Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism

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Abstract

Objective: Hypoparathyroidism is a common complication after thyroidectomy. It is not yet possible to predict in which patients hypoparathyroidism will persist. We aim to determine whether a decrease in PTH levels, measured at the first postoperative day, can identify patients with a high risk for persistent hypoparathyroidism one year after thyroidectomy.

Design: Prospective multi-center cohort study.

Methods: Patients undergoing total or completion thyroidectomy were included. We measured PTH levels preoperatively and on the first postoperative day. Primary outcome is the proportion of patients with persistent hypoparathyroidism, defined as the need for calcium supplementation one year after surgery.

Results: We included 110 patients of which 81 were used for analysis of the primary outcome. At discharge 72.8% of patients were treated with calcium supplementation. Persistent hypoparathyroidism was present in 14 patients (17.3%) at one-year follow-up, all of them had a decrease in PTH >70% at the first postoperative day. These 14 were 43.8% of the 32 patients who had such a decrease. In the group of 49 patients (59.8%) without a PTH >70% decrease, none had persistent hypoparathyroidism one year after surgery (P -value <0.001). A decrease of >70% in PTH levels had a sensitivity of 100.0% (95% CI: 85.8–100.0%), a specificity of 73.1% (95% CI: 62.5–83.7%) and an area under the curve of 0.87 (95% CI: 0.79–0.94) to predict the risk for persistent hypoparathyroidism.

Conclusion: In our study a decrease in PTH levels of >70% after total or completion thyroidectomy is a reliable predictor for persistent hypoparathyroidism, and this should be confirmed in larger cohorts.

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Introduction

Surgical treatment of both benign and malignant thyroid diseases often necessitates total thyroidectomy. This procedure is considered safe, but has specific postoperative complications such as hoarseness due to damage of the recurrent nerves and hypoparathyroidism

because of surgery-related factors such as inadvertent devascularization, bruising or accidental removal of parathyroid glands. Clinical signs of hypocalcaemia are perioral numbness, paraesthesia and muscle cramps. Severe hypocalcaemia can cause seizures,

spasms and cardiac arrhythmias. Patients are therefore routinely monitored for clinical signs and symptoms of hypocalcaemia and serum calcium levels are measured at set times. Postoperative hypocalcaemia is treated with oral or intravenous calcium supplementation and, in some cases, additional vitamin D supplementation (1). In most cases, parathyroid function will recover within weeks after surgery and calcium levels will normalize (2, 3).

However, most studies show that less than 5% of the patients will develop persistent hypoparathyroidism (persistent HypoPT, defined as the persistent need for calcium supplementation 1 year after surgery) (4, 5, 6, 7). But higher rates of up to 14% have been reported (8). Given the rates of patients with permanent voice problems and other postoperative complications, the surgical risk of a total thyroidectomy may be higher than what surgeons anticipate.

Persistent HypoPT impairs quality of life (9) of an otherwise relatively healthy population and poses a burden of disease (10). It may even be associated with an increased risk of death (11). Therefore, early identification of high-risk patients allows clinicians not only to inform patients, but also to schedule tailored postoperative outpatient follow-up visits. Patients with a low risk for persistent HypoPT can be offered less visits and blood withdrawals and an early reduction of calcium supplementation, being favorable from both patient and cost-effective perspectives. Current predictive factors for post-surgical hypoparathyroidism include perioperative calcium and parathyroid hormone (PTH) levels as well as surgical factors (12, 13). Serum PTH concentration obtained between 4 and 24 h postoperatively is currently the best parameter to predict postoperative hypocalcaemia (4, 14, 15, 16, 17). In this multicenter prospective cohort study our primary aim is to determine if a decrease in PTH levels, measured at the first postoperative day, is able to identify patients with a high risk for persistent HypoPT 1 year after thyroidectomy.

