RESEARCH

A symptom-based algorithm for calcium management after thyroid surgery: a prospective multicenter study

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[†](Details of the Thyroid Network Study Group is presented in the Acknowledgements section)

Abstract

Objective: Evidence-based treatment guidelines for the management of postthyroidectomy hypocalcemia are absent. The aim of this study was to evaluate a newly developed symptom-based treatment algorithm including a protocolized attempt to phase out supplementation.

Methods: In a prospective multicenter study, patients were treated according to the new algorithm and compared to a historical cohort of patients treated with a biochemically based approach. The primary outcome was the proportion of patients receiving calcium and/or alfacalcidol supplementation. Secondary outcomes were calcium-related complications and predictors for supplementation.

Results: One hundred thirty-four patients were included prospectively, and compared to 392 historical patients. The new algorithm significantly reduced the proportion of patients treated with calcium and/or alfacalcidol during the first postoperative year (odds ratio (OR): 0.36 (95% CI: 0.23–0.54), $P < 0.001$), and persistently at 12 months follow-up (OR: 0.51 (95% CI: 0.28–0.90), $P < 0.05$). No severe calcium-related complications occurred, even though calcium-related visits to the emergency department and readmissions increased (OR: 11.5 (95% CI: 4.51–29.3), $P <0.001$) and (OR: 3.46 (95% CI: 1.58–7.57), $P < 0.05$), respectively. The proportional change in pre- to postoperative parathyroid hormone (PTH) was an independent predictor for supplementation (OR: 1.04 (95% CI: 1.02–1.07), $P < 0.05$).

Conclusions: Symptom-based management of postthyroidectomy hypocalcemia and a protocolized attempt to phase out supplementation safely reduced the proportion of patients receiving supplementation, although the number of calcium-related hospital visits increased. For the future, we envision a more individualized treatment approach for patients at risk for delayed symptomatic hypocalcemia, including the proportional change in pre- to post- operative PTH.

Keywords

- hypocalcemia
- hypoparathyroidism
- thyroidectomy
- symptomatic hypocalcemia
- treatment algorithm

https://etj.bioscientifica.com
https://doi.org/10.1530/ETJ-23-0044

Introduction

Hypocalcemia after total or completion thyroidectomy occurs in 30–60% of patients and is the result of impaired production of parathyroid hormone (PTH) due to inadvertent resection, bruising, edema, or ischemia of the parathyroid glands (1, 2). The impaired parathyroid function is characterized by a decline in PTH and calcium concentrations during and shortly after thyroidectomy (3). In most patients parathyroid function fully recovers over time, but in 5–16% hypoparathyroidism will persist (4, 5). Patients with hypocalcemia may be asymptomatic or experience symptoms ranging from mild paresthesia and muscle cramps to severe symptoms such as cardiac arrhythmias, seizures, and laryngospasms (6, 7). On the other hand, calcium supplementation is not without risks, patients are exposed to adverse effects related to calcium supplementation, including kidney stones, constipation, heartburn, and hypercalcemia (8).

Standardized guidelines for postoperative calcium management are absent. The optimal treatment strategy is much debated in literature ranging from prophylactic calcium with or without active vitamin D supplementation in all thyroidectomy patients to selective supplementation based on biochemical parameters such as calcium and PTH levels (9, 10, 11, 12, 13, 14). Phasing out of supplementation is forgotten in up to 16% of patients, leading to prolonged use of supplementation and misclassification of patients with already recovered parathyroid gland function (15).

One monocenter study showed that a symptom-based approach, irrespective of serum calcium concentration, reduces the proportion of patients receiving supplementation and was a safe strategy (16). However, validation of these observations is needed in hospitals with varying numbers of thyroid surgeries and experience.

Therefore, we developed a symptom-based treatment algorithm for our multicenter thyroid network. A protocolized schedule to phase out supplementation was included. We hypothesized that this treatment approach would be safe and would lead to less patients starting and continuing unnecessary supplementation. In addition, risk factors and predictors for supplementation were identified.

Materials and methods

A prospective multicenter study was performed in one academic and nine regional hospitals in the Southwestern region of the Netherlands. The participating hospitals are part of a collaboration (Thyroid Network) with the intent to harmonize and improve thyroid care (15). This study was approved by the medical ethical board of the Maasstad Hospital (MEC 2017-06) and all prospectively included patients gave written informed consent. For the historical control group, the requirement for informed consent was waived, given the retrospective inclusion of these patients.

Patient selection

Patients were recruited between March 2017 and October 2019 and were eligible for inclusion if they were at least 18 years old, had an indication for total or completion thyroidectomy, and had a normal preoperative serum calcium concentration. Exclusion criteria included a history of parathyroid dysfunction or (epileptic) seizures, current pregnancy, and inability to give informed consent. A historical cohort of patients who underwent a total or completion thyroidectomy between January 2014 and December 2016 served as a control group. To maximize baseline comparability between the cohorts, historical patients were recruited in the same hospitals in the 3 years preceding the introduction of the new algorithm and equal inclusion criteria were applied for both cohorts (15). The symptom-based treatment algorithm was expected to reduce the number of patients treated with calcium and/or alfacalcidol with 14% based on incidence rates reported in the literature (1, 16). A calculated minimum sample size of 100 patients for the prospective cohort was required to detect a projected difference of 14% with 80% power and 5% alpha level, accounting for loss to follow-up, protocol violations and loss of precision when adjusting for confounders in multivariable analysis.

