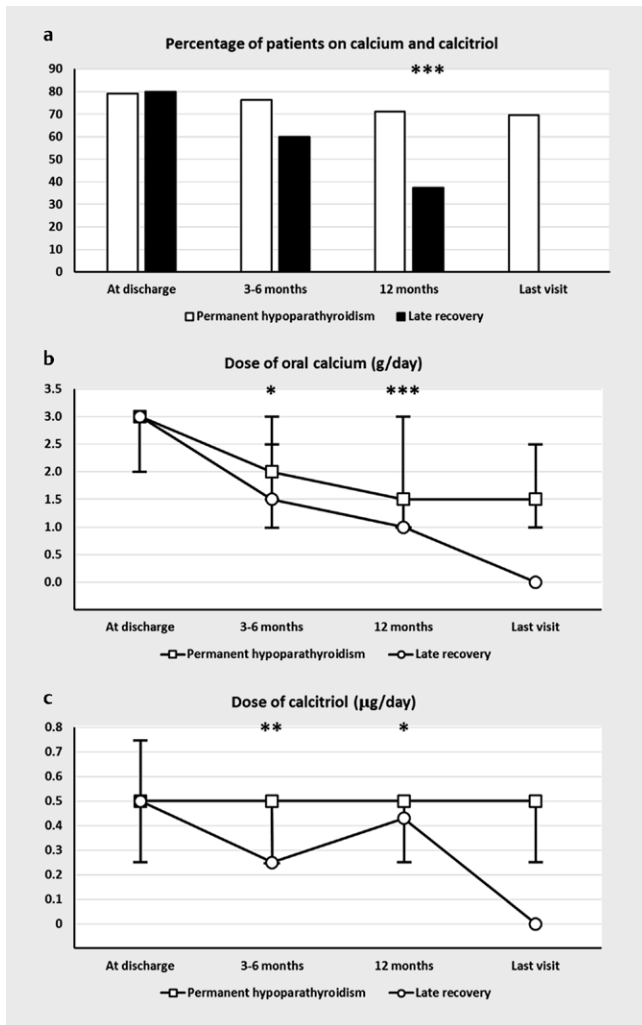
HIT 12 mo: High intensity therapy with Ca and calcitriol at 12 months. Therapeutic features: high intensity therapy with Ca and calcitriol at discharge, and at 3–6 months. Demographic features: gender, age (years) and time of follow-up (months). Surgical features: specialized surgical team, lymph node dissection, 2-stage thyroidectomy, surgical complications, identification of parathyroid glands and autotransplantation. Pathological features: parathyroid tissue at histology and thyroid cancer.

show that patients who recover parathyroid function after the first year of thyroidectomy did not receive more intensive treatment than patients who eventually develop definitive hypoparathyroidism. In fact, our patients in the late recovery group were treated with lower doses of both Ca and calcitriol, during the second semester after thyroidectomy. The percentage of patients requiring oral Ca and calcitriol treatment at 3–6 months and at 12 months was also lower in the late recovery group compared to the permanent hypoparathyroidism group.

To date, some studies have reported a few cases of late recovery of parathyroid function in postsurgical hypoparathyroidism, but we have not found any that define the demographic, surgical or clinical characteristics of these patients. The most extreme cases in terms of time elapsed since surgery were reported by Cusano et al. [22] in 4 patients who recover parathyroid function 8–16 years after surgery. This study was performed in 3 patients with parathyroid surgery and one patient with thyroidectomy for Graves' disease, and all of them in the context of treatment with exogenous

PTH(1–84). In patients undergoing total thyroidectomy for thyroid disease, Ritter et al. [18] reported that 9 out of 189 patients (4.8%) with low PTH after thyroidectomy showed resolution of hypoparathyroidism between 6–12 months. Of the 33 patients with hypoparathyroidism studied by Youngwirth et al. [23], 24 returned to normal parathyroid function within 1 week of surgery, and 3 (9.1%) more at their last known follow-up (at least 1 year after intervention).

