# Preoperative vitamin D deficiency is associated with increased risk of postoperative hypocalcemia after total thyroidectomy

Eun Ho Eunice Choi [1], Fares Qeadan,[2] Eyas Alkhalili,[3] Christina Lovato,[4] Mark R Burge [4]

[1]Clinical and Translational Science Center, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[2]Department of Family and Preventive Medicine, University of Utah Health, Salt Lake City, Utah, USA
[3]Department of Surgery, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA
[4]Department of Internal Medicine and Endocrinology, University of New Mexico Hospital, Albuquerque, New Mexico, USA

**Correspondence to**
Eun Ho Eunice Choi, Clinical and Translational Science Center, University of New Mexico Health Sciences Center, Albuquerque, NM 87131-5001, USA; echoi@salud.unm.edu

Accepted 9 March 2021



**To cite:** Choi EHE, Qeadan F, Alkhalili E, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2020-001644

## ABSTRACT

Prior single-institution studies suggest that preoperative vitamin D deficiency (VDD) is associated with postoperative hypocalcemia and a prolonged length of hospital stay following total thyroidectomy. In this study, we employ a multi-institutional, de-identified electronic health records database to address this issue. We hypothesize that total thyroidectomy patients with preoperative VDD will be at an increased associated risk of postoperative hypocalcemia and hospitalization. Using Cerner Health Facts, we identified 2447 patients who underwent total or subtotal thyroidectomy between 2008 and 2016 and who had a documented 25-hydroxyvitamin D concentration obtained within 12 months of the surgery date using International Classification of Diseases 9/10, Current Procedural Terminology and Healthcare Common Procedure Coding System codes. Data from 984 patients who underwent total thyroidectomy were analyzed. Analysis of variance models estimated the effect of VDD on postoperative numerical variables. Multiple logistic regression estimated the risk of postoperative hypocalcemia and hospital stay, adjusting for any imbalanced demographic variables and operative characteristics. On average, postoperative total calcium concentrations in the VDD group were lower by 0.3 mg/dL compared with that of the non-VDD group (p<0.01). The risk of postoperative hypocalcemia was 2.2 times higher in the VDD group compared with the non-VDD group (p<0.01). Although the length of hospital stay after thyroidectomy was longer in the VDD group compared with the non-VDD group (p=0.03), VDD is not an independent risk factor for prolonged hospitalization following thyroidectomy (p=0.13). VDD is associated with a higher risk of hypocalcemia following total thyroidectomy. Prethyroidectomy operative screening for VDD should be considered.

## Significance of this study

**What is already known about this subject?**

- Hypocalcemia is a common complication following total thyroidectomy.
- Vitamin D plays a critical role in calcium homeostasis.
- Findings from previous studies do not agree about the effect of preoperative vitamin D deficiency on the associated risk of postoperative hypocalcemia.

**What are the new findings?**

- Using a large electronic health records database compiling over 9 years of data, we found the adjusted risk of postoperative hypocalcemia was 2.2 times greater in vitamin D-deficient patients undergoing total thyroidectomy compared with those who were not vitamin D-deficient (p<0.01).
- We also found that the adjusted risk of prolonged hospitalization following thyroidectomy was not higher in vitamin D-deficient patients compared with those who were not vitamin D-deficient (p=0.11).

**How might these results change the focus of research or clinical practice?**

- We recommend that preoperative vitamin D concentrations be determined prior to the performance of total thyroidectomy and that consideration be given to preoperative vitamin D repletion in those who are deficient.

## INTRODUCTION

Hypocalcemia is a commonly occurring postoperative complication following thyroidectomy[1–4] and is associated with other postoperative complications, such as delayed discharge after surgery, unexpected reoperation, and an increased rate of recurrent laryngeal nerve injury.[5–7] In a retrospective cross-sectional study, about 19.1% of 126,766 patients who underwent total thyroidectomy developed postoperative hypocalcemia within 30 days of surgery.[8] The spectrum of clinical manifestations of hypocalcemia varies from ectodermal and dental changes and cataracts in chronic hypocalcemia, to tetany, papilledema, and life-threatening seizures in acute hypocalcemia.[9–13] While the presentation of hypocalcemia is well characterized, the threshold of serum calcium concentration used for the diagnosis of hypocalcemia may be loosely defined as varying from serum calcium concentration of <7.5 mg/dL to 8.4 mg/dL.[14–16]