Procedures

Treatment algorithm for postoperative hypocalcemia

The symptom-based treatment algorithm dictated supplementation in patients with hypocalcemic symptoms and/or in patients with serum calcium concentrations below 1.85 mmol/L (Fig. 1). The cutoff of 1.85 mmol/L was chosen for reasons of safety as calcium concentration below this cutoff have been associated with serious complications (9, 17, 18, 19). Hypocalcemic symptoms were defined as new-onset and persisting

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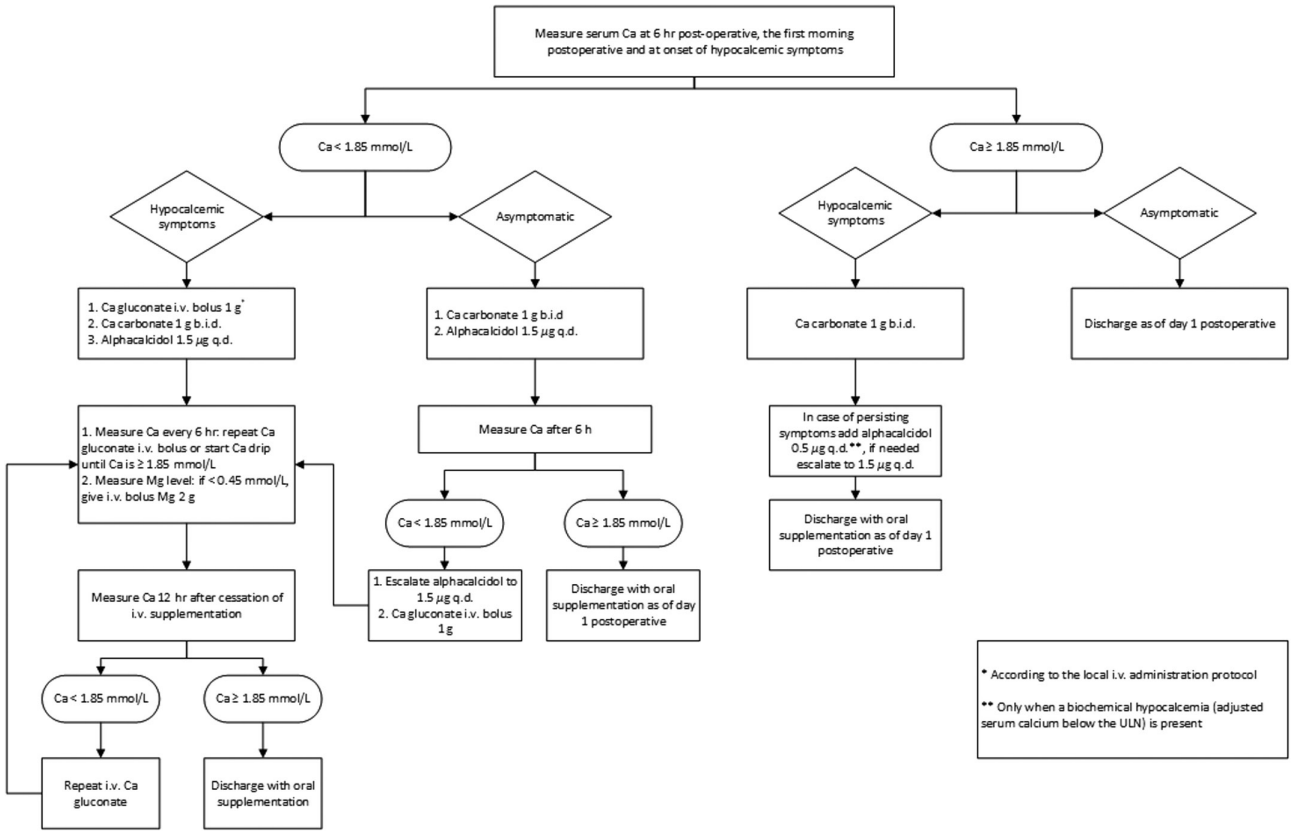

Figure 1
Symptom-based treatment algorithm for postthyroidectomy hypocalcemia. Ca, calcium; Mg, magnesium; i.v. intravenous; b.i.d., *bis in die* (two times a day); q.d., *quaque die* (one time a day).

paresthesia and/or muscle cramps. Postoperative supplementation consisted of calcium carbonate, alfacalcidol (active vitamin D), intravenous calcium gluconate or a combination of these. In case of preoperative vitamin D deficiency, defined as a serum 25-hydroxy vitamin D concentration below 50 nmol/L, vitamin D supplementation was initiated before surgery and consisted of a cholecalciferol (inactive vitamin D) bolus of 25.000 international units (IU) followed by 800 (IU) once daily to be continued until after surgery. An electrocardiogram was performed before surgery and at postoperative day one (POD 1). Calcium and PTH were measured preoperatively, 6 h postoperative and at POD 1 in the morning. Patients on supplementation at discharge received instructions to phase out medication at home according to a predefined schedule (Supplementary Fig. 1, see section on supplementary materials given at the end of this article). All patients received information on hypocalcemic symptoms and instructions to contact the hospital in case these symptoms appeared at home. Follow-up visits were scheduled at 2 weeks, 6 months, and 12 months postoperatively. In the historical cohort, postoperative hypocalcemia was treated with a biochemically based approach. The treatment was not protocolized in nine out of ten hospitals. Treatment decisions were mainly based on serum calcium concentrations. In the academic center, a treatment protocol dictated supplementation when the calcium concentration fell below the lower limit of normal. Although not protocolized, in general the same approach was applied in the other participating centers. Measurement of PTH was not part of clinical decision-making. None of the hospitals used prophylactic supplementation and an attempt to taper supplementation was also not protocolized. Relevant clinical data were collected in a dedicated study database. Data for the historical cohort were retrieved from medical charts as published previously (15).

