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Gastrointestinal surgery, malabsorptive conditions, and postoperative hypocalcemia after neck surgery

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ABSTRACT

Background: Postoperative hypocalcemia is a common complication of thyroid and parathyroid surgery. Patients with prior gastric bypass face increased risk of postoperative hypocalcemia, but the impact of other malabsorptive conditions is not well understood. In this study, we evaluated the relationship between multiple medical and surgical malabsorptive states and hypocalcemia after thyroid and parathyroid surgery.
Methods: We performed a retrospective cohort study of patients who underwent total thyroidectomy and/or parathyroidectomy in Optum's deidentified Clinformatics Data Mart Database (2004–2022). Patients were categorized as having surgical (foregut/midgut: gastrectomy, intestinal bypass, enterectomy, enterostomy, pancreatectomy, or hindgut: colectomy/colostomy) or medical (Crohn or Celiac disease) malabsorptive conditions. The primary outcomes were early (<7 days) and late (7–365 days) postoperative hypocalcemia. Logistic regression was performed to determine the associations between malabsorptive conditions and outcomes.
Results: Of 25,400 patients (56.9% total thyroidectomy, 40.8% parathyroidectomy, and 2.4% both procedures), 4.0% had a pre-existing malabsorptive condition. Early postoperative hypocalcemia occurred in 8.8% of patients, and late hypocalcemia in 18.3%. Thyroidectomy was associated with a greater likelihood of hypocalcemia than parathyroidectomy (odds ratio: 1.22; $P < .001$). Pancreatectomy was associated with twice the adjusted odds of postoperative hypocalcemia (odds ratio: 2.27; $P = .031$) across both procedures. Patients with prior foregut/midgut surgery were at higher risk after total thyroidectomy (odds ratio: 1.65, $P = .002$). This association was significant in late (odds ratio: 1.82, $P < .001$) rather than early hypocalcemia (odds ratio: 1.33, $P = .175$). Hindgut surgery and medical malabsorption did not demonstrate such associations.
Conclusion: Prior foregut and midgut resections may predispose patients to postoperative hypocalcemia, particularly in patients undergoing total thyroidectomy.

Introduction

Postoperative hypocalcemia is the most common complication of thyroid and parathyroid surgery. Transient postoperative hypocalcemia may occur in over half of patients undergoing total thyroidectomy and a quarter of patients undergoing parathyroidectomy, with a small portion (13% and 4%, respectively) going on to develop permanent hypocalcemia.[1–6] The underlying etiology of postoperative hypocalcemia is most commonly hypoparathyroidism due to intraoperative parathyroid devascularization or inadvertent partial or complete resection of parathyroid gland(s).[7] Clinically, postoperative hypocalcemia may lead to significant morbidity including muscle spasms, tetany, and altered mental status, and has also been associated with longer hospital stays and higher health care costs.[8] Patients with postoperative hypocalcemia are reliant on frequent calcium supplementation and report significantly impaired quality of life.[9]

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Gastrointestinal physiology plays a critical role in calcium homeostasis, compensating for calcium excretion from the urine to maintain neutral calcium balance. Although the entire intestine can passively uptake calcium, active calcium transport occurs in the duodenum and jejunum. Both passive and active transport are modulated by vitamin D metabolism.[10] Iatrogenic alterations in gastrointestinal anatomy and pathologic malabsorptive states may lead to deficiencies in calcium homeostasis through changes in calcium uptake. Such alterations may also lead to hypomagnesemia, which potentiates hypocalcemia.[11] Hypocalcemia is a known potential complication of gastric and bowel resection, with differential risk based on the procedure performed.[12,13] Rates of hypocalcemia after bariatric surgery can be as high as 25%, and patients with a history of Roux-en-Y gastric bypass who later undergo thyroidectomy have a 2-fold higher risk of postoperative hypocalcemia than patients with a history of sleeve gastrectomy or adjustable gastric band.[12–14] However, studies describing the relationship between surgical malabsorptive conditions and postoperative hypocalcemia after thyroid and parathyroid surgery are largely limited to small cohorts of patients who underwent bariatric procedures. Little is known about the impact of other malabsorptive conditions, such as other types of gastrointestinal surgery or medical conditions such as inflammatory bowel disease, which could contribute to postoperative hypocalcemia via multiple potential mechanisms.[15] Therefore, the goal of this study was to assess the incidence of postoperative hypocalcemia in patients undergoing thyroid and parathyroid procedures with respect to medical and surgical malabsorptive conditions.

Methods

Data source

We performed a retrospective cohort study using Optum's deidentified Clinformatics Data Mart Database (CDM) to evaluate rates of postoperative hypocalcemia in patients who underwent parathyroidectomy or total thyroidectomy from January 2004 to June 2022. CDM is a nationwide claims database including over 77 million patients enrolled in a commercial insurance plan or Medicare Advantage plan. It allows longitudinal evaluation of data abstracted from patient medical records, laboratory results, pharmaceutical prescriptions, and hospital and physician claims.[16] This study was deemed exempt from review by the institutional review board of the University of Pennsylvania and followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines throughout its design and implementation (Supplementary Table S1).[17]

Study cohort

All adult patients who underwent parathyroidectomy and/or total thyroidectomy were identified for inclusion by the Current Procedural Terminology (CPT) code and International Classification of Diseases (ICD) ninth and tenth edition codes (Supplementary Table S2). Receipt of simultaneous lymph node dissection was noted, as applicable. Each patient's index date was defined as the date of the qualifying procedure. Patients were excluded if continuous insurance coverage data were not available for 4 years before the index date and/or 1 year after the index date, with up to a 30-day gap in coverage deemed permissible. Patients carrying a diagnosis of end-stage renal disease, short gut syndrome, eating disorder, pancreatic steatorrhea, or "unspecified" types of malabsorption were excluded to limit potential confounding. Patients with diagnosis codes indicating prior bariatric surgery but without an associated procedure code within the study period were also excluded (Figure 1).