Methods

Patients and data collection

Patients were recruited between March 2014 and March 2016 at one University Medical Center (Erasmus MC, Rotterdam, the Netherlands) and one local hospital (Reinier de Graaf Gasthuis, Delft, the Netherlands). All adult patients undergoing a total thyroidectomy or a completion thyroidectomy were included. Patients were excluded if they were unable to provide informed

consent or if they were suffering from disorders of calcium homeostasis. Patients who underwent a second head and neck surgery (e.g. central cervical lymph node dissection) or patients who underwent external beam radiation therapy of the neck (18) within 1 year of the index procedure were excluded from the study. Baseline characteristics such as gender, age, preoperative diagnosis, medical history and blood values were obtained at the outpatient clinic. Preoperative calcium, albumin, PTH and vitamin D serum levels were measured. All patients were admitted overnight, according to standard postoperative care in both hospitals. Following surgery, blood samples were drawn on the day of surgery (6 h postoperatively) and on the first postoperative day (within 24 h postoperatively). Postoperative calcium, albumin and PTH levels were assessed. Primary measurement for the analysis is the PTH level on the first postoperative day. This enables easy implementation in daily practice and is shown to accurately predict direct postoperative hypocalcaemia. Standard study follow-up including laboratory screening is performed at 2 weeks and 1 year postoperatively. Other outpatient visits were scheduled according to the discretion of the treating medical specialist. Approval was obtained from the Medical Ethical committee of Erasmus MC (MEC-2013-233). The STROBE guidelines for reporting observational studies were used (Supplementary file 1, see section on [supplementary materials](#) given at the end of this article).

Laboratory findings and treatment of hypocalcaemia

Serum calcium levels were adjusted for albumin levels according to the formula: adjusted total calcium (mmol/L) = measured calcium (mmol/L) + $(0.025 \times 40 - (\text{albumin (g/L)}))$. The reference value for calcium is 2.20–2.65 mmol/L. The reference value for PTH is 1.4–7.3 pmol/L. Hypocalcaemia was treated according to the local calcium supplementation protocol with calcium carbonate and vitamin D. According to the hospitals protocol, a corrected calcium level lower than 2.20 mmol/L warrants calcium supplementation. If calcium levels remain beneath 2.20 mmol/L for 2 consecutive days, supplementation with active vitamin D is started.

Reference change value

The reference change value (RCV) is an objective tool for the assessment of the significance of differences in serial

results from an individual, based on intra-individual biological and analytical coefficient of variation. To assess the within-subject biological variation, we used the most recent database on biological variation by Ricos *et al.* (19). The RCV for PTH is calculated with the following formula (20):

$$\text{RCV} = \sqrt{2} \times Z_{\alpha} \times \sqrt{\text{CV}_A^2 + \text{CV}_I^2}$$

where:

Z_{α} is the normal probability distribution function at the desired P -value;

CV_A is the analytical variation and

CV_I is the within-biological variation.

For $\alpha=0.05$, the normal probability distribution function is 1.96. The analytical variation in our lab is 2.2%, the within-biological variation for PTH is 25.3% (19), which is an assumption obtained from the table of Ricos *et al.* This resulted in a RCV of 70%. In this article, we define patients with a PTH level change of more than the RCV (70%) as patients with a 'significant PTH change'. This is referred to as a decrease in PTH >70% in the text. The change in PTH levels was calculated using the following formula: PTH change = ((pre-operative PTH – post-operative PTH)/pre-operative PTH) × 100%.

Outcome measurements

Primary outcome of the study was the proportion of patients with persistent HypoPT 1 year after surgery, when comparing the group with a decrease in PTH >70% vs the group without this decrease in PTH levels on the first postoperative day. Persistent HypoPT was defined as the persisting need for calcium supplementation 1 year after thyroid surgery and inability to be tapered off supplementation. Tapering was protocolized, yet the initiation and time frame was left to the discretion of the treating physician. The 1-year moment was chosen as, in daily practice, not all patients are tapered off calcium supplementation by their physician within the first 6 months after surgery and because of expected restoration of parathyroid function within the first year after surgery. Secondary outcomes were postoperative outcomes such as histologic diagnosis, hospital stay and follow-up data regarding the serum calcium, PTH levels, calcium- and active vitamin D supplementation and the diagnostic accuracy of the RCV.