Study outcomes

The primary outcome of the study was the difference between the prospective and historical cohort in the proportion of patients treated with calcium and/or

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https://doi.org/10.1530/ETJ-23-0044

alfacalcidol during the first postoperative year, and more specifically at discharge after surgery and at 12 months postoperatively. Secondary outcomes were calcium-related visits to the emergency department (ED), calcium-related readmissions, serious calcium-related complications (cardiac arrhythmias, seizures, and laryngospasm) and hospitalization days. Exploratory outcomes included clinical and biochemical predictors for supplementation.

Persistent hypoparathyroidism was defined as the use of alfacalcidol 12 months after surgery, with a documented unsuccessful attempt to phase out supplementation. This definition is in line with the proposed definition in the European Society of Endocrinology expert consensus on parathyroid disorders (9).

ED visits were defined as a calcium-related visit to the ED, without the need for hospital readmission. Permanent laryngeal nerve paralysis was defined as fibroscopically proven laryngeal nerve paralysis at 12 months after thyroidectomy. Wound infections were defined as infections requiring either incision and drainage or antibiotic treatment. The number of parathyroid glands remaining in situ (PGRIS) were scored according to the score proposed by Lorente-Poch *et al.*; four minus the sum of glands auto grafted and glands found in the pathology specimen (20).

Laboratory measurements

Serum calcium concentration was adjusted for albumin according to the formula: adjusted calcium (mmol/L) = measured calcium (mmol/L) + 0.025 × (40 − (albumin (g/L)) (21). A normal preoperative serum calcium concentration was defined as a calcium concentration within the assay-specific reference range. In this multicenter study different assays were used for the measurement of intact PTH. To account for between-method variation, the proportional difference between preoperative and postoperative PTH concentrations was explored as a predictor for supplementation and persistent hypoparathyroidism (22). When the PTH concentration was undetectable, the functional sensitivity of the particular assay was plotted (i.e. when a PTH concentration was reported as < 0.25 pmol/L, it was plotted as 0.25).

Statistical analysis

A per protocol analysis was performed. A protocol violation in the management of postoperative calcium occurred in three patients as these patients received calcium supplementation although symptoms were absent and the calcium concentration was above 1.85 mmol/L. These patients were excluded for analysis, except for the outcome of persistent hypoparathyroidism, as in all three patients phasing out of supplementation was attempted. Loss to follow-up was treated as missing data. Receiver operating characteristic curve analysis was used to identify the optimal cutoff for biochemical variables as a predictor for supplementation and persistent hypoparathyroidism. Correlations were tested by calculating the Pearson's product–moment correlation coefficient and Spearman's rank correlation coefficient, where appropriate. A logistic regression model was used to investigate predictors for calcium and/or alfacalcidol supplementation. IBM SPSS , version 25 (IBM Corp.), was used to perform all statistical analyses.

Results

Between April 7, 2017, and September 17, 2019, a total of 134 patients were included in the prospective cohort. One (0.7%) patient was lost to follow-up after 6 months. The historical cohort consisted of 392 patients. Baseline characteristics of both cohorts are summarized in Table 1.

Calcium management: symptom based vs biochemically based

Overall, during the first postoperative year, calcium and/or alfacalcidol supplementation was used by 33.6% (44 out of 131) of patients in the prospective cohort, compared to 59.0% (214 out of 363) of patients in the historical cohort (odds ratio (OR): 0.36 (95% confidence interval (CI): 0.23 – 0.54), $P < 0.001$) (Table 2, Fig. 2). Preoperatively, cholecalciferol supplementation was prescribed in 53.1% (17 out of 32) vitamin D deficient patients. Postoperative supplementation with calcium and/or alfacalcidol was initiated during initial hospital admission in 19.1% (25 out of 131) of patients in the prospective cohort, compared to 55.6% (218 out 392) of patients in the historical cohort (OR: 0.19 (95% CI: 0.12–0.30), $P < 0.001$). In 72% (18 out of 25) of patients who received supplementation, this was started at POD 1 (range: POD 0 to 6) (Fig. 3). Calcium-related symptoms was the reason for initiation of supplementation in all patients in the prospective cohort, except for one asymptomatic patient with a

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Table 1 Baseline characteristics. Data are expressed as *n* (%), mean± S.D. or as median (IQR).