Definitions

The primary exposure was defined as the presence of a malabsorptive condition, classified as either surgical or medical. Surgical malabsorption was defined as receipt of a qualifying

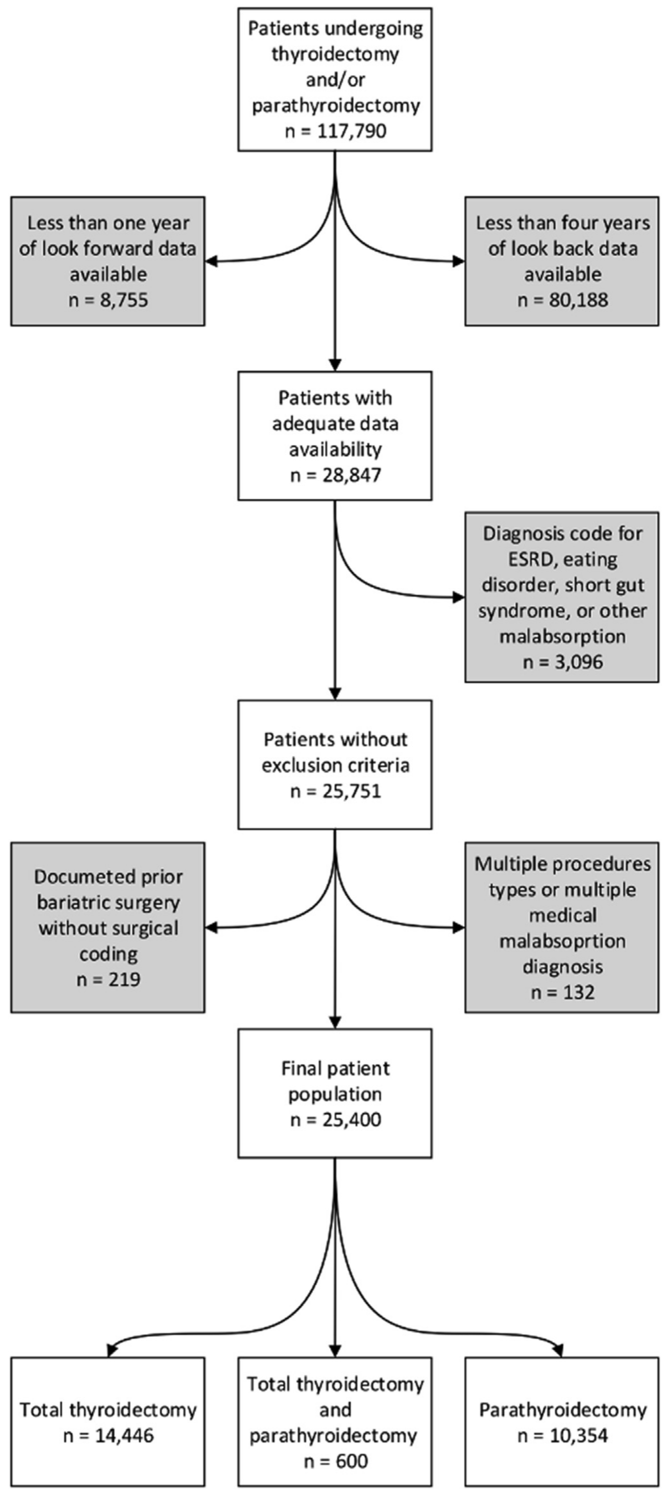

Figure 1. CONSORT diagram demonstrating included patient population. *ESRD*, end-stage renal disease.

gastrointestinal surgery before the index date, with surgical procedures categorized by anatomic distribution. These included gastrectomy (total gastrectomy, partial gastrectomy, or gastric restrictive procedures), intestinal bypass (all bypass procedures originating with the stomach or intestine), enterectomy, enterostomy, pancreatectomy (partial and total pancreatectomy, as well as Whipple procedure), and colectomy/colostomy, as defined by the CPT or ICD9/10 code. Medical malabsorption was defined by the presence of either Crohn's disease or Celiac disease, as defined by the ICD-9/10 code; these conditions were selected because of their predilection for the foregut and midgut (Supplementary Table S3). Patients with multiple surgical codes within the study period were excluded unless both surgeries occurred on the same date and were able to be defined as a single surgery on expert review (eg, pancreatectomy and duodenectomy codes on the same date could be defined as a Whipple procedure). Covariates abstracted included index year, age, sex, race and ethnicity, household income, education, chronic kidney disease state, Elixhauser comorbidities, and coincident prescriptions for an H2 blocker or proton pump inhibitor. The Elixhauser category “fluid and electrolyte comorbidities” was excluded because of collinearity with our outcome (prevalence of 19.0% in patients with a malabsorptive condition versus 7.8% in patients without, $P < .001$). Body mass index was not abstracted because of missingness. Laboratory values for pre- and postoperative calcium, parathyroid hormone, vitamin D, magnesium, and phosphorus were abstracted but had notable missingness and so were not integrated as predictive factors.