Calcium homeostasis is maintained by the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25$(OH)_2$ D), in the intestine, kidney and bone.[17–20] In the intestine, 1,25$(OH)_2$ D directly promotes intestinal calcium absorption.[17] In the kidney and bone, parathyroid hormone (PTH) plays a major role in restoring calcium homeostasis by increasing the production of 1,25$(OH)_2$ D, which subsequently acts to increase calcium reabsorption into the bloodstream.[18–20] As such, many research efforts have been made to study the association between vitamin D deficiency (VDD) and postoperative hypocalcemia after thyroidectomy.[5 7 14 21–23] It is difficult, however, to generalize the findings from such studies due to their relatively small sizes and regionally isolated sample selections. In this study, we aim to ascertain the effect of VDD (25-hydroxyvitamin D ≤20 ng/mL) on serum calcium concentrations and length of stay following total thyroidectomy using a large-scale, multi-institutional electronic health records database. We hypothesize that VDD in total thyroidectomy patients will be associated with decreased serum calcium concentration and increased length of hospital stay compared with that of patients without VDD.

## METHODS

### Settings

This is a retrospective observational study using a large-scale, multi-institutional, de-identified electronic health records database called Health Facts, which provides diagnostic and medical laboratory data from hundreds of participating clinics and hospitals that employ Cerner PowerChart electronic health records across the USA. Specifically, Health Facts contains de-identified data from more than 68 million unique patients from more than 600 hospitals and clinics across the USA. Using this database, all patients who underwent total or subtotal thyroidectomy between 2008 and 2016 (inclusive) were identified using International Classification of Diseases 9/10 codes (06.3, 06.39, 06.4, 06.5, 06.50, 06.51, 06.52, 06.8, 06.81, 06.89) and Current Procedural Terminology/Healthcare Common Procedure Coding System codes (60210–60225, 60260, 60240, 60271, 60252, 60254, 60270).

### Inclusion/Exclusion

Inclusion criteria were performance of total or subtotal thyroidectomy on adult patients (≥18 years) and a documented 25-hydroxyvitamin D concentration obtained within 12 months of the date of surgery. Exclusion criteria were performance of a partial thyroidectomy or parathyroidectomy or lack of a documented 25-hydroxyvitamin D concentration obtained within the 12-month window surrounding the surgery.

### Measurements

Patients included in the analysis were divided into two groups: a vitamin D-deficient (VDD) group and a non-vitamin D-deficient (non-VDD) group. The VDD group was defined by a 25-hydroxyvitamin D concentration ≤20 ng/mL and the non-VDD group by a 25-hydroxyvitamin D concentration >20 ng/mL. In all cases, preoperative and postoperative laboratory measurements obtained closest to the surgery date were analyzed. Preoperative variables included patient demographics such as age and sex, indication for surgery, and preoperative laboratory measurements for 25-hydroxyvitamin D, serum calcium, phosphate, and albumin concentrations. Outcome variables included postoperative laboratory measurements such as serum calcium, albumin, phosphate, and PTH concentrations. The primary outcome variables (corrected serum calcium concentrations and length of hospital stay) were dichotomized into binary variables for analysis. Hypocalcemia was defined as a corrected serum calcium concentration <8 mg/dL. Hospitalization was defined as the absence of same-day discharge indicated by a length of hospital stay >0 days.

### Statistical analysis

For descriptive statistics, $\chi^2$ tests or Fisher's exact tests were used to assess any association between preoperative and postoperative categorical variables, and two-sample t-tests were used to compare group means for preoperative numerical variables. For postoperative numerical variables displaying normal distribution, analysis of variance models estimated the effect of VDD in the VDD group compared with the non-VDD group. For postoperative variables displaying exponential distribution, a likelihood ratio test was used for mean comparison between groups. For the two dichotomized primary outcome variables, hypocalcemia and prolonged length of hospital stay, multiple logistic regression modeling estimated the risk of postoperative hypocalcemia and prolonged hospital stay, adjusting for any imbalanced demographic variables and operative characteristics. The imbalanced demographic variables (age, race, urban/rural status) were included in the logistic regression model to account for any confounding effect from these group differences. Since the performance of neck dissection is known to be associated with postoperative hypocalcemia,[24] performance of this procedure was also adjusted for in the logistic regression model to account for any potential effect on the primary outcome. Finally, a sensitivity analysis was conducted on patients with vitamin D measurements taken within 90 days of surgery to ascertain the effect of the inclusion time period on the estimates. All analyses were performed using SAS V.9.4.

## RESULTS

### Sample selection

Figure 1 illustrates the sample selection. A total of 48,526 patients underwent total or partial thyroidectomy with or without concomitant parathyroidectomy within the predefined study interval. Of these, 18,887 patients who underwent parathyroidectomy or partial thyroidectomy were excluded. Of those who underwent total or subtotal thyroidectomy, 28,655 were excluded due to to lack of a 25-hydroxyvitamin D level being obtained within the predefined 12-month window. Data from the remaining 984 patients were analyzed. As shown in table 1, there were 488 patients in the non-VDD group and 496 patients in the VDD group. There were 410 vitamin D measurements obtained preoperatively and 574 obtained postoperatively.