Characteristics	Prospective cohort	Historical cohort	*P*-value
Total *n*	134	392	
Females	100 (74.6%)	305 (77.8%)	0.450
Age (years)	50 (36–59)	51 (36–63)	0.382
Baseline medication			
Thyroid hormone supplementation	20 (14.9%)	71 (18.1%)	0.380
Cholecalciferol supplementation	21 (15.7%)	41 (10.5%)	0.108
Calcium supplementation	5 (3.7%)	22 (5.6%)	0.385
Indication for surgery			
Malignancy	74 (55.2%)	193 (49.2%)	0.231
Bethesda III, IV, V thyroid nodule	9 (6.7%)	30 (7.7%)	0.721
Bethesda I thyroid nodule	0 (0.0%)	3 (0.8%)	0.310
Multinodular goiter	20 (14.9%)	83 (21.2%)	0.116
Graves' disease	28 (20.9%)	76 (19.4%)	0.705
Symptomatic benign nodule	0 (0.0%)	1 (0.3%)	0.558
Other	5 (3.7%)	6 (1.5%)	0.124
Preoperative laboratory values			
Serum calcium (mmol/L)[a]	2.31 ± 0.1	2.29 ± 0.1	0.212
25-OH-Vitamin D (nmol/L)	57 (40–71)	–	–
PTH (pmol/L)	4.20 (2.60–6.40)	–	–
Hospital of surgery			
Academic hospital	56 (41.8%)	182 (46.4)	0.362
Regional hospital	78 (58.2%)	209 (53.3%)	
Surgical characteristics			
Thyroidectomy			0.160
1-stage	98 (73.1%)	261 (66.6%)	
2-stage	36 (26.9%)	131 (33.4%)	
Lymph node surgery	29 (21.6%)	70 (17.9%)	0.296
Only central lymph node surgery	10 (7.5%)	26 (6.6%)	0.711
Only lateral lymph node surgery	2 (1.5%)	0 (0.0%)	
Central and lateral lymph node surgery	17 (12.7%)	44 (11.2%)	0.648
Surgical complications			
Reoperation for bleeding	2 (1.5%)	16 (4.1%)	0.182
Wound infection	1 (0.7%)	5 (1.3%)	0.637
Permanent RLNP	14 (10.4%)	19 (4.8%)	0.027
Hospital stay (days)	1.00 (1.00–2.00)	2.00 (1.00–3.00)	<0.001

[a]Calcium adjusted for albumin.
PTH, parathyroid hormone; RLNP, recurrent laryngeal nerve paralysis.

serum calcium below 1.85 mmol/L. Intravenous calcium supplementation was prescribed during the initial admission in 6.1% (8 out of 131) of patients in the prospective cohort compared to 26.7% (98 out of 367) of patients in the historical cohort (OR: 0.18 (95% CI: 0.08–0.38), $P < 0.001$). Intravenous calcium supplementation was prescribed in 13.0% (17 out of 131) of patients in the prospective cohort, compared to 28.6% (105 out of 367) of patients in the historical cohort (OR: 0.37 (95% CI: 0.21–0.65), $P < 0.001$). These numbers include intravenous calcium prescribed during readmission. In the prospective cohort, the median initial hospital stay was 2 days (range: 2–15), compared to a median of 3 days (range: 2–28) in the historical cohort ($P < 0.001$). Including readmission days, the median hospital stay for both cohorts remained unchanged ($P < 0.001$).

After discharge: follow-up and phasing out of supplementation

Supplementation of calcium and/or alfacalcidol was started between discharge and the 2 week follow-up visit in 14.5% (19 out of 131) of patients in the prospective cohort. In these patients, the mean calcium concentration at POD 1 was 2.13 mmol/L (range: 1.90–2.42), the median proportional change in PTH preoperative to 6 h postoperative was 85.2% (interquartile range (IQR): 70.9–97.9) and the median proportional change in PTH preoperative to POD 1 was 82.9% (IQR: 56.4–92.4) (Supplementary Table 1). According to the study protocol, in the prospective cohort, phasing out of supplementation was attempted in 100% (44 out of 44) of patients. For the historical cohort an attempt to

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Table 2 Postoperative calcium-related outcomes. Data are expressed as *n* (%).

	Prospective cohort	Historical cohort	OR (CI)	*P*-value
POD 1 serum calcium[a]				0.233
<1.85 mmol/L	2 (1.6%)	5 (1.7%)		
1.85–2.20 mmol/L	62 (48.1%)	171 (56.6%)		
≥2.20 mmol/L	65 (50.4%)	126 (41.7%)		
Supplementation in the first postoperative year			0.36 (0.23–0.54)	<0.001
No supplementation	86 (65.6%)	149 (38.0%)		
Any supplementation	44 (33.6%)	214 (54.6%)		
Supplementation at discharge			0.19 (0.12–0.30)	<0.001
No supplementation	106 (80.9%)	171 (43.6%)		
Any supplementation	25 (19.1%)	218 (55.6%)		
Calcium only	12 (9.2%)	118 (30.1%)		
Alphacalcidol only	0 (0.0%)	3 (0.8%)		
Calcium + alphacalcidol	13 (9.9%)	97 (24.7%)		
Unknown	0 (0.0%)	3 (0.8%)		
Supplementation at 12 months postoperative			0.51 (0.28–0.90)	0.021
No supplementation	116 (86.6%)	282 (71.9%)		
Any supplementation	16 (11.9%)	77 (19.6%)		
Calcium only	6 (4.5%)	31 (7.9%)		
Alphacalcidol only	2 (1.5%)	3 (0.8%)		
Calcium + alphacalcidol	8 (6.0%)	43 (11.0%)		
Unknown	2 (1.5%)	33 (8.4%)		
Persistent hypoparathyroidism[b]	10/133 (7.5%)	32/357 (9.0%)	0.83 (0.39–1.73)	0.611
Calcium-related complications				
Readmission	14 (10.4%)	13 (3.3%)	3.46 (1.58–7.57)	0.002
ED visit	20 (14.9%)	6 (1.5%)	11.5 (4.51–29.3)	<0.001
Other				
IV calcium	17 (13.0%)	105 (28.6%)	0.37 (0.21–0.65)	<0.001
Hospital stay (days)*	2 (2–3)	3 (2–4)		<0.001