Outcomes

The primary outcomes were hypocalcemia at 3 timepoints: early (within 7 days postoperatively), late (7–365 days postoperatively), and overall (0–365 days postoperatively). Hypocalcemia was defined by the presence of an ICD9/10 code for hypocalcemia or hypoparathyroidism, documented administration of intravenous calcium, or laboratory results demonstrating a serum calcium level below the lower limit of normal.

Statistical analysis

Cohort demographic characteristics, surgical and medical malabsorption prevalence, and rates of early and late postoperative hypocalcemia were evaluated, and descriptive statistics were calculated. Means with standard deviations (SD) or medians with interquartile ranges were used to present data for normally distributed and non-normally distributed continuous variables, respectively, whereas frequencies with percentages were used for categorical variables. Group comparisons were performed using χ^2 tests, Student’s t tests, Wilcoxon rank-sum tests, and analysis of variance, as appropriate. CDM requires redaction of count data with $n < 5$, so these values were omitted.

Univariable and multivariable logistic regression analyses were performed to determine associations between demographic and clinical characteristics and the occurrence of early or late postoperative hypocalcemia. Variables with significance below $P = .20$ on univariable analysis, as well as important demographic factors such as sex and race and ethnicity, were incorporated into the multivariable models. Subanalysis was performed by location in the gastrointestinal tract, defined as either “foregut/midgut” (gastrectomy, intestinal bypass, enterectomy, enterostomy, or pancreatectomy) or “hindgut” procedures (colectomy/colostomy), with Celiac and Crohn's disease grouped as “medical malabsorption.” Additional stratification by cervical procedure type (parathyroidectomy versus thyroidectomy) was performed; patients who received simultaneous thyroidectomy and parathyroidectomy ($n = 600$) were excluded from this subanalysis. In the subanalyses, any abdominal procedure with a sample size smaller than 10 was omitted. A P value of less than .05 was considered significant.

Results

Cohort characteristics

Of 25,400 included patients, 56.9% ($n = 14,446$) underwent total thyroidectomy, 40.8% ($n = 10,354$) parathyroidectomy, and 2.4% ($n = 600$) both procedures (Table I). The mean age was 59.9 (SD 15.0) years, 77.1% ($n = 19,573$) were female, and 72.9% ($n = 18,511$) were non-Hispanic White. In total, 1,011 patients had a pre-existing malabsorptive condition: 61 gastrectomy, 53 enterectomy, 36 enterostomy, 29 pancreatectomy (19 distal pancreatectomies, 5 Whipple procedures, 1 total pancreatectomy, and 4 unknown extent), 140 intestinal bypass, 266 colectomy/colostomy, 255 Crohn's disease, and 205 Celiac disease. Patients with malabsorptive conditions differed significantly from those without malabsorptive conditions in demographic and clinical characteristics (Table I). Only 51.9% of patients with a malabsorptive condition and 43.7% of patients without such a condition had a preoperative calcium value recorded. The mean serum calcium level was 9.14 (SD 1.17) mg/dL in patients with a malabsorptive condition and 9.21 (SD 1.14) mg/dL in those without a malabsorptive condition ($P = .18$). A total of 15.7% of patients with malabsorption were prescribed calcitriol before or on the date of the surgery versus 13.0% of patients without a malabsorptive condition ($P = .014$).

Rates of postoperative hypocalcemia

Overall, hypocalcemia occurred in 22.4% ($n = 5,701$) of patients. A minority (8.8%, $n = 2,231$) experienced early hypocalcemia, whereas 18.3% ($n = 4,657$) experienced late hypocalcemia. There was no significant difference in unadjusted rates of early or late hypocalcemia between patients with medical malabsorptive conditions and those without (Table II). On the other hand, compared with patients without malabsorptive conditions, the rates of late hypocalcemia were significantly higher among patients with prior intestinal bypass (25.7% vs 18.1%, $P = .020$), pancreatectomy (41.4% vs 18.1%, $P = .001$), and colectomy/colostomy (22.9% vs 18.1%, $P = .042$). Similarly, any hypocalcemia was more common among patients with prior intestinal bypass (30.0% vs 22.2%, $P = .028$), enterostomy (36.1% vs 22.2%, $P = .045$), and pancreatectomy (44.8% vs 22.2%, $P = .003$) than among patients without malabsorption.

Adjusted risk of postoperative hypocalcemia

For the primary analysis, risk of postoperative hypocalcemia within 1 year was assessed. Unadjusted, patient demographic and clinical characteristics such as Hispanic ethnicity, chronic kidney disease diagnosis, and Elixhauser score were associated with greater odds of hypocalcemia. Patients who underwent total thyroidectomy (odds ratio [OR]: 1.22, 95% confidence interval [CI]: 1.15–1.30, $P < .0001$), combined thyroidectomy/parathyroidectomy (OR: 2.39, 95% CI: 2.01–2.84, $P < .0001$), or concurrent lymphadenectomy (OR: 1.89, 95% CI: 1.74–2.05, $P < .0001$) also were more likely to develop hypocalcemia. A history of intestinal bypass was associated with 50% greater odds of hypocalcemia (OR: 1.50, 95% CI: 1.04–2.15, $P = .0293$) and enterostomy nearly double the odds (OR: 1.98, 95% CI: 1.00–3.90, $P = .0497$). Patients with prior pancreatectomy demonstrated nearly triple the odds (OR: 2.84, 95% CI: 1.36–5.90, $P = .0052$) as patients without a surgical history.