Statistical analysis

Data were assessed for normality using the Shapiro–Wilk normality test. Continuous variables were expressed as means and s.d. or medians with interquartile ranges as appropriate. Categorical variables were described as count and percentages. Differences between groups were analyzed with independent samples t -test or the Mann–Whitney U test for continuous variables and Pearson Chi-square test with continuity correction for categorical variables. To determine the diagnostic accuracy of a change in postoperative PTH levels, we calculated the area under the curve (AUC). The sensitivity, specificity and overall accuracy of PTH change in predicting persistent HypoPT were calculated. A sample size calculation was performed based on a sensitivity of 100% (as it is undesirable to miss potential cases) and a specificity of 80%, a maximum acceptable clinical width of the 95% CI of 10%. Assuming a prevalence of 5% in our study group, we would need to include 65 patients, in case of a prevalence of 10%: 69 cases and with 20%: 77 cases (21). Therefore our sample of 81 cases can be considered sufficient. Two-tailed $P < 0.05$ values were considered statistically significant. Statistical analyses were performed with IBM SPSS version 24.0.

Results

Study population and baseline characteristics

We included 110 patients in this study between April 2014 and April 2016, out of 172 patients assessed for eligibility (Fig. 1). For the analysis of the primary outcome, a total of 20 patients were excluded from the study due to missing data on PTH decrease at the first postoperative day and another nine because of missing data on the primary outcome, leading to a final study cohort of 81 patients. Demographic, clinical and laboratory data of the final study cohort are summarized in Table 1. The median age of our final study cohort was 53.0 (41.0–65.0) years and 72.8% were female. Total thyroidectomy was performed in 79.0% of the patients, completion thyroidectomy in 21.0% and 33.3% underwent a concomitant cervical lymph node dissection. The indication for surgery was carcinoma in 59.8%, multi-nodular goiter in 18.5%, Graves' disease in 16.0% of patients and 6.2% for other indications.

Figure 1

Flowchart of patient enrollment.

Table 1 Demographic, clinical and laboratory data of the total study cohort ($n = 81$). Data are expressed as a percentage or as median (IQR).

Clinical values	<i>n</i> (%)
Sex	
Male	22 (27.2%)
Female	59 (72.8%)
Age (years)	53.0 ((41.0–65.0))
ASA-classification	
I	21 (25.9%)
II	54 (66.7%)
III	6 (7.4%)
Preoperative serum calcium	2.24 ((2.19–2.30))
Preoperative serum vitamin D	48.0 ((30.3–66.0))
Preoperative serum PTH	4.7 ((3.5–5.7))
Indication for surgery ^a	
Papillary carcinoma	40 (49.9%)
Multi nodular goiter	15 (18.5%)
Graves	13 (16.0%)
Follicular carcinoma	4 (4.9%)
Medullary carcinoma	2 (2.5%)
Hürthle cell carcinoma	2 (2.5%)
Other	5 (6.2%)
Surgery	
Total	64 (79.0%)
Completion	17 (21.0%)
CLND ^b	27 (33.3%)
CCLND	26 (32.1%)
LCLND	22 (27.2%)

Serum calcium in mmol/L; serum PTH in pmol/L; serum vitamin D in nmol/L.

^aIndication for surgery as diagnosed pre-operatively; ^bConcomitant cervical lymph node dissection (CLND); CCLND, Central CLND (level VI); LCLND, Lateral CLND (level II–IV).

Decline of postoperative PTH levels and risk of persistent HypoPT

In Table 2, patient characteristics are summarized and stratified by decrease in PTH >70%. A total of 32 patients (39.5%) had a decrease in PTH >70% on the first postoperative day. Besides age, there were no statistically significant differences at baseline in patients with this decrease in PTH vs patients without this PTH decrease (48.0 ((34.5–62.0)) vs 59.0 ((49.5–66.3)) years of age, P -value=0.045). Persistent HypoPT was present in 14 patients (17.3%) at 1-year follow-up, all of them had a decrease in PTH >70% at the first postoperative day. These 14 were 43.8% of the 32 patients who had such a decrease (Table 3). In the group of 49 patients (59.8%) without a PTH >70% decrease, none had persistent HypoPT 1 year after surgery (P -value <0.001). A decrease of >70% in PTH levels had a sensitivity of 100.0% (95% CI 85.8–100.0%), a specificity of 73.1% (95% CI 62.5–83.7%) and an area under the curve of 0.87 (95% CI 0.79–0.94) to predict the risk for persistent HypoPT.

