Hypocalcemia after parathyroidectomy in patients with a history of bariatric surgery

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Research Article

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Abstract

Purpose

A growing body of literature has suggested that a history of bariatric surgery increases the risk of hypocalcemia after subsequent thyroidectomy, however little is known about the risk after parathyroidectomy. The purpose of this study was to determine the incidence of hypocalcemia after parathyroidectomy in patients with prior bariatric surgery.

Methods

The TriNetX Research Network was queried using diagnosis and procedure codes to identify patients with a history of bariatric surgery who were subsequently diagnosed with primary hyperparathyroidism (PHP) and underwent parathyroidectomy between 2012 and 2022. The rate of short-term and permanent hypocalcemia after parathyroidectomy was compared between those with a history of bariatric surgery and matched controls who underwent parathyroidectomy alone.

Results

There were 34,114 patients diagnosed with PHP who underwent parathyroidectomy. Of this cohort, 1.5% (n = 520) had prior bariatric surgery. There were 91% females and 9% males in this subset of patients, and the average age was 59 years. Compared to matched controls who underwent parathyroidectomy alone, these patients had a significantly increased risk of short-term (RR, 95% CI, P) (21.5% vs. 12.3%; 1.8, 1.3–2.3, P < 0.001) and permanent (7.7% vs. <1.9%; 4.0, 2.0-7.9) hypocalcemia.

Conclusion

The current study is the first to indicate that patients with a history of bariatric surgery are at increased risk for short-term and permanent hypocalcemia after parathyroidectomy. Further research is required to determine optimal prevention and treatment strategies to decrease associated morbidity in this subset of patients.

Introduction

Obesity is associated with significant morbidity and mortality [1], and its prevalence continues to rise worldwide [2]. Bariatric surgery, which includes Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), gastric band (GB), and biliopancreatic diversion with duodenal switch (BPD), is performed on the morbidly obese when diet and exercise haven't succeeded or when a patient encounters serious health problems because of their weight [3, 4]. Unfortunately, the malabsorptive and restrictive mechanisms by which these procedures contribute to weight loss are also responsible for some of their complications, which include vitamin D deficiency, hypocalcemia, and secondary hyperparathyroidism [5–7].

The number of bariatric operations being performed is increasing [8]. There are reports of patients who are post-bariatric surgery going on to develop endocrine abnormalities of the thyroid and parathyroid glands, including primary hyperparathyroidism (PHP) [9–14]. Although there is a growing body of literature supporting that patients with a history of bariatric surgery who undergo subsequent thyroidectomy are at increased risk for hypocalcemia [15, 16], hypocalcemia after parathyroidectomy is not well-studied. Therefore, this research aimed to utilize an extensive database to determine the risk of hypocalcemia after parathyroidectomy in patients with a history of bariatric surgery.

Materials And Methods

Data was collected on July 15, 2022, from the TriNetX Research Network (Cambridge, MA), which included electronic medical records from over 100 million individuals and more than 50 healthcare organizations (HCOs) [17]. The TriNetX Research Network provides users with uniformly processed clinical data, including demographics, diagnoses, imaging, lab results, medications, procedures, and other interventions [18]. TriNetX complies with the Health Insurance Portability and Accountability Act (HIPAA). Any data displayed on the TriNetX platform in aggregate form, or any patient-level data provided in a data set generated by the TriNetX platform, only

contains de-identified data as per the de-identification standard defined in Section § 164.514(a) of the HIPAA Privacy Rule. The Penn State Institutional Review Board reviewed and approved STUDY00018629 as exempt according to institutional policies and applicable federal regulations.

The database was queried using ICD-10 and CPT codes to identify a cohort of patients diagnosed with PHP who underwent a parathyroidectomy between 2012 and 2022. Among this group, patients with a history of bariatric surgery prior to parathyroidectomy were identified via procedure codes for bariatric surgery (RYGB, SG, GB, BPD) or the diagnosis code for bariatric surgery status. The codes utilized to complete the search criteria are listed in Supplement 1.

The rates of short-term and permanent hypocalcemia were compared between patients with a history of bariatric surgery who underwent parathyroidectomy and controls matched for age, sex, race, ethnicity, and prior calcium and vitamin D supplementation who underwent parathyroidectomy alone. Short-term hypocalcemia was defined as that which was recorded in the patient record within six months following parathyroidectomy, and permanent hypocalcemia was recorded between six months and one year after surgery. Hypocalcemia was defined as a serum calcium ≤ 8.4 mg/dL or an ionized calcium ≤ 4.6 mg/dL or ≤ 1.1 mmol/L. Hypocalcemia was also defined using the diagnosis code for hypocalcemia for patients without biochemical values available. Although the definition of hypocalcemia may vary across laboratories, these values are commonly accepted [19].

All statistical analyses were performed within the TriNetX platform. Propensity score matching was performed via 1:1 nearest neighbor matching with a difference between propensity scores ≤ 0.1 and a tolerance level of 0.01. In addition, relative risks and associated 95% confidence intervals (CIs) were calculated to compare the incidence of hypocalcemia between each matched cohort. For results experienced by 1–9 patients, TriNetX rounds up to ten to ensure patient confidentiality. T-tests were also performed to compare the mean pre- and postoperative calcium, calcidiol, and PTH values between groups. Statistical significance was specified as $P < 0.05$.