On multivariable analysis, female sex, chronic kidney disease, increasing comorbidity burden, combined thyroidectomy and

Table I
Demographic, clinical, and surgical characteristics of included patients

Characteristic	All patients	With malabsorptive condition (*n* = 1,011)	No malabsorptive condition (*n* = 24,389)	*P* value
Age, yr, mean (SD)	59.9 (15.0)	62.2 (13.8)	59.8 (15.1)	<.001
Sex, *n* (%)				
Female	19,573 (77.1)	811 (80.2)	18,762 (76.9)	.046
Male	5,820 (22.9)	200 (19.8)	5,620 (23.0)	
Unknown	7 (0.0)	0 (0.0)	7 (0.0)	
Race and ethnicity, *n* (%)				
Non-Hispanic White	18,511 (72.9)	766 (75.8)	17,745 (72.8)	.026
Non-Hispanic Black	2,882 (11.3)	107 (10.6)	2,775 (11.4)	
Non-Hispanic Asian	747 (2.9)	15 (1.5)	732 (3.0)	
Hispanic	2,338 (9.2)	94 (9.3)	2,244 (9.2)	
Unknown	922 (3.6)	29 (2.9)	893 (3.7)	
Household income, *n* (%)				
<$40K	4,924 (19.4)	217 (21.5)	4,707 (19.3)	.034
$40–49K	1,740 (6.9)	70 (6.9)	1,670 (6.8)	
$50–59K	1,917 (7.5)	86 (8.5)	1,831 (7.5)	
$60–74K	2,474 (9.7)	101 (10.0)	2,373 (9.7)	
$75–99K	3,976 (15.7)	168 (16.6)	3,808 (15.6)	
≥$100K	8,447 (33.3)	317 (31.4)	8,130 (33.3)	
Unknown	1,922 (7.6)	52 (5.1)	1,870 (7.7)	
Education level, *n* (%)				
Less than 12th grade	79 (0.3)	6 (0.6)	73 (0.3)	.389
High school diploma	5,107 (20.1)	216 (21.4)	4,891 (20.1)	
Less than bachelor's degree	14,199 (55.9)	559 (55.3)	13,640 (55.9)	
Bachelor's degree or greater	5,381 (21.2)	204 (20.2)	5,177 (21.2)	
Unknown	634 (2.5)	26 (2.6)	608 (2.5)	
Procedure type, *n* (%)				
Total thyroidectomy	14,446 (56.9)	551 (54.5)	13,895 (57.0)	.073
Parathyroidectomy	10,354 (40.8)	427 (42.2)	9,927 (40.7)	
Both thyroidectomy and parathyroidectomy	600 (2.4)	33 (3.3)	567 (2.3)	
Lymphadenectomy, *n* (%)	3,096 (12.2)	117 (11.6)	2,979 (12.2)	.541
H2 blocker use, *n* (%)	409 (1.6)	32 (3.2)	377 (1.5)	<.001
PPI use, *n* (%)	3,467 (13.6)	205 (20.3)	3,262 (13.4)	<.001
Chronic kidney disease, *n* (%)	3,634 (14.3)	187 (18.5)	3,447 (14.1)	.001
Elixhauser comorbidities, *n* (%)				
0	14,200 (55.9)	357 (35.3)	13,843 (56.8)	<.001
1	3,543 (13.9)	129 (12.8)	3,414 (14.0)	
2	2,587 (10.2)	131 (13.0)	2,456 (10.1)	
≥3	5,070 (20.0)	394 (39.0)	4,676 (19.2)	

PPI, proton pump inhibitor; *SD*, standard deviation.

Table II
Hypocalcemia rates, unadjusted

Types of malabsorption	All hypocalcemia, *n* (%)	*P* value*	Early hypocalcemia, *n* (%)	*P* value	Late hypocalcemia, *n* (%)	*P* value*
No malabsorption	5,421 (22.2)		2,134 (8.7)		4,414 (18.1)	
Medical malabsorption						
Crohn disease	64 (25.1)	.273	23 (9.0)	.880	56 (22.0)	.111
Celiac disease	50 (24.4)	.458	22 (10.7)	.318	43 (21.0)	.287
Surgical malabsorption						
Gastrectomy	16 (26.2)	.453	7 (11.5)	.452	13 (21.3)	.515
Intestinal bypass	42 (30.0)	.028	16 (11.4)	.264	36 (25.7)	.020
Enterectomy†	– (22.6)	.942	– (<15%)	.200	– (20.8)	.616
Enterostomy	13 (36.1)	.045	6 (16.7)	.093	11 (30.6)	.053
Colectomy/colostomy	70 (26.3)	.111	17 (6.4)	.175	61 (22.9)	.042
Pancreatectomy†	– (44.8)	.004	– (<15%)	.337	– (41.4)	.001

* *P* values compared with patients without malabsorptive conditions.
† Sample size redacted due to small *n* within "early hypocalcemia."

parathyroidectomy, and concurrent lymphadenectomy were associated with higher odds of postoperative hypocalcemia (Figure 2). Patients with a history of pancreatectomy demonstrated over twice the odds of hypocalcemia compared with patients without a history of pancreatectomy (OR: 2.27, 95% CI: 1.08–4.79, *P* = .031). Individually, the other gastrointestinal surgical procedures examined (gastrectomy, intestinal bypass, enterectomy, enterostomy, and colectomy/colostomy) and medical malabsorptive diseases (Crohn's and Celiac disease) were not significantly associated with postoperative hypocalcemia. After grouping the prior gastrointestinal surgical procedures by anatomic subdivision (foregut/midgut versus hindgut), history of a foregut/midgut-related surgery was associated with increased odds of postoperative hypocalcemia (OR: 1.35, 95% CI: 1.06–1.73, *P* = .015) (Figure 2). Hindgut surgery and medical malabsorptive conditions did not demonstrate any association with hypocalcemia.