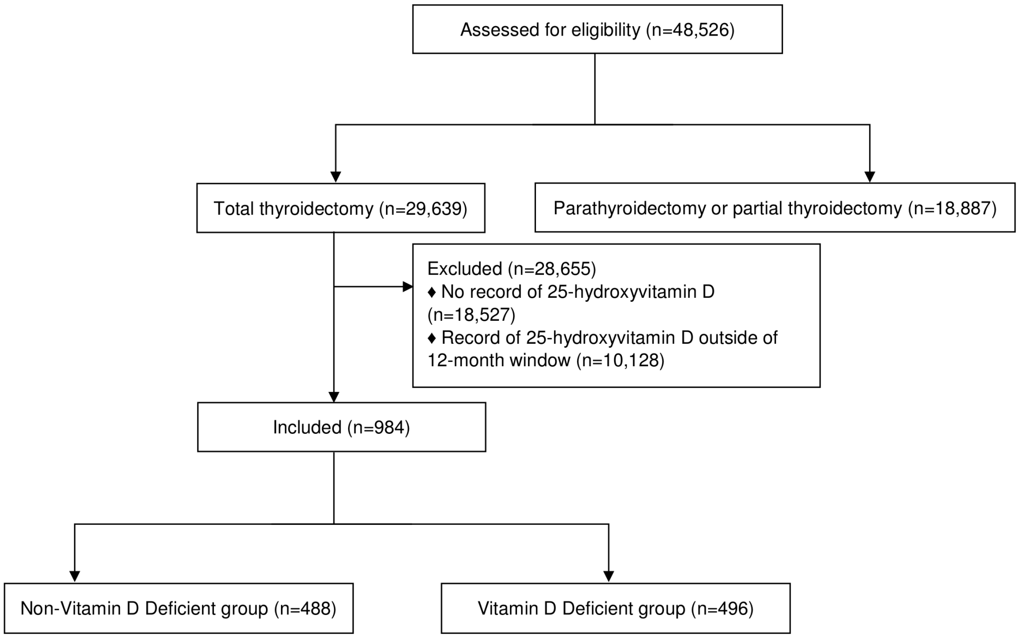


**Figure 1** Study flow chart.

## Preoperative characteristics

The average length of time between vitamin D measurement and surgery was 15±169 days in the VDD group compared with 44±167 days in the non-VDD group (p<0.01). The mean age in the VDD group was younger compared with the non-VDD group (p<0.01). As expected, the mean preoperative vitamin D concentration in the VDD group (9.6±8.3 ng/mL) was significantly lower than that of the non-VDD group (32.6±12.0 ng/mL, p<0.01). The mean preoperative serum calcium was also significantly lower in the VDD group (8.4±1.0 mg/dL) compared with that of the non-VDD group (8.6±0.9 mg/dL, p<0.01). Although Caucasians were most prevalent in both groups, there was a statistically significant difference in race and ethnicity between the two groups (p<0.01). Similarly, although most patients were from an urban setting as opposed to a rural setting in both groups, the VDD group showed a significantly higher proportion of patients from an urban setting compared with the non-VDD group (p=0.03). A higher rate of performance of neck dissection was observed in the non-VDD group compared with VDD group (p<0.01). Other demographic and clinical characteristics such as sex, body mass index, malignancy in surgical pathology, and season of surgery were also considered but did not show a statistically significant difference between the two groups.

## Postoperative characteristics

As shown in table 2, postoperative total calcium concentration was significantly lower by 0.3 mg/mL, on average, compared with that of the non-VDD group (p<0.01). Same-day discharge was significantly higher in the non-VDD group compared with the VDD group (p=0.03), and the length of hospital stay after thyroidectomy was prolonged in the VDD group by 5 hours, on average, compared with the non-VDD group (p=0.03). The proportion of patients who were prescribed calcium and/or vitamin D supplemental therapy on discharge was significantly higher in the non-VDD group compared with the VDD group (p<0.01). Postoperative serum magnesium concentration was slightly higher in the non-VDD group compared with the VDD group (p<0.01), and serum creatinine concentration was also significantly higher in the non-VDD group compared with the VDD group (p=0.01). Other postoperative variables such as ionized serum calcium concentration, serum phosphate concentration, and serum albumin concentration were analyzed and found to be similar between the two groups.