*value is median (IQR); [a]Calcium adjusted for albumin. [b]Persistent hypoparathyroidism is defined as the need for alphacalcidol 12 months after surgery, with a documented unsuccessful attempt to phase out supplementation.
ED, emergency department; IV, intravenous; POD 1, post-operative day 1; OR, odds ratio.

phase out supplementation was documented in 21.5% (46 out of 214) of patients. Twelve months after surgery, supplementation with calcium and/or alfacalcidol was used by 11.9% (16 out of 134) of patients in the prospective cohort, compared to 19.6% (77 out of 392) of patients in the historical cohort (OR: 0.51 (95% CI: 0.28–0.90), $P < 0.05$). The rate of persistent hypoparathyroidism (defined as the need for alfacalcidol 12 months after surgery, with a documented unsuccessful attempt to phase out supplementation), was 7.5% (10 out of 133) in the prospective cohort, compared to 9.0% (32 out of 357) in the historical cohort (OR: 0.83 (95% CI: 0.39–1.73), $P = 0.611$).

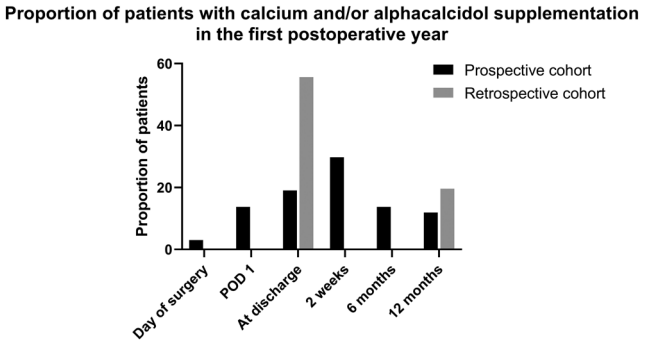

Figure 2
The use of calcium and/or active vitamin D supplementation during the first postoperative year. POD, postoperative day.

Hypocalcemic symptoms

Calcium-related symptoms were reported by 50.7% (68 out of 134) of patients at some point during follow-up. In 16.4% (22 out of 134) these symptoms did not require supplementation because the symptoms were short-lived and resolved spontaneously or an alternative explanation other than calcium-related was deemed more likely. On the day of surgery, symptoms were reported by 30.8% (12 out of 39) of patients with a calcium concentration <2.20 mmol/L measured 6 h postoperative and by 14.6% (seven out of 48) of patients with a calcium concentration ≥ 2.20 mmol/L. At POD 1, symptoms were reported by 51.1% (23 out of 45) of patients with an early morning calcium concentration

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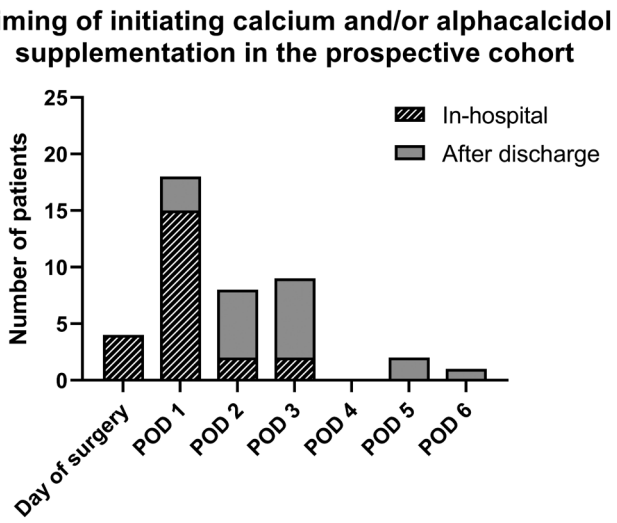

Figure 3
Timing of initiating calcium and/or alfacalcidol supplementation in the prospective cohort. POD, postoperative day.

<2.20 mmol/L and by 31.5% (17 out of 54) of patients with a calcium concentration ≥2.20 mmol/L. All patients who were diagnosed with persistent hypoparathyroidism at 12 months postoperative, reported symptoms at some point during follow-up, and 40% (4 out of 10) of patients did so during initial hospital admission.