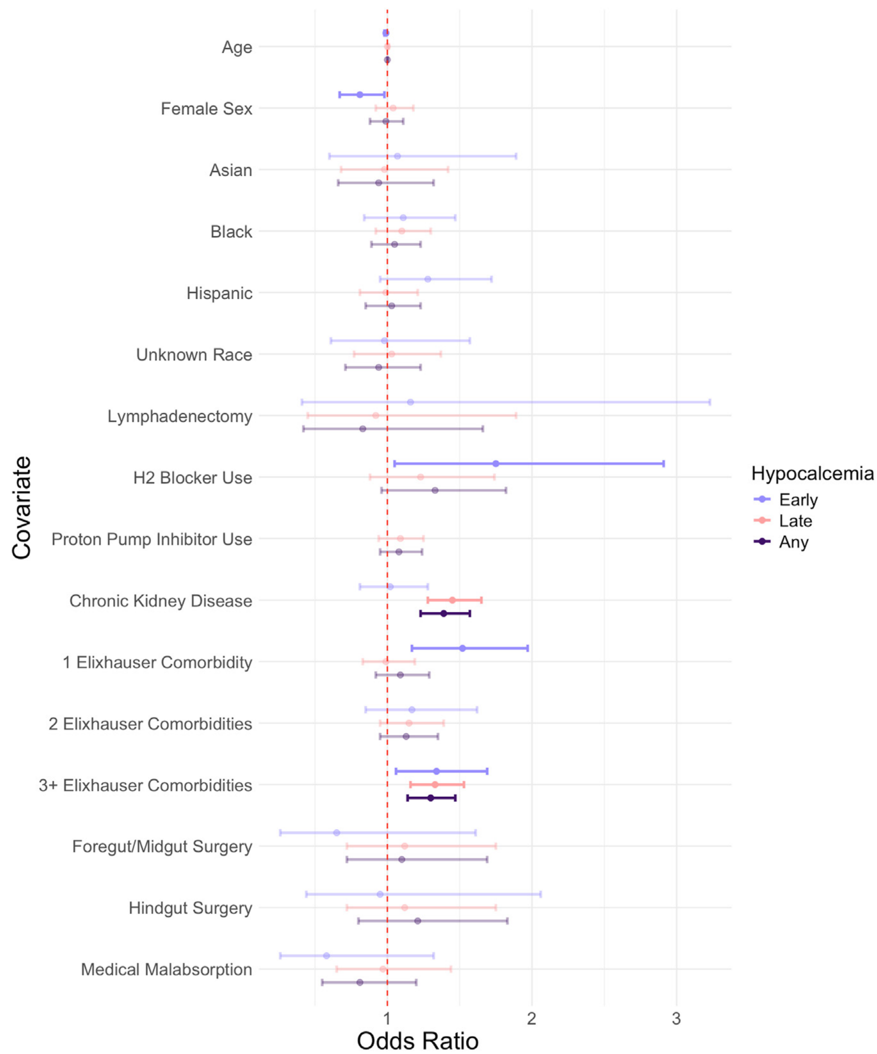

Figure 2. Forest plot demonstrating odds of early, late, and any postoperative hypocalcemia across all included cervical procedures, stratified by foregut/midgut, hindgut, or medical malabsorption. Significant findings are indicated by darker coloration.

Subset analysis by cervical procedure type

As patients who underwent total thyroidectomy were found to be more likely to develop postoperative hypocalcemia than those who underwent parathyroidectomy, subset analysis by surgery type was performed to further delineate factors unique to each procedure (Figure 3). For patients who underwent parathyroidectomy, chronic kidney disease and the presence of multiple other comorbidities were associated with postoperative hypocalcemia; however, none of the malabsorptive conditions demonstrated a significant association with hypocalcemia. In contrast, for patients who underwent total thyroidectomy, several additional factors were significantly associated with hypocalcemia. Female sex, higher comorbid disease burden, and concurrent lymphadenectomy were associated with greater odds of hypocalcemia, whereas Black race and older age were protective. Furthermore, patients with a history of intestinal bypass (OR: 1.85, 95% CI: 1.16–2.94, $P = .009$) or enterostomy (OR: 2.35, 95% CI: 1.06–5.18, $P = .035$) were at a significantly higher risk of hypocalcemia after thyroidectomy. History of any foregut/midgut surgery was associated with hypocalcemia after total thyroidectomy (OR: 1.65, 95% CI: 1.21–2.26, $P = .002$) but not after parathyroidectomy (OR: 1.10, 95% CI: 0.72–1.69, $P = .647$) (Figure 3). Medical disease was associated with hypocalcemia within 1 year in thyroidectomy patients only (OR: 1.38, 95% CI: 1.04–1.84, $P = .027$).