As shown in table 3, multiple logistic regression modeling demonstrated that the adjusted odds of postoperative hypocalcemia were 2.2 times greater in the VDD group compared with the non-VDD group (95% CI 1.6 to 3.1, p<0.01), and that the adjusted odds of prolonged hospitalization following thyroidectomy were not higher in the VDD group compared with the non-VDD group (p=0.13).

## Sensitivity analysis

A sensitivity analysis was performed to assess the validity of using a 12-month window for 25-hydroxyvitamin D levels compared with a 90-day window. A total of 594 individuals were available for this sensitivity analysis. As shown in tables 4 and 5, the sensitivity analysis replicated the findings of our larger cohort. Specifically, the average postoperative total calcium concentration was 0.4 mg/dL lower in the VDD group compared with the non-VDD group (p<0.01). The postoperative PTH concentration, on average, was 6.6 pg/mL higher in the VDD group compared with the non-VDD group (p=0.04). The postoperative magnesium and creatinine levels were also significantly higher in the non-VDD group compared with the VDD group (both p<0.01), and the adjusted odds of postoperative hypocalcemia were 2.5 times higher in the VDD group compared with the non-VDD group (95% CI 1.6 to 3.9, p<0.01).

**Table 1** Patient demographics and preoperative clinical characteristics

| | VDD (≤20 ng/mL) (n=496) Mean (±SD) or n (%) | Non-VDD (>20 ng/mL) (n=488) Mean (±SD) or n (%) | P value |
|---|---|---|---|
| Age | 48 (±15) | 51 (±15) | <0.01 |
| Sex | | | 0.83 |
| Female | 407 (82.1) | 403 (82.6) | |
| Male | 89 (17.9) | 85 (17.4) | |
| BMI (kg/m$^2$) | 30.2 (±7.8) | 29.5 (±7.3) | 0.48 |
| Preoperative vitamin D (ng/mL) | 9.6 (±8.3) | 32.6 (±12.0) | <0.01 |
| Length of time from vitamin D measurement to surgery date (days) | 14.6 (±168.7) | 44.3 (±166.5) | <0.01 |
| Preoperative serum calcium (mg/dL) | 8.4 (±1.0) | 8.6 (±0.9) | <0.01 |
| Preoperative PTH (pg/mL) | 36.4 (±28.5) | 34.8 (±27.0) | 0.60 |
| Race/ethnicity | | | <0.01* |
| Caucasian | 315 (63.5) | 363 (74.4) | |
| African American | 115 (23.2) | 67 (13.7) | |
| Asian | 10 (2.0) | 15 (3.1) | |
| Native American | 7 (1.4) | 7 (1.4) | |
| Hispanic | 5 (1.0) | 4 (0.8) | |
| Other | 44 (8.9) | 32 (6.6) | |
| Urban | 388 (78.2) | 352 (72.1) | 0.03 |
| Rural | 108 (21.8) | 136 (27.9) | |
| Diuretic use | 24 (4.8) | 24 (4.9) | 0.95 |
| Proton pump inhibitor use | 66 (13.3) | 55 (11.3) | 0.33 |
| Surgical pathology | 253 (66.2) | 274 (68.0) | 0.60 |
| Malignant | | | |
| Season of surgery | | | 0.43 |
| Winter | 114 (23.0) | 94 (19.3) | |
| Spring | 118 (23.8) | 133 (27.3) | |
| Summer | 127 (25.6) | 124 (25.4) | |
| Autumn | 137 (27.6) | 137 (28.1) | |
| Performance of neck dissection | 2 (0.4) | 13 (2.7) | <0.01* |

$\chi^2$ test and Fisher's exact test for categorical variables and t-test for numerical variables.
*Fisher's exact test.
BMI, body mass index; PTH, parathyroid hormone; VDD, vitamin D deficiency.

## DISCUSSION

This retrospective, multi-institutional study demonstrates that preoperative VDD is associated with a higher risk of postoperative hypocalcemia and a slightly longer hospital stay among inpatients, but it is not associated with an increased risk of postoperative hospitalization after adjusting for baseline variables. These findings confirm our previous single-institution study.[5]

There is ongoing debate about the predictive value of preoperative VDD in the development of postoperative hypocalcemia. Some studies have found VDD to be predictive of postoperative hypocalcemia. For example, in a retrospective study of 166 patients with total thyroidectomy performed between 2006 and 2009, Kirkby-Bott *et al*[7] reported that a 19% higher proportion of vitamin D-deficient patients who underwent total thyroidectomy experienced hypocalcemia compared with those who were vitamin D-sufficient. Additionally, Kim *et al*[25] found the occurrence of symptomatic hypocalcemia to be 13% higher in vitamin D-deficient patients with thyroid cancer following total thyroidectomy and central compartment neck dissection.