Postoperative outcomes and follow-up

Postoperative outcomes and follow-up data regarding the serum calcium, PTH levels and calcium and vitamin D supplementation are summarized in Table 3. At discharge, 59 patients (72.8%) used calcium supplementation and 30 patients (37.0%) used vitamin D supplementation in addition to calcium supplementation. Both calcium and vitamin D supplementation were more frequent in patients with a decrease in PTH >70% (respectively 61.2% vs 90.9%, P -value=0.004 and 24.5% vs 56.3%,

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Table 2 Demographic, clinical and laboratory data of the total study cohort according to PTH change. Data are expressed as a percentage or as median (IQR).

Clinical values	No decrease PTH>70% (n = 49)	Decrease PTH>70% (n = 32)	P-value
Sex			0.091
Male	10 (20.4%)	12 (37.5%)	
Female	39 (79.6%)	20 (62.5%)	
Age (years)	48.0 ((34.5–62.0))	59.0 ((49.5–66.3))	0.045
ASA-classification			0.860
I	13 (26.5%)	8 (25.0%)	
II	33 (67.3%)	21 (66.6%)	
III	3 (6.2%)	3 (9.4%)	
Preoperative serum calcium	2.24 ((2.18–2.31))	2.23 ((2.19–2.32))	0.877
Preoperative serum vitamin D	50.0 ((30.8–67.5))	44.0 ((28.8–64.5))	0.718
Preoperative serum PTH	4.6 ((3.5–5.4))	4.8 ((3.5–6.0))	0.292
Indication for surgery ^a			0.650
Papillary carcinoma	23 (46.9%)	17 (53.1%)	
Multi nodular goiter	9 (18.4%)	6 (18.8%)	
Graves	7 (14.3%)	6 (18.8%)	
Follicular carcinoma	3 (6.1%)	1 (3.1%)	
Medullary carcinoma	1 (2.0%)	1 (3.1%)	
Hürthle cell carcinoma	1 (2.0%)	1 (3.1%)	
Other	5 (10.2%)	0 (0.0%)	
Surgery			0.338
Total	37 (75.5%)	27 (84.4%)	
Completion	12 (24.5%)	5 (15.6%)	
CLND ^b	14 (28.6%)	13 (40.6%)	0.261
CCLND	13 (26.5%)	13 (40.6%)	0.184
LCLND	10 (20.4%)	12 (37.5%)	0.091

Serum calcium in mmol/L; serum PTH in pmol/L; serum vitamin D in nmol/L.

^aIndication for surgery as diagnosed pre-operatively; ^bConcomitant cervical lymph node dissection (CLND); CCLND, Central CLND (level VI); LCLND, Lateral CLND (level II–IV).

P -value=0.004). This difference remained present over time up till 1 year of follow-up.

Patients with this PTH decrease tend to have lower serum calcium levels at the day of surgery, the first postoperative day and 1 year postoperatively. This difference was not present at 2 weeks after surgery. A difference in PTH serum levels was seen at each time point. We also demonstrated that patients with this PTH decrease had a longer hospital stay (3.0 ((3.0–3.0)) vs 4.0 ((3.0–6.5)), P -value=0.001) and more laboratory visits in the first year after surgery (3.5 ((2.0–5.0)) vs 7.0 ((4.0–8.0)), P -value $\leq$ 0.001). Patients with a decrease in PTH >70% but without persisting hypoparathyroidism needed a median time of 3.0 ((1.0–8.0)) months to taper off their calcium and/or vitamin D medication.