Early versus late hypocalcemia

The odds of early and late hypocalcemia were assessed separately, according to the variables of interest. Interestingly, while most relevant variables (female sex, comorbidity burden, and cervical procedure type) were associated with both early and late postoperative hypocalcemia, the effects of prescribed H2 blockade and surgical malabsorption were temporally specific (Figure 2). Antihistamine prescriptions were significantly associated with higher odds of early postoperative hypocalcemia after all procedures (OR: 1.67, 95% CI: 1.23–2.28; $P = .001$), as well as after total thyroidectomy (OR: 1.66, 95% CI: 1.11–2.49; $P = .013$) and after parathyroidectomy (OR: 1.75, 95% CI: 1.05–2.91; $P = .032$) individually (Figure 3). However, antihistamine prescriptions were not significantly associated with late hypocalcemia.

In contrast, no gastrointestinal surgical procedure was significantly associated with early hypocalcemia. “Foregut/midgut” procedures as a group were associated with late hypocalcemia (OR: 1.44, 95% CI: 1.11–1.85, $P = .006$) but not early hypocalcemia (OR: 1.13, 95% CI: 0.79–1.62, $P = .508$) across all patients (Figure 2).

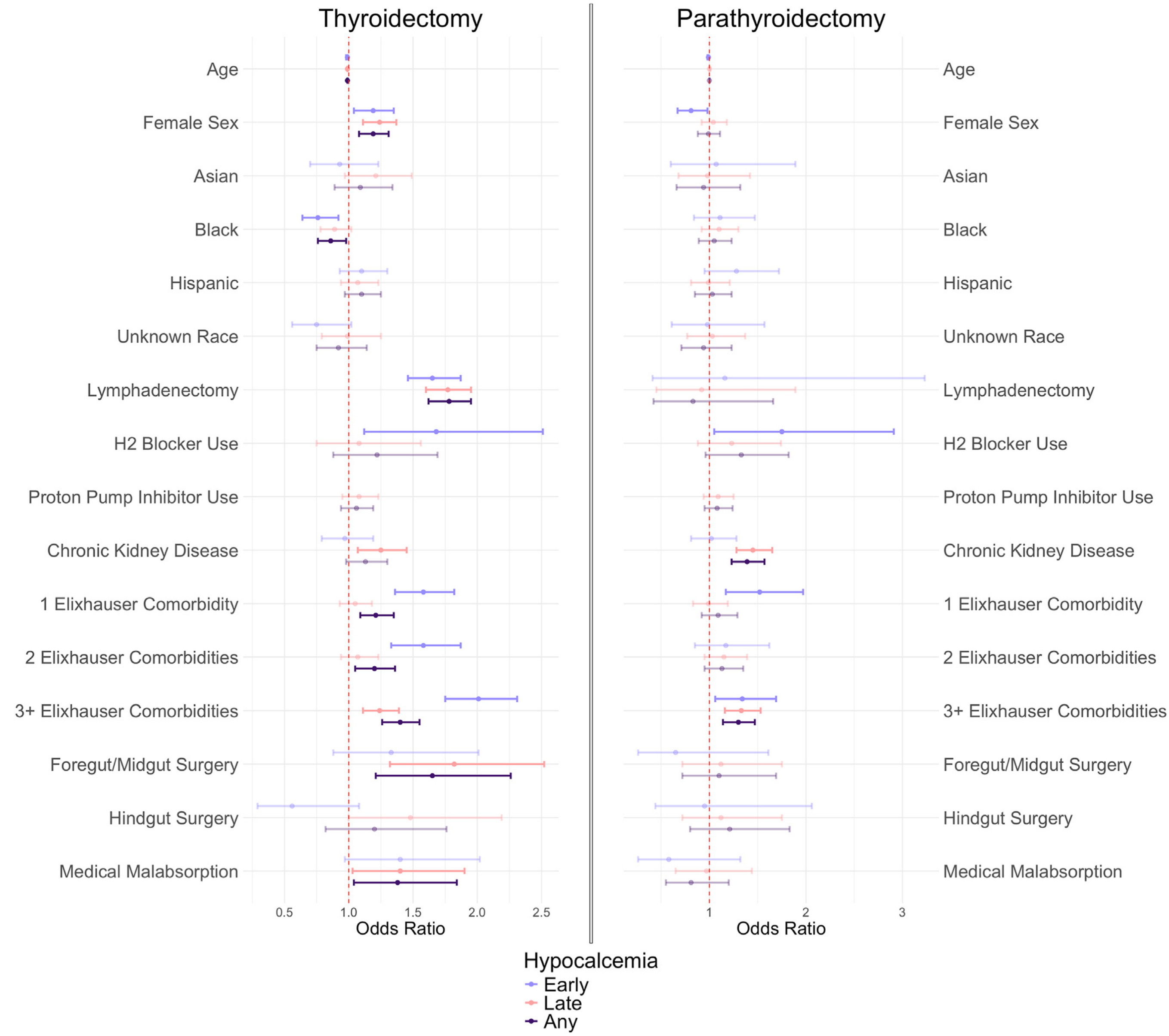

Figure 3. Forest plot demonstrating odds of early, late, and any postoperative hypocalcemia in patients undergoing thyroidectomy or parathyroidectomy, stratified by foregut/midgut, hindgut, or medical malabsorption. Significant findings are indicated by darker coloration.