Calcium-related complications

The decline in calcium concentration pre- to postoperative was significantly associated with a pre- to postoperative increase in electrocardiographic QTc interval (Pearson correlation coefficient: −0.374, $P = 0.001$). No cardiac arrhythmias, seizures, or laryngospasms occurred in both cohorts. In the prospective cohort, 10.4% (14 out of 134) of patients were readmitted for hypocalcemia, compared to 3.3% (13 out of 392) of the patients in the historical cohort (OR: 3.46 (95% CI: 1.58–7.75), $P < 0.05$). In the prospective cohort, 58.3% (seven out of 12) of 30-day readmissions occurred at POD 2 or POD 3. Of the readmitted patients 57.1% (eight out of 14) were classified as having persistent hypoparathyroidism at 12 months follow-up. All readmitted patients with available PTH measurements had a ≥90% decrease in PTH preoperative to 6 h postoperative and ≥83% decrease in PTH preoperative to POD 1 (Supplementary Table 2). Two patients were readmitted during a trial of phasing out supplementation. Calcium-related ED visits occurred in 14.9% (20 out of 134) of patients in the prospective cohort, compared to 1.5% (6 out of 392) of patients in the historical cohort (OR: 11.5 (95% CI: 4.51 – 29.3), $P < 0.001$). In the prospective cohort, 55% (11 out of 20) of these patients presented with a biochemical hypocalcemia.

Predictors for supplementation and persistent hypoparathyroidism in the prospective cohort

In univariable analysis, a one-stage thyroidectomy (OR: 3.39 (95% CI: 1.29–8.94), $P < 0.05$), lymph node surgery (OR: 3.43 (95% CI: 1.41–8.35), $P < 0.05$), and a PGRIS score < 3 (OR: 6.52 (95% CI: 1.54–27.7), $P < 0.05$) were associated with calcium and/or alfacalcidol supplementation in the first postoperative year. The proportional change in PTH preoperative to 6 h postoperative was the most accurate biochemical predictor for supplementation with a median decrease of 85.1% (IQR: 67.4–92.4) in patients with supplementation compared to 47.3% (IQR: 22.3 – 71.0) in patients without supplementation (AUC: 0.809 (95% CI: 0.707–0.910)) (Table 3, Supplementary Fig. 2). No patients with a PTH decline of less than 71% preoperative to 6 h postoperative required supplementation. In multivariable analysis, the proportional change in PTH preoperative to 6 h postoperative was the only independent predictor of supplementation (OR: 1.04 (95% CI: 1.02–1.07), $P < 0.05$) (Table 4).

In the prospective cohort 6.0% (8 out of 134) of patients had (additional) lymph node surgery in the first year after thyroidectomy. Only one of these patients developed persistent hypoparathyroidism. A sensitivity analysis excluding patients with additional lymph node surgery did not alter the results.

Discussion

A symptom-based treatment algorithm for the management of postthyroidectomy hypocalcemia significantly and safely reduced the proportion of patients treated with calcium and/or alfacalcidol. Severe calcium-related complications did not occur. Long-term supplementation was avoided in every seven out of 100 patients when compared to a historical cohort of patients treated with a biochemically based approach. However, this came at the cost of an increased number of calcium-related readmissions and ED visits.

The reduction in the proportion of patients treated with calcium supplementation was a combined effect of both the in-hospital algorithm and the

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Table 3 Clinicopathological, procedural and postoperative predictors for calcium and/or alphacalcidol supplementation in the prospective cohort. Data are expressed as *n* (%), median (IQR) or as mean ± s.d.

	P-HypoPT	T-supp in the first year	No-supp	Supp vs No-supp		T-supp vs P-HypoPT	
				OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Total *n*	10	34	86				
Females, *n*	6 (60.0%)	28 (82.4%)	64 (74.4%)	1.17 (0.50–2.75)	0.721	3.11 (0.67–14.5)	0.149
Age (years)	46 (28–66)	45 (34–53)	51 (37–61)	0.98 (0.96–1.01)	0.172	0.99 (0.94–1.04)	0.642
Baseline medication							
Levothyroxine	2 (20.0%)	4 (11.8%)	14 (16.3%)	0.83 (0.30–2.35)	0.731	0.55 (0.09–3.58)	0.533
Cholecalciferol	0 (0.0%)	6 (17.6%)	14 (16.3%)	0.83 (0.30–2.35)	0.731	–	0.309
Baseline laboratory (serum)							
Calcium (mmol/L)	2.28 ± 0.1	2.31 ± 0.1	2.32 ± 0.1	–	0.427	–	0.473
25-OH-Vitamin D (nmol/L)	43.0 (34.0–60.0)	51.0 (39.8–71.0)	60.0 (51.0–73.0)	–	0.051	–	0.234
PTH (pmol/L)	4.60 (2.95–6.85)	4.10 (2.38–7.48)	4.20 (2.50–6.30)	–	0.524	–	0.777
Hospital							
Academic hospital	5 (50.0%)	14 (41.2%)	34 (39.5%)	0.86 (0.41–1.80)	0.689	1.43 (0.35–5.88)	0.620
Regional hospital	5 (50.0%)	20 (58.8%)	52 (60.5%)				
Surgical characteristics							
Thyroidectomy							
1-stage	8 (80.0%)	30 (88.2%)	53 (61.6%)	3.39 (1.29–8.94)	0.013	1.88 (0.29–12.1)	0.510
2-stage	2 (20.0%)	4 (11.8%)	30 (34.9%)				
Lymph node surgery	3 (30.0%)	12 (35.3%)	11 (12.8%)	3.43 (1.41–8.35)	0.007	1.27 (0.28–5.85)	0.757
Histological characteristics							
Malignant	5 (50.0%)	24 (70.6%)	48 (55.8%)	1.53 (0.72–3.26)	0.269	2.40 (0.57–10.16)	0.234
Graves' disease	1 (10.0%)	5 (14.7%)	15 (17.4%)	0.75 (0.27–2.08)	0.578	1.55 (0.16–15.1)	0.705
Multinodular goiter	3 (30.0%)	5 (14.7%)	20 (23.3%)	0.73 (0.29–1.83)	0.506	0.40 (0.08–2.10)	0.280
Parathyroid glands							
PGRIS score							
4	5 (50.0%)	15 (44.1%)	20 (23.3%)	Ref		Ref	
3	3 (30.0%)	9 (26.5%)	20 (23.3%)	1.68 (0.70–4.05)	0.247	1.00 (0.19– 5.22)	1.000
1 or 2	2 (20.0%)	5 (14.7%)	3 (3.5%)	6.53 (1.54–27.7)	0.011	1.20 (0.18–8.24)	0.853
Surgical complication[a]	3 (30.0%)	5 (14.7%)	13 (15.1%)	1.23 (0.47–3.24]	0.674	2.49 (0.48–13.0)	0.280
Postoperative laboratory values							
Calcium (mmol/L) 6 h postoperative	2.17 (2.08–2.38)	2.17 (2.09–2.26)	2.23 (2.16–2.38)	–	0.009	–	0.818
Calcium (mmol/L) POD 1	2.08 ± 0.2	2.12 ± 0.1	2.23 ± 0.1	–	<0.001	–	0.448
PTH (pmol/L) 6 h postoperative	0.32 (0.10–0.50)	0.90 (0.50–1.80)	2.21 (1.00–3.65)	–	<0.001	–	0.008
PTH (pmol/L) POD 1	0.41 (0.16–0.83)	0.85 (0.50–1.89)	1.90 (1.20–3.12)	–	<0.001	–	0.051
Pre- to 6 h postoperative PTH% change	93.4 (87.1–96.5)	79.3 (61.1–88.7)	47.3 (22.3–71.0)	–	<0.001	–	0.008
Pre-to POD 1 PTH% change	91.6 (80.4–95.5)	77.3 (52.7–90.2)	50.6 (31.3–65.7)	–	<0.001	–	0.055