Data regarding patients with persistent HypoPT are summarized in Table 4. All cases had a PTH level at the first postoperative day below the reference value of 1.4 pmol/L. At discharge, all patients with persistent HypoPT were prescribed oral calcium supplementation and ten patients were prescribed vitamin D in addition to the oral calcium supplementation. At 2 weeks of follow-up,

another two patients were prescribed vitamin D because of persisting low serum calcium levels. One patient was readmitted because of a symptomatic hypocalcaemia at the 17th postoperative day and was prescribed vitamin D in addition to his oral calcium. At 1 year of follow-up, all patients with persistent HypoPT used oral calcium supplementation, dosage varying from 500 mg to 4000 mg daily and ten patients used vitamin D with dosage varying from 0.25 μ g to 2.5 μ g daily. In six patients with persistent HypoPT, PTH levels were within the normal range after 1 year.

The graphs in Fig. 2 show this relation between PTH levels, corrected calcium levels and whether calcium supplementation was provided at the first postoperative day, 2 weeks postoperatively and 1 year postoperatively. It shows the normalization of the serum PTH levels and corrected calcium levels over time. However, patients with persistent HypoPT, defined as the patients with a persisting need of calcium supplementation, tend to stay below the limit of normal or in the low normal range of serum calcium and PTH levels after 1 year.

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Table 3 Postoperative outcomes and follow-up data according to PTH decrease. Data are expressed as a percentage or as median (IQR).

Clinical values	Total cohort (n = 81)	No decrease PTH >70% (n = 49)	Decrease PTH >70% (n = 32)	P-value
Day of surgery				
Serum calcium	2.16 ((2.09–2.23))	2.16 ((2.10–2.24))	2.11 ((2.08–2.22))	0.046
Serum PTH (nine missing)	1.5 ((0.6–2.7))	2.5 ((1.5–3.8))	0.5 (0.3–0.8)	<0.001
Oral calcium supplementation	17 (21.0%)	8 (16.3%)	9 (28.1%)	0.202
IV calcium supplementation	16 (19.8%)	7 (14.3%)	9 (28.1%)	0.126
First postoperative day				
Serum calcium	2.12 (2.05–2.21)	2.14 (2.08–2.22)	2.06 (1.93–2.17)	<0.001
Serum PTH	1.6 (0.7–2.8)	2.4 (1.7–3.2)	0.6 (0.3–0.9)	<0.001
Oral calcium supplementation	59 (71.6%)	29 (59.2%)	29 (90.6%)	0.002
IV calcium supplementation	16 (19.8%)	3 (6.1%)	13 (40.6%)	<0.001
Vitamin D supplementation	8 (9.9%)	4 (8.2%)	4 (12.5%)	0.522
Discharge				
Calcium supplementation	59 (72.8%)	30 (61.2%)	29 (90.9%)	0.004
Vitamin D supplementation	30 (37.0%)	12 (24.5%)	19 (56.3%)	0.004
Histologic diagnosis ^a				0.868
Benign	32 (39.5%)	19 (38.8%)	13 (40.6%)	
Malignant	50 (61.0%)	30 (61.2%)	20 (60.6%)	
Hospital stay (days)	3.0 (3.0–4.0)	3.0 (3.0–3.0)	4.0 (3.0–6.5)	0.001
2 weeks postoperative				
Serum calcium (one missing)	2.28 (2.17–2.33)	2.27 (2.19–2.33)	2.29 (2.15–2.31)	0.562
Serum PTH (ten missing)	1.9 (0.9–3.8)	2.9 (1.7–4.6)	0.9 (0.5–1.9)	<0.001
Calcium supplementation	50 (61.7%)	21 (42.9%)	29 (90.6%)	<0.001
Vitamin D supplementation	27 (33.3%)	7 (14.3%)	20 (62.5%)	<0.001
1 year postoperative				
Persistent hypoparathyroidism	14 (17.3%)	0 (0.0%)	14 (43.8%)	<0.001
Serum calcium (12 missing)	2.22 (2.13–2.27)	2.25 (2.16–2.29)	2.17 (2.06–2.25)	0.001
Serum PTH (12 missing)	2.8 (2.0–4.5)	3.1 (2.0–4.9)	2.5 (1.4–2.9)	<0.001
Calcium supplementation	14 (17.3%)	0 (0.0%)	14 (43.8%)	<0.001
Vitamin D supplementation	10 (12.3%)	0 (0.0%)	10 (31.3%)	<0.001
Number of lab visits	4.0 (3.0–7.0)	3.5 (2.0–5.0)	7.0 (4.0–8.0)	<0.001

Serum calcium in mmol/L; serum PTH in pmol/L; serum vitamin D in nmol/L. Oral calcium supplementation with calcium carbonate; Oral vitamin D supplementation with alfacalcidol.