This association was present in thyroidectomy patients (early [OR: 1.33, 95% CI: 0.88–2.01, $P = .175$] versus late [OR: 1.82, 95% CI: 1.32–2.52, $P < .001$]) but not parathyroidectomy patients when stratified by cervical procedure type (Figure 3). A similar pattern was seen in patients with medical disease, who demonstrated significantly higher odds of late hypocalcemia rather than early hypocalcemia. When assessed by each specific malabsorptive condition, pancreatectomy and intestinal bypass were both individually associated with greater odds of late hypocalcemia in total thyroidectomy patients.

Discussion

Postoperative hypocalcemia remains one of the most common complications of thyroidectomy and parathyroidectomy. Despite the intimate relationship between dietary calcium absorption and calcium homeostasis, the relationship between preexisting malabsorptive conditions and hypocalcemia after thyroid and parathyroid surgery remains poorly characterized. Here, we describe acute and delayed rates of hypocalcemia across a large national cohort over the past 2 decades, with attention to the relationship with preexisting malabsorptive conditions. We found that rates of hypocalcemia were significantly higher among patients who underwent total thyroidectomy than among those who underwent parathyroidectomy, and that the risk of hypocalcemia in these patients was strongly associated with a history of foregut/midgut surgery, including prior intestinal bypass, enterostomy, or pancreatectomy. This association was primarily driven by higher rates of late postoperative hypocalcemia, whereas the risk of early postoperative hypocalcemia was predicted by other patient demographic and clinical factors.

Although this study does not specifically address the mechanisms by which patients with prior foregut/midgut surgery may have higher odds of hypocalcemia, there are multiple potential mechanisms that may explain this relationship. First and foremost, calcium absorption is known to occur via both passive and active transport mechanisms. Passive transport occurs in a paracellular manner across the entire gastrointestinal tract; active transport occurs in a transcellular manner in the duodenum and proximal jejunum and is dependent on vitamin D–regulated mechanisms.[18] Passive transport accounts for only 8%–23% of calcium absorption at typical intake levels.[19] Thus one may expect that the reduction of this critical absorptive surface area in the proximal intestine would lead to corresponding deficiencies in calcium homeostasis. Notably, calcium bioavailability is also reduced as higher pH levels, which are also seen in a number of these resections as a result of gastric antral resection or exclusion.[20] In our study, patients with enterostomy and gastric bypass were at higher risk of postoperative hypocalcemia (on univariable analysis and after total thyroidectomy), correlating with each of these mechanisms, respectively. Vitamin D metabolism, key to calcium homeostasis via upregulation of active transport in the proximal gut, is also altered in many procedures of the foregut and midgut.[21] Patients with sleeve gastrectomy and gastric bypass have been shown to have greater rates of hypovitaminosis D requiring supplementation, possibly as a result of fat malabsorption or alterations in gut acidity.[22,23] Such patterns are also found in those with exocrine pancreas insufficiency, alongside deficiencies in other fat-soluble vitamins.[24] This may be a result of the dependence of vitamin D on fat vehicles for absorption, which require pancreatic enzymes for intraluminal metabolism.[25] This mechanism is of great interest, as we see a profound effect of pancreatectomy on rates of hypocalcemia in this study.

When stratified by early versus late timing of hypocalcemia, we found higher rates of late hypocalcemia rather than early hypocalcemia in both patients with and without a malabsorptive condition. This finding seems counterintuitive, as relative hypoparathyroidism should be more pronounced early on in the postoperative phase, and it may represent an artifact of data collection instead of the prevalence of hypocalcemia. Patients getting postoperative bloodwork in the week following the procedure may only represent the portion for whom hypocalcemia was clinically suspected, whereas those being tested later may only be being seen assessed as part of regular health maintenance—a significantly greater population. These differences may also reflect the conclusion of regular postoperative calcium supplementation prophylaxis programs, leading to more pronounced differences in hypocalcemia between control groups and those with malabsorptive conditions. Differences in vitamin D absorption may also explain these findings. Vitamin D turnover in the body is slower than that of calcium, and so differences in hypocalcemia attributable to hypovitaminosis D may be slower to present. Finally, there may be baseline differences in hypocalcemia rates between these groups, though we notably did not see a difference in baseline serum calcium values.

These findings have important implications for risk stratification and individualized preventive care for patients undergoing thyroid and parathyroid surgery. Patients with a history of foregut/midgut surgery should be identified as high risk for hypocalcemia and managed accordingly to minimize risk in the pre-, intra-, and postoperative phases of care. Preoperatively, concomitant vitamin D deficiency should be diagnosed and treated, as vitamin D deficiency can exacerbate hypocalcemia. Some institutions use "prehabilitation" protocols to replete calcium and vitamin D before surgery in select patients.[26,27] We would suggest that this practice be extended to all patients with altered foregut/midgut anatomy as a universal precaution. During the intraoperative phase of care, the extent of thyroidectomy and lymphadenectomy correlate strongly with the risk of postoperative hypocalcemia.[28] Given the nonaggressive behavior of most well-differentiated thyroid cancers, the increased risk of more extensive thyroid resection on rates of hypocalcemia should be considered when determining operative extent in patients with altered foregut/midgut anatomy. Providers caring for patients with surgical malabsorption may consider less aggressive resection in these patients when oncologically acceptable.