Results

Of 34,114 patients who underwent parathyroidectomy for PHP, 1.5% (n = 520) had a history of bariatric surgery. The mean age at the time of parathyroidectomy was 59 years for this subset, with 91% females and 9% males. Relevant cohort demographics are described in Table 1. Patients who underwent bariatric surgery were more likely to be female and have a history of calcium (28.8% vs. 16.0%, P < 0.001) and vitamin D supplementation (36.7% vs. 29.8%, P < 0.001) compared to those who underwent parathyroidectomy alone. The mean pre- and postoperative calcium, vitamin D, and PTH levels of each cohort are listed in Table 2. On average, patients with a history of bariatric surgery had lower pre- and post-parathyroidectomy calcium levels and higher vitamin D and PTH levels than those who underwent parathyroidectomy alone.

Table 1
Sample Demographics and Select Clinical Characteristics (n = 34,114)

	Before Matching			After Matching		
	History of Bariatric Surgery and Parathyroidectomy (n = 520)	Parathyroidectomy Alone (n = 33,594)	P-Value	History of Bariatric Surgery and Parathyroidectomy (n = 520)	Parathyroidectomy Alone (n = 520)	P-Value
Age	58.6 +/- 10.7	60.8 +/- 13.1	< 0.001	58.6 +/- 10.7	58.2 +/- 11.3	0.48
Sex						
Male	46 (8.8%)	7,709 (22.9%)	< 0.001	46 (8.8%)	45 (8.7%)	0.91
Female	474 (91.2%)	25,883 (77.0%)	< 0.001	474 (91.2%)	475 (91.3%)	0.91
Race						
White	357 (68.7%)	21,614 (64.3%)	0.04	357 (68.7%)	365 (70.2%)	0.59
Black or African American	82 (15.8%)	4,704 (14.0%)	0.25	82 (15.8%)	77 (14.8%)	0.67
Asian	< 10 (< 1.9%)	545 (1.6%)	0.59	< 10 (< 1.9%)	< 10 (< 1.9%)	1.0
Native Hawaiian or Other Pacific Islander	0 (%)	17 (0.1%)	0.61	0 (%)	0 (%)	-
American Indian or Alaska Native	< 10 (< 1.9%)	99 (0.3%)	< 0.001	< 10 (< 1.9%)	0 (0%)	0.002
Unknown	78 (15.0%)	6,615 (19.7%)	0.008	78 (15.0%)	76 (14.6%)	0.63
Ethnicity						
Not Hispanic or Latino	425 (81.7%)	27,451 (81.7%)	0.99	425 (81.7%)	433 (83.3%)	0.51
Hispanic or Latino	30 (5.8%)	1,729 (5.1%)	0.52	30 (5.8%)	27 (5.2%)	0.68
Unknown	65 (12.5%)	4,414 (13.1%)	0.67	65 (12.5%)	60 (11.5%)	0.63
Other Features						
Calcium Supplementation	150 (28.8%)	5,360 (16.0%)	< 0.001	150 (28.8%)	143 (27.5%)	0.63
Vitamin D Supplementation	191 (36.7%)	10,024 (29.8%)	< 0.001	191 (36.7%)	188 (36.2%)	0.85

Table 2
Pre- and Postoperative Biochemical Values

Biochemical Values	History of Bariatric Surgery and Parathyroidectomy	Parathyroidectomy Alone	*P*-Value
Preoperative			
Calcium (mg/dL)	10.4 +/- 0.8 (n = 365)	10.7 +/- 0.8 (n = 21,165)	< 0.001
Calcidiol (ng/mL)	36 +/- 16 (n = 144)	32 +/- 15 (n = 6,941)	< 0.001
PTH (pg/mL)	170 +/- 185 (n = 316)	146 +/- 219 (n = 17,066)	0.01
Postoperative			
Calcium (mg/dL)	9.3 +/- 0.8 (n = 360)	9.4 +/- 0.7 (n = 20,920)	0.001
Calcidiol (ng/mL)	40 +/- 15 (n = 109)	36 +/- 15 (n = 5,363)	< 0.001
PTH (pg/mL)	76 +/- 57 (n = 302)	57 +/- 72 (n = 17,141)	< 0.001
Abbreviations: PTH, parathyroid hormone			

After matching, patients with a history of bariatric surgery had a significantly increased risk of short-term (RR, 95% CI, P) (1.8, 1.3–2.3, < 0.001) and permanent hypocalcemia (4.0, 2.0-7.9, P < 0.001) after parathyroidectomy compared to individuals who underwent parathyroidectomy alone (Table 3).