^aDiagnosis after histopathological examination.

Discussion

This study evaluates the use of PTH levels obtained at the first postoperative day after total or completion thyroidectomy in predicting the risk for persistent HypoPT 1 year after surgery. It shows that a decrease in PTH >70%, measured at the first postoperative day after total or completion thyroidectomy, predicts persistent HypoPT. Also, the absence of this PTH change excludes the development of persistent HypoPT. This is, to the best of our knowledge, the first study that uses the RCV to assess a change (and not just a biological variation) of PTH levels in predicting persistent HypoPT after thyroidectomy. Calculation of the reference change value takes the biological and analytical variation into account when interpreting the change in PTH levels.

Our results are supported by other studies showing that a decrease in PTH levels is likely to predict persistent

HypoPT. Wang *et al.* evaluated the postoperative 24-h PTH decline in 110 patients undergoing a total or completion thyroidectomy (22). They showed that a 24-h PTH level decline of more than 88.4% is an accurate predictor of persistent HypoPT with a sensitivity of 100%, specificity of 83% and a AUC of 0.965 (95% CI 0.925–1.000). In another study, Suwannasarn *et al.* even suggested that a 72% decline in PTH levels 4 h after surgery could identify patients with a high risk for persistent HypoPT with a 100% sensitivity and 80.4% specificity (23). This study included 65 patients and a 72% threshold, enabling prediction of persistent HypoPT, was obtained by ROC analyses. A recent study by Calvo Espino *et al.* found that a single postoperative PTH measurement can serve as a predictor of persistent hypoparathyroidism because of its high negative predictive value (AUC 0.87, 95% CI 0.84–0.91) (24). A study by Al-Dhahri *et al.* evaluated PTH recovery by repeated PTH measurements in 53 patients

Table 4 Demographic, clinical and laboratory data of 14 patients with persistent hypoparathyroidism.

Clinical value	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age (y)	56	62	70	45	71	60	41	29	47	69	48	74	66	73
Sex	Male	Male	Male	Female	Female	Female	Female	Female	Male	Male	Male	Female	Female	Female
Diagnosis ^a	PTC	PTC	MTC	MNG	PTC	MNG	PTC	FTC	PTC	PTC	PTC	MNG	PTC	MNG
Surgery ^b	CT	TT	TT	TT	TT	CT	TT	TT	TT	CT	TT	TT	TT	TT
CLND ^c	CCLND + LCLND	CCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND	CCLND + LCLND
Preoperative serum calcium	2.26	2.18	2.13	2.19	2.20	2.24	2.22	2.30	2.23	2.14	2.22	2.19	2.09	2.43
Preoperative serum PTH	3.9	5.2	5.9	5.5	4.9	3.9	5.6	3.2	6.6	4.2	5.1	10.1	9.5	3.4
6 h postoperative serum calcium	2.07	2.08	2.15	1.95	2.00	2.09	2.08	2.31	2.16	2.07	1.98	2.05	2.08	2.32
6 h postoperative serum PTH	0.7	0.3	0.4	0.6	1.6	0.3	0.4			0.5	0.3	0.3	0.6	0.3
24 h postoperative serum calcium	1.92	2.17	2.19	1.93	2.20	2.08	1.94	2.09	1.95	2.16	1.92	2.02	1.82	2.16
24 h postoperative serum PTH	0.7	0.3	0.3	0.4	1.2	0.3	0.6	0.6	0.3	0.4	0.3	0.4	0.6	0.3
Calcium dosage at discharge (mg)	3000	4000	3000	4000	3000	4000	4000	3000	3000	3000	4000	3000	4000	3000
Vitamin D dosage at discharge (µg)	2	2	0.5	3			2	0.5		0.5	1.25	2	2	
Symptoms during admission	-	-	+	+	-	-	+	+	-	-	+	+	+	Unknown
2 weeks postoperative serum calcium	2.29	2.54	1.83	2.06	2.20	1.83	2.01	2.21	2.00	2.43	2.13	2.50	2.45	2.16
2 weeks postoperative serum PTH	0.5	0.3	0.3	2.0		0.7		1.1	0.7	0.4	0.9	0.6	0.3	0.6
Calcium dosage at 2 weeks (mg)	3000	4000	3000	4000	2000	4000	2000	1500	3000	2000	3000	2000	4000	3000
Vitamin D dosage at 2 weeks (µg)	1	2	1	3		1	1	0.5		0.5	1.25	2	2	0.5
1 year postoperative serum calcium	2.17	2.04	2.00	2.05	2.05	1.98	1.90	2.20	2.20	2.10	1.95	2.25	1.94	2.28
1 year postoperative serum PTH	2.0	0.8	0.3	1.2	5.1	0.9	2.4	1.1	0.9	2.7	3.4	1.6	1.0	0.6
Calcium dosage at 1 year (mg)	2000	2000	3000	4000	2000	1000	1500	1000	1500	1500	500	500	2000	4000
Vitamin D dosage at 1 year (µg)	1	0.75	1.25	2.5			0.5	0.5	2		0.25		1	0.5