In an interesting study, Villarroya-Marquina et al. [7] analyzed 142 patients with protracted hypoparathyroidism, defined as hypoparathyroidism 1 month after surgery. Of them, 21 (14.8%) recovered parathyroid function within 6–12 months (intermediate recovery) and 12 (8.5%) after 1-year follow-up (late recovery). In this relevant study the number of parathyroid glands remaining in situ (PGRIS), high-normal serum Ca at one-month, detectable PTH and cancer were clinical and metabolic variables influencing positively a late recovery. The study by Kim et al. [19] was conducted in 22 patients with definitive hypoparathyroidism, defined as serum



► **Fig. 1** Intensity of therapy depicted by the percentage of patients who required oral calcium and calcitriol treatment (a) throughout the study (open rectangles, permanent hypoparathyroidism patients; black rectangles, late recovery patients), and by the dose of oral calcium (b) and calcitriol (c) throughout the study in the two groups of studied patients (squares, permanent hypoparathyroidism patients; circles, late recovery patients). Abscissa scale: time points in relation to thyroidectomy. Ordinate scale: Percentage of patients (a) and median of doses of oral calcium (g/day) (b) and calcitriol (µg/day) (c). In b and c median is the circle or the square. The bottom and top 'whiskers' are the lower (Q1) and upper (Q3) quartiles, respectively. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (permanent hypoparathyroidism patients vs. late recovery patients).

levels of PTH < 15 pg/ml for at least 1 year. Recovery from permanent hypoparathyroidism, defined as return to normal serum levels of PTH and Ca without exogenous supplementation, was observed in 5 patients (22.7%, late recovery).

Possible mechanisms for the delayed recovery of parathyroid function have not been fully elucidated. It is reasonable to think that the slow but steady recovery of blood flow via neovascularization occurring over the surface area of the remaining parathyroid glands plays a major role. This is in direct relation to the number of PGRIS, a value that has been considered a predictor of parathyroid function recovery by some authors [7, 20]. Despite we were unable to analyze the number of PGRIS in this study, we assessed the

surgical identification of the parathyroid glands or the presence of parathyroid tissue in the specimen and none of them were related to late recovery of parathyroid function. In agreement with other authors [20, 21, 24], parathyroid autotransplantation was not related to functional recovery.

The late recovery of parathyroid function could also be related to the pre- and postoperative PTH levels. It has been suggested that a better preoperative baseline parathyroid function, a higher absolute value of postoperative PTH and a lower drop in serum PTH in the immediate postoperative period would reflect less intraoperative parathyroid gland injury [6, 9, 11, 25]. Sitges-Serra et al. [26] showed that high-normal serum calcium and detectable PTH concentrations at 1 month after thyroidectomy were associated with better outcome of protracted hypoparathyroidism. A further study of the same group [7] suggested that serum Ca concentration at 1 month was associated with late recovery of parathyroid function, and that this was influenced by higher doses of Ca and calcitriol being prescribed at discharge.

The protective influence of high-normal Ca concentrations during the first weeks after surgery has been accounted for by a parathyroid splinting effect. According to this hypothesis, high-normal Ca levels would allow the injured, but viable, glands to rest, which would favor their long-term recovery [7]. If we apply this hypothesis to our patients, we would expect that those subjects who have received more intense treatment with Ca and calcitriol during the first year would have a greater probability of late recovery of parathyroid function. However, we obtained the opposite result; therefore, we think that this hypothesis, although applicable to early recovery, is not valid for late recovery. Besides, our study was only able to analyze Ca and PTH levels in a fraction of patients in the immediate postoperative period (24–48 h) and not in the first month or throughout the first year after surgery.

The most relevant finding of this study has therefore been the negative relationship between treatment intensification and recovery of parathyroid function. This association does not imply causality between treatment and recovery since our retrospective study cannot demonstrate any causal relationships. However, this finding allows us to speculate on the possibility that there is an association between the intensity of treatment and the physiological phenomena that lead to the functional reactivation of the synthesis and secretion of PTH. In fact, it is known that calcitriol exerts a negative regulation of parathyroid function [27, 28]. Based on this, it might be thought that high and sustained doses of calcitriol could somehow prevent or delay functional recovery. On the contrary, it could also be speculated that, in patients with lower intensity treatment, different episodes of hypocalcemia throughout the natural history of the disease would progressively stimulate the numb glands and bring on their final reactivation. Reduced supplement requirements might decrease the inhibitory action of Ca and vitamin D on parathyroid cells, resulting in increasing PTH secretion. In turn, PTH could exert trophic effects on parathyroid tissue, triggering pathways leading to enhanced vascularization as suggested by Cusano et al. [22].