Regarding the postoperative phase of care, there is considerable variability by institution in prophylactic regimens to prevent hypocalcemia.[28] In general, most protocols emphasize prevention of *transient* hypocalcemia through administration of calcium and/or vitamin D supplementation for a short period after surgery.[28] Although the specific dosing and duration of these regimens vary by study, it has been demonstrated that these medications (especially in tandem) can prevent transient hypocalcemia postoperatively, though they have no effect on rates of permanent hypocalcemia.[28] In this study, we identified several risk factors associated with early postoperative hypocalcemia for which such regimens could be tailored, such as female sex, comorbid disease burden, and H2 blocker use. Importantly, though, we also found that surgical malabsorptive conditions were associated with *late* hypocalcemia, which is typically not addressed in standard algorithms. For these patients, more appropriate interventions may include longer-term monitoring of calcium and vitamin D levels, planning for prolonged supplementation, and targeted optimization of their malabsorptive condition (such as through aggressive management of enterostomy output or pancreatic insufficiency). In addition, administration of calcium citrate rather than calcium carbonate has been established as an effective mechanism for the management of hypocalcemia after bariatric gastric bypass due to its improved solubility at higher pH levels.[29–31] Based on our findings, we suggest that calcium citrate should be used preferentially in all patients with altered foregut/midgut anatomy, not just those with prior bariatric gastric bypass; further research will be needed to assess the role of calcium citrate in this population. However, given the risks associated with chronic calcium supplementation, novel therapeutic approaches may also have to be considered.[32]

One notable finding from this study was the specific risk of postoperative hypocalcemia after pancreatectomy. Although the altered intestinal anatomy following reconstruction after pancreatic head resections may partially explain this finding, our population consisted of primarily distal pancreatectomies, and this effect persisted when patients with Whipple procedures were evaluated separately. This result raises questions regarding the role of relative pancreatic insufficiency after partial pancreatectomy in the uptake of fat-soluble vitamin D, which warrants further investigation.[24,33–35]

Study limitations

Although this study represents one of the most comprehensive evaluations of the risk of postoperative hypocalcemia in relation to surgical malabsorption, our findings must be viewed within the context of the limitations of our data source and study design. First, we are unable to differentiate between patients with asymptomatic versus symptomatic hypocalcemia. Given high utilization of oral calcium and vitamin D supplementation, determining when a patient is administered additional or increased dosages based on symptomatology is infeasible in this retrospective database study; we are only able to capture biochemical hypocalcemia, diagnosis codes, and extreme cases requiring intravenous calcium administration, which are quite rare. Although differences in late hypocalcemia rates in patients with altered foregut/midgut anatomy exist, they may not be clinically relevant if patients did not develop symptoms. Our detection windows for early versus late hypocalcemia are relatively arbitrary and differences in rates between these timeframes may be a product of ascertainment bias rather than mechanistic in nature. We also did not differentiate use of calcium carbonate versus calcium citrate given differing practice patterns regarding regular postoperative prophylaxis.

Although CDM features expansive multidimensional claims data, there is significant missingness in several covariates, such as body mass index and specific laboratory values including serum calcium (>50% of subjects), parathyroid hormone (approximately 80% missingness), vitamin D (approximately 80%), magnesium (approximately 95%), and phosphorus (approximately 90%), which may impact risk of hypocalcemia. This is a significant limitation, as we are unable to account for preoperative differences in these associated laboratory values, nor are we able to quantify postoperative differences across study groups to determine if malabsorption is directly related to postoperative hypoparathyroidism, rather than hypocalcemia. It is possible that rates of postoperative hypocalcemia reflect only pre-existing rates of hypocalcemia rather than increased risk secondary to the cervical procedures studied. This, however, does not change our finding of higher postoperative hypocalcemia rates in certain subpopulations; in fact, we would expect that those with hypocalcemia at baseline should still have higher rates postoperatively. We are also unable to adjust calcium for albumin levels given missingness of this variable; it is possible that patients with altered foregut/midgut anatomy have higher rates of hypoalbuminemia, confounding biochemical serum calcium testing. Despite these limitations of the CDM, the use of this database also retains significant advantages in that it reflects one of the largest and most cross-sectional data sources available to assess this question, as opposed to more granular but less externally valid studies using data from a single institution.

We were unable to account for granular details of surgical procedures given our reliance on claims data; for example, although we were able to determine that a patient underwent a small bowel resection, intestinal bypass, or enterostomy, we were unable to determine the extent of intestine resected, bypassed, or excluded respectively. Similarly, there was no mechanism by which we could determine disease severity for patients with Crohn's or Celiac disease. In addition, CDM only includes patients insured by a single private payer, introducing selection bias. Furthermore, to capture the exposures and outcomes of interest, we required patients to have 4 years of continuous insurance coverage before their index thyroid or parathyroid surgery as well as 1 year of coverage following their procedure, which selects for patients with stable long-term insurance coverage. Thus, our findings may not be representative of patients facing greater socioeconomic disadvantage who may vary in receipt of postoperative access to care. Finally, because of sample size considerations, we were unable to look back further than 4 years in each patient. As a result, we may not have captured distant past surgical history, likely leading to misclassification of some patients with a malabsorptive condition into the control group.

In conclusion, while postoperative hypocalcemia may occur in any patient undergoing anterior cervical surgery, patients undergoing total thyroidectomy are at higher risk. A history of prior intestinal foregut/midgut surgery is associated with significantly greater risk of delayed postoperative hypocalcemia after thyroidectomy; these patients warrant enhanced observation and treatment protocols. Future investigations should evaluate optimal prevention and treatment strategies in patients with malabsorptive conditions to prevent this common postoperative complication.

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Conflict of Interest/Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2024.08.057].

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