[a]Composite variable including recurrent nerve paralysis, bleeding, hematoma, wound infection and chylous leak.
No-supp, no supplementation; P-HypoPT, persistent hypoparathyroidism; PTH, parathyroid hormone; T-supp, temporary supplementation; Supp, supplementation; 25(OH) vitamin D, 25-hydroxyvitamin D; PGRIS, score for parathyroid glands (PTG) remaining *in situ* (4 minus (autotransplanted PTG plus PTG detected at histopathology); 6hr, 6 hours; POD 1, postoperative day one; ref, reference.

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protocolized attempt to taper supplementation. At time of discharge after surgery, the proportion of patients that used supplementation was significantly lower in the prospective cohort compared to the historical cohort. Tapering of calcium supplementation further contributed to the prevention of unnecessary long-term supplementation. Reducing the number of patients who start supplementation, will decrease the number of patients of whom the supplementation needs to be tapered, also reducing health care resources.

The incidence of postthyroidectomy hypocalcemia was comparable to other multicenter and nationwide studies, reporting rates of 7.3–16.7%, but higher than rates reported by single center studies (4, 23, 24, 25). Half of the included patients had malignant disease that may have required more extensive surgery, including lymph node dissections. These factors are reported to increase the risk for surgical complications such as recurrent laryngeal nerve paralysis and hypocalcemia with an inferred higher need for intravenous calcium supplementation. Yet, the symptom-based protocol did lead to a reduction in intravenous calcium compared to the historical cohort.

All patients who were classified as having persistent hypoparathyroidism experienced hypocalcemic symptoms at some point during the first postoperative year. Patients reported only mild neuromuscular symptoms. Severe symptoms such as cardiac arrhythmias, seizures, or laryngospasm did not occur, which is concordant with previous studies treating only symptomatic patients after thyroidectomy (16, 26). Although severe and life-threatening symptoms have been attributed to hypocalcemia, the precise causal role of hypocalcemia is unclear as valid alternative causes for these symptoms were reported (6, 17, 27, 28, 29). In otherwise healthy patients, the concerns for potentially life-threatening complications of hypocalcemia might therefore be inflated.

A shortened length of hospital stay combined with the conservative use of calcium and alfacalcidol supplementation may well explain the increased readmission rate in the prospective cohort. The majority of readmitted patients were asymptomatic during the initial admission and the nadir of calcium concentration and the onset of hypocalcemic symptoms occurred in the first 3 days after discharge. In the historical cohort, a larger proportion of patients was discharged with supplementation which may have prevented a steep drop in calcium concentration and the emergence of hypocalcemic symptoms leading to a hospital visit. In two other studies examining a symptom-based treatment approach the mean hospital stay was either significantly longer or not reported (16, 26).

Table 4 Multivariable analysis for the primary endpoint of calcium and/or alfacalcidol supplementation in the first postoperative year ($n = 130$).

	OR (CI)	***P***
One-stage thyroidectomy	2.19 (0.37–13.0)	0.389
Lymph node surgery	1.49 (0.39–5.73)	0.560
PGRIS score	0.17 (0.16–1.10)	0.076
Pre- to 6 h postoperative PTH% decrease	1.04 (1.02–1.07)	0.001

OR, odds ratio; PGRIS, score for parathyroid glands remaining *in situ*; PTH, parathyroid hormone.