Serum calcium in mmol/L; serum PTH in pmol/L. Oral calcium supplementation with calcium carbonate; Oral vitamin D supplementation with alfacalcidol.

^aDiagnosis after histopathological examination; ^bType of surgery performed; CT, completion thyroidectomy; ^cConcomitant cervical lymph node dissection (CLND); CCLND, Central CLND (level VI); LCLND, Lateral CLND (level II-IV); TT, total thyroidectomy.

PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma; MTC = medullary thyroid carcinoma; MNG = multinodular goiter.

Figure 2

Relation between serum PTH levels, corrected serum calcium levels and calcium supplementation at the first postoperative day (A), 2 weeks post-operatively (B) and 1 year post-operatively (C). Reference values of serum PTH levels and corrected serum calcium levels are shown in the shaded areas. Every circle corresponds to one single patient. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-20-0116>.

until normalization of PTH levels or up to 6 months (25). They showed that if PTH levels after surgery dropped by more than 88% compared with baseline measurements, the patient only had a chance of 10% of recovery of PTH levels within 6 months. However, the use of calcium supplementation was not reported in that study, so the clinical implication remains unknown.

One of the strengths of our study is the use of the RCV to calculate a predetermined cut-off value for the PTH change. Another strength is the use of one hypocalcaemia treatment algorithm. Our study is limited by the patient selection, as extrapolation of the results to non-tertiary thyroid surgeries could be debatable. This study was initially set up as a multicenter study. Unfortunately, logistics did not allow us to fully use the inclusion potential of our participating peripheral hospital, as can be seen in Fig. 1. The vast majority of patients were included at the Erasmus University medical center and therefore these data should be interpreted as a mono-center study. Another limitation of this study is the high percentage of missing endpoint data, for which 26.4% subjects were excluded from the analysis. However, clinical characteristics did not differ between the included and excluded population as can be seen in the supplementary data Table 2. Although this study was powered to answer the primary research question in this cohort, it should be confirmed in larger cohorts.

Second, it would have been interesting to be able to provide details about parathyroid glands preserved during surgery or found during pathology. However, these data were not complete and thus this study led to the implementation of a more standardized operation reporting protocol including detailed information regarding parathyroid glands. As it seems that the number of parathyroid glands remaining *in situ* (PGRIS) is critical in preventing persistent HypoPT (26), it is of paramount importance to optimize and validate promising novel techniques, such as the use of methylene blue and indocyanine green fluorescence angiography, to facilitate the *in situ* preservation of parathyroid glands and reduce the risk of persistent HypoPT (27, 28, 29).