Table 3
Rate of Hypocalcemia Following Parathyroidectomy (n = 34,114)

	History of Bariatric Surgery and Parathyroidectomy (n = 520; 520 after matching)	Parathyroidectomy Alone (n = 33,594; 520 after matching)	RR (95% CI)	*P*-Value
Complication				
Short-Term Hypocalcemia	112 (21.5%)	64 (12.3%)	1.8 (1.3–2.3)	< 0.001
Permanent Hypocalcemia	40 (7.7%)	< 10 (< 1.9%)	4.0 (2.0-7.9)	< 0.001
Abbreviations: RR, relative risk				

Discussion

According to the World Health Organization, obesity is one of the most severe worldwide epidemics of the twenty-first century [20]. Bariatric surgery has been demonstrated to be an effective treatment for achieving sustained weight loss [3]. However, both morbid obesity and subsequent bariatric surgery may cause nutritional and metabolic deficiencies. Obese patients may have abnormal calcium homeostasis because of an unbalanced diet and decreased sun exposure [21–23]. In addition, malabsorptive and restrictive processes induced by bariatric surgery may lead to disturbances in calcium homeostasis, changes in bone mass, and increased preexisting metabolic derangements [5–7].

While bariatric procedures are well known to be associated with secondary hyperparathyroidism [24–27], recent studies suggest that bariatric surgery may also raise the risk of developing primary hyperparathyroidism (PHP) and the formation of parathyroid adenomas [9–14]. Keskin et al. reported five cases of PHP in patients who underwent prior SG, and suggested that there may be a relationship between bariatric surgery and PHP [13]. In the present study, 1.5% of patients in our cohort with PHP who underwent parathyroidectomy had a history of bariatric surgery, which is evidence that this is a clinically relevant population.

There is a growing body of literature suggesting that patients with a history of bariatric surgery have an increased risk of hypocalcemia after thyroidectomy [15], however far less is known about hypocalcemia after parathyroidectomy. Patients with weight loss surgery rely on compensatory increases in PTH production by the parathyroid glands to maintain adequate serum calcium

levels. Therefore, in the setting of parathyroid gland excision, whether incidental during a thyroidectomy or during a planned parathyroidectomy, these patients may be at increased risk for severe recalcitrant hypocalcemia. Palal et al. reported a case of life-threatening hypocalcemia in a patient with a previous RYGB who underwent subtotal parathyroidectomy to treat calciphylaxis associated with renal failure [28]. Monte et al. reported a case of hypocalcemia in a patient with prior RYGB who underwent parathyroidectomy for PHP, despite being discharged with calcium carbonate and calcitriol [9]. Conversely, Chen et al. described a series of ten patients with prior RYGB who underwent parathyroidectomy for PHP, however there were no postoperative complications [10]. In our current study, these patients were nearly twice as likely to experience short-term hypocalcemia and four times as likely to suffer from permanent hypocalcemia compared to patients who underwent parathyroidectomy alone.

There are no guidelines for the prevention or management of hypocalcemia after parathyroidectomy in patients with a history of bariatric surgery. There is evidence that patients who are vitamin D deficient can safely begin supplementation prior to surgery [29]. Therefore, it may be beneficial to offer this cohort of patients preoperative vitamin D screening and calcitriol supplementation. In the postoperative period, prophylactic calcium and vitamin D supplementation should be administered. Calcium citrate may be preferable to calcium carbonate, as it is better absorbed [30]. Patients who develop hypocalcemia should be prescribed the maximum doses of calcium citrate and calcitriol, and magnesium should be repleted. A prolonged hospital stay may be necessary for administration of intravenous calcium gluconate/acetate. Those with permanent hypocalcemia may consider adding the PTH analog teriparatide [29].

Although we are the first to present an analysis of a large sample size of patients with prior bariatric surgery who underwent parathyroidectomy, our study has limitations. First, a considerable portion of our cohort was identified using the diagnosis code for “bariatric surgery status,” and therefore did not have information on the specific type of bariatric procedure they underwent. As such, it was not possible to compare the rates of hypocalcemia in patients who underwent malabsorptive versus restrictive operations, which could potentially be associated with differing risks. Despite this, there is reason to believe that all bariatric procedures may be associated with an increased risk of hypocalcemia, as they are all associated with secondary hyperparathyroidism and an increased dependence on the parathyroid glands to maintain calcium homeostasis [24]. Additionally, we do not have information regarding the number of patients who had multi-gland disease or underwent a focused surgical approach versus bilateral neck exploration. These represent important areas of future research.

In conclusion, patients with a history of bariatric surgery may be at increased risk for both short-term and permanent hypocalcemia after parathyroidectomy. Surgeons should discuss this increased risk with these patients when obtaining informed consent. Efforts to improve outcomes in this population should focus on determining optimal prevention and treatment guidelines.

Declarations

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Ethics Approval: This is an observational study. The Penn State Institutional Review Board reviewed and approved STUDY00018629 as exempt according to institutional policies and applicable federal regulations.

Consent to Participate: This is an observational study. Any data displayed on the TriNetX platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX platform, only contains de-identified data. Therefore, the need for informed

consent was waived.

Consent to Publish: This is an observational study. Any data displayed on the TriNetX platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX platform, only contains de-identified data. Therefore, consent to publish was not applicable.

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