Multiple studies have described delayed onset of hypocalcemic symptoms, with an average interval between thyroid surgery and the onset of symptoms of 37–41 h (30, 31, 32). Patients in the prospective cohort were typically discharged at POD 1 and thus before this reported average onset of symptoms. Patients who started supplementation after discharge had mild biochemical hypocalcemia during admission, but a significant proportional decrease in pre- to postoperative PTH. Carvalho *et al.* analyzed a similar group of patients with discordant PTH and calcium concentrations and identified bilateral central neck dissection and a pre- to postoperative PTH reduction as predictors of transient hypocalcemia (33). These findings suggest that PTH measurements may be used to select patients at risk of delayed onset of relevant symptomatic hypocalcemia.

The number of ED visits was higher in the prospective cohort compared to the historical cohort. It turned out, however, that almost 50% of patients who visited the ED for calcium-related symptoms, had biochemical normocalcemia. At study inclusion and at discharge after thyroidectomy, patients were counseled about hypocalcemic symptoms. Increased awareness and focus on physical sensations may have caused the higher number of patients seeking medical care (34).

The symptom-based treatment algorithm included a protocolized attempt to phase out supplementation with the aim to reduce unwarranted long-term supplementation. Previously, we have shown the discrepancy in the incidence of hypoparathyroidism in patients with and without a dedicated effort to phase out supplementation (15). The feasibility of a protocolized phasing out is supported by Cayo *et al.* who showed that this approach reduced the duration of supplementation (35). The reported delayed functional

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recovery of parathyroid glands more than 12 months after surgery suggests that it may even be feasible to repeat a trial of phasing out supplementation after a previously unsuccessful attempt (4, 36).

Clinical predictors for calcium and/or alfacalcidol supplementation were in line with literature and included a one-stage thyroidectomy, lymph node surgery and a lower PGRIS score (1). The proportional change in PTH preoperative to 6 h postoperative was found to be the most accurate biochemical predictor. The use of PTH as a predictor has several limitations caused by biological variation, the influence of vitamin D status and between-method variation due to a lack of standardization of PTH assays (22). Forty different PTH cutoffs have been identified as the most reliable threshold to detect hypoparathyroidism, as reported in a recent meta-analysis (37). To account for between-method variation, we calculated the proportional difference in pre- to postoperative PTH and confirmed the higher sensitivity compared to a single postoperative PTH value (38). The high negative predictive value for calcium and/or alfacalcidol supplementation enables its use as a rule-out test. The positive predictive value, however, did not exceed 62% and remains a limitation to the use of PTH measurements (39, 40, 41). Keeping this in mind, the proportional change in PTH can be used to identify patients at risk of delayed symptomatic hypocalcemia who require more extensive monitoring. Additionally, it can be used to inform patients about the risk for persistent hypoparathyroidism and subsequently the chance of a successful attempt to phase out medication.

The multicenter character of this study, including a large academic as well as nine regional hospitals, with variable levels of experience in thyroid surgery, increases generalizability of the study results. Implementation of the algorithm was readily possible due to the easy to follow algorithm, as reflected by the good adherence to the study protocol.

Despite the care of data collection, observation bias may have been introduced and data of the historical cohort may have been incomplete due to heterogeneity in medical documentation. When evaluating the effect of the new algorithm, differences between the cohorts should be taken into account. Although the cohorts were comparable with respect to baseline characteristics and postoperative calcium concentrations, the differences in hospitalization days and the level of symptom awareness is expected to have affected the number of hospital visits. Unfortunately, the data collection did not include sufficient data to properly perform a cost-effectiveness analysis.

This study validates the safety of a symptom-based treatment approach that reduced the number of patients receiving calcium and/or alfacalcidol supplementation, without missing patients who eventually developed persistent hypoparathyroidism. Fewer patients required intravenous calcium supplementation. As such, the symptom-based algorithm can be considered an improvement of postoperative calcium management even though the number of readmissions and emergency department visits did increase. For the future, we envision a more individualized approach, using the proportional change in pre- to post- operative PTH combined with clinical risk factors, to identify patients at risk for delayed symptomatic hypocalcemia. High risk patients will need more intensive monitoring in the first postoperative week and may benefit from on-demand supplementation.

Supplementary materials

This is linked to the online version of the article at https://doi.org/10.1530/ETJ-23-0044.

Declaration of interest

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

Funding

This research did not receive any specific grant form any funding agency in the public, commercial, or not-for-profit sector.

Author contribution statement

CMJvK and IL contributed to the study design, data collection, analysis, interpretation of data, and manuscript draft. CvN, TMvG, WEV, and RPP contributed to the study design, interpretation of data, and critical review. The Thyroid Network Study Group contributed to the inclusion of patients. All authors approved the final version of the manuscript.

Acknowledgements

The authors thank the members of the Thyroid Network Study Group: Kees van den Berge, Michel P Brugts, Matthijs J Faber, Richard P R Groenendijk, Saskia M T H ten Have, Sigridur Jakobsdóttir, Marlies E Kevenaar, Snježana Kos, Joke van der Linden, Elske T Massolt, Erik M von Meyenfeldt, Charles C van Rossem, Ellen van Schaik, Maarten Staarink and Hans F. Zengerink.

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Received 3 March 2023
Accepted 30 August 2023
Available online 1 September 2023
Version of Record published 3 October 2023