According to most studies, less than 5% of the patients develop persistent HypoPT (4, 5, 6, 7). We would like to provide a framework in which our above average persistent HypoPT rate (17.3%) could be interpreted. First, we used a clinical definition of persistent HypoPT, namely the use of calcium supplementation 1 year after surgery and inability to be tapered off supplementation. Daily calcium supplementation dosages 1 year after surgery varied from 500 to 4000 mg per patient per day. There is currently no international standardized definition for persistent HypoPT, which results in many definitions described in the literature (30, 31). The British Association of Endocrine and Thyroid Surgeons (BAETS), for example, defines persistent HypoPT as the need of calcium and/or active vitamin D supplements to maintain normocalcaemia at 6 months or more following surgery

(32). Almost the same definition is used by the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE); however, they define persistent HypoPT as the requirement for medical regimen for longer than 12 months (33). The European Society of Endocrinology considers persistent HypoPT in patients with a low calcium and inappropriately low intact parathyroid hormone (iPTH) at more than 6 months (34). When adjusting our case definition to calcium and vitamin D supplementation 1 year after surgery instead of calcium supplementation alone, our rate of persistent HypoPT would be 12.3%. In addition, if those same patients with PTH levels within the normal range are excluded, the rate of persistent HypoPT would be 7.9%. This demonstrates the impact of different definitions on the persistent HypoPT rate as shown previously by Mehanna *et al.* (35) and stresses the need for an international consensus on the definition of persistent HypoPT.

Second, the hospital's hypocalcaemia treatment protocol was quite cautious and warrants calcium supplementation when calcium levels are below the lower limit of normal (<2.20 mmol/L). A lower serum calcium threshold would presumably result in a lower amount of patients with calcium supplementation and therefore a lower number of patients with persistent HypoPT. Third, we perceive our patient population as a selected group of patients with higher risk for postoperative hypoparathyroidism as the majority of the patients are tertiary referrals. Lastly, it is not certain whether the true incidence of persistent HypoPT is known. Most articles report persistent HypoPT rates below 5%. However, in striking contrast, in a survey from the Thyroid Cancer Alliance (8), the rate of persistent HypoPT was reported to be around 14%. The BAETS reported a percentage of 12.1% in their fourth national audit (36). This is clearly discordant with other studies (4, 5, 6, 7). Differences can be explained by publication bias, differences in case mix, definitions or data registration of persistent HypoPT.

Since PTH measurements on the first postoperative day are able to select patients with a high risk of persistent HypoPT, we therefore propose the following use in clinical practice (Fig. 3). Every hospital should calculate its own RCV, as it is influenced by the laboratory's specific analytical imprecision. We recommend a preoperative PTH level blood test and a PTH level blood test on the first postoperative day to determine the change in PTH levels. If the percentage change in PTH levels is lower than the calculated RCV, then there is no significant change in PTH levels. These patients can be informed about their very low risk (0.0%) of persistent HypoPT and can start tapering off

Figure 3

Proposed use of the RCV in clinical practice. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-20-0116>.

their calcium and vitamin D supplementation in the first week after surgery.

If the percentage change in PTH levels is higher than the calculated RCV, then the risk of persistent HypoPT is high (43.8%). Patients should be informed about their high risk of persistent HypoPT and a longer hospital stay can be expected. In this study, we had two standard follow-up laboratory visits, the first at 2 weeks after surgery and the second after 1 year. However, we showed that, in practice, patients are subjected to vena punctures more often. This was even more frequent in patients with a high risk of persistent HypoPT when compared to the low-risk patients. We showed that these patients needed a median time of 3 months to taper off their calcium and/or vitamin D medication.

Therefore, we suggest tapering off their calcium and that vitamin D supplementation should not be initiated in the first 3 months. This would improve efficiency in patient care as well as cost effectiveness.

In conclusion, we show that a decrease of PTH >70% on the first postoperative day after total or completion thyroidectomy is a predictive factor for persistent HypoPT

and can be used to improve efficiency of postoperative follow-up and provide patients with tailored information regarding the future.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-20-0116>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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