Lymph node dissection was more often found in patients with permanent hypoparathyroidism versus patients with late recovery (51.5 vs. 37.5%), but the proportion of patients with thyroid cancer were higher in the group of patients who recover parathyroid

function (82.5 vs. 73.1%). Although outside the scope of this study, these data suggest that lymph node dissection hinders functional recovery, probably related to greater parathyroid injury and difficulty in neovascularization in patients with lymphadenectomy, as reported by others [7, 19, 20]. Interestingly, the presence of cancer on histology is positively associated with late recovery, perhaps related to more careful surgical manipulation than in patients with benign disease [7]. In addition, these data are consistent with those obtained in the total cohort of 1792 patients previously reported in our initial study [8]. However, in this case-control study, none of these associations reached the level of statistical significance.

We believe that our results have relevance in the clinical care of patients undergoing treatment for chronic hypoparathyroidism. The diagnosis of this serious condition entails impact on the patient's quality of life, economic burden for the health system, and a lifelong medical follow-up with drug treatment and the possibility of adverse effects such as hypercalcemia and impaired kidney function [29, 30]. Our data suggest that in patients with low needs for replacement therapy with Ca and calcitriol, a trial of medication withdrawal can be performed with close monitoring of symptoms and laboratory values. In those who remain asymptomatic and normocalcemic, that is, late recovery patients, a lifetime medication that is not without adverse effects might be withdrawn.

The main limitation of this study is its retrospective nature. For this reason, we lack some variables that would have been of interest in our analysis (Ca and PTH concentrations in different follow-up times, number of PGRIS, vitamin D status). The doses of Ca and calcitriol were not available in all study subjects. We acknowledge that Ca and calcitriol treatment may not be more intensive therapy than calcitriol alone in some patients as the need for Ca replacement may be dependent in part on dietary Ca intake. However, this is a multicentric and nation-wide study with data from real clinical practice. The prevalence of definitive hypoparathyroidism in our cohort was higher than that reported in other studies. This may be due to the fact that this study was carried out in the setting of clinical practice of endocrinology clinics, where it is foreseeable that gather patients with greater complications and needs of follow-up after thyroidectomy. We must acknowledge that the possibility that the association of lower doses with the discontinuation of treatment is reverse causation, that is, patients with better residual parathyroid function and/or on the way to recovery need less medication. The main strength of the study lies in its sample size, since this is the first study including 40 patients with late recovery of parathyroid function, and, to our knowledge, it is the first survey dealing with the clinical characterization of patients who recover parathyroid function after one year after thyroidectomy and with the putative influence of replacement therapy in this late recovery process.

In few words, two theories have been raised to explain the relationship between replacement therapy, and the recovery of parathyroid function after an inadvertent injury during thyroidectomy. According to some authors, intensive treatment with Ca and calcitriol allows the parathyroid glands to be kept in a silent or numb state (splinting of the parathyroid glands), and this would favor functional recovery [7]. Other authors believe that it is convenient to maintain Ca values at the lower limit of the reference interval or slightly below this limit to avoid hypercalcemia and stimulate the

parathyroid glands for the production of PTH and avoid its numbness [30, 31]. Our data, although with limitations, due to the lack of serum levels of Ca and calcitriol throughout time in the studied patients, do not support the former and seem to favor the latter.

In conclusion, although most patients with hypoparathyroidism lasting more than 12 months will continue to require Ca and calcitriol supplements for life, there is a fraction of patients (13.3% in our cohort) who were able to discontinue medical therapy after 12 months, especially in patients whose needs of treatment with Ca and calcitriol were reducing over time. This may reflect recovery of parathyroid function, although other possibilities exist. Further studies are needed to fully characterize these late recovery patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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