Conversely, several studies have suggested that VDD is not a risk factor for postoperative hypocalcemia in patients undergoing thyroidectomy. In a retrospective study of 121 patients, Griffin *et al*[26] found a similar incidence rate of postoperative hypocalcemia among vitamin D deficient and sufficient total thyroidectomy patients between 2009 and 2012. This study included only 11 patients in the vitamin D-sufficient group, however. In the current study, we identified 496 patients in the vitamin D-deficient group and 488 patients in the vitamin D-sufficient group. In another retrospective study of 150 patients performed between 2007 and 2013, Cherian *et al* found that VDD defined by a vitamin D concentration <20 ng/mL did not increase the risk of postoperative hypocalcemia in thyroidectomy patients.[27] However, this study included all thyroidectomy patients. In the current study, we excluded patients who received parathyroidectomy and/or partial thyroidectomy, thereby preventing any potential confounding effect that may arise from known and unknown effects of PTH removal or less extensive surgery on hypocalcemia. In another retrospective study of 368 patients who had total thyroidectomy performed from 2012 to 2015, VDD was defined by vitamin D concentrations <50 nmol/L (approximately 20 ng/mL), and no relationship was found between VDD and risk of postoperative hypocalcemia.[28] However,

**Table 2** Postoperative clinical findings and outcomes

| | n | VDD (≤20 ng/mL) (n=496) Mean (95% CI) or n (%) | n | Non-VDD (>20 ng/mL) (n=488) Mean (95% CI) or n (%) | P value |
|---|---|---|---|---|---|
| Total calcium (mg/dL) | 247 | 8.1 (8.0 to 8.2) | 421 | 8.4 (8.3 to 8.5) | <0.01 |
| Within 48 hours of surgery | 115 | 8.0 (7.8 to 8.2) | 192 | 8.3 (8.2 to 8.4) | <0.01 |
| After 48 hours of surgery | 132 | 8.0 (7.8 to 8.2) | 229 | 8.3 (8.2 to 8.4) | <0.01 |
| Corrected calcium (mg/dL) | 186 | 8.3 (8.2 to 8.4) | 319 | 8.5 (8.4 to 8.6) | 0.04 |
| Within 48 hours of surgery | 73 | 8.0 (7.8 to 8.3) | 115 | 8.2 (8.1 to 8.3) | 0.20 |
| After 48 hours of surgery | 113 | 8.3 (8.1 to 8.5) | 204 | 8.5 (8.4 to 8.6) | 0.06 |
| Ionized calcium (mmol/L) | 115 | 1.1 (1.1 to 1.1) | 170 | 1.1 (1.1 to 1.2) | 0.11 |
| Phosphorus (mg/dL) | 165 | 3.3 (3.1 to 3.4) | 230 | 3.4 (3.3 to 3.5) | 0.15 |
| PTH (pg/mL) | 169 | 35.0 (30.3 to 41.0) | 308 | 30.6 (27.5 to 34.3) | 0.10* |
| Magnesium (mg/dL) | 144 | 1.7 (1.6 to 1.7) | 207 | 1.8 (1.7 to 1.8) | <0.01 |
| Creatinine (mg/dL) | 151 | 0.7 (0.7 to 0.8) | 297 | 0.8 (0.8 to 0.8) | 0.01 |
| Albumin (g/dL) | 327 | 3.8 (3.7 to 3.9) | 338 | 3.8 (3.7 to 3.8) | 0.69 |
| Length of stay, hours | 270 | 35.6 (31.7 to 40.2) | 232 | 30.3 (26.8 to 34.6) | 0.03* |
| Same-day discharge | | 232 (47.5) | | 270 (54.4) | 0.03 |
| Intravenous calcium therapy | | 4 (0.8) | | 6 (1.2) | 0.54 |
| Calcium and/or vitamin D supplement on discharge | | 214 (43.2) | | 264 (54.1) | <0.01 |

$\chi^2$ test for categorical variables, ANOVA for normally distributed variables and likelihood ratio test for exponentially distributed variables.
*Likelihood ratio test.
ANOVA, analysis of variance; PTH, parathyroid hormone; VDD, vitamin D deficiency.

these conclusions were based on unadjusted correlation analyses. In the current study, we used logistic regression modeling to report ORs appropriate for risk assessment and adjusted for imbalances present in patients' demographic variables.

Compared with our previous, single-institution study, we observed an increase in hospital stay of only 5 hours among patients with VDD, compared with an increase of 2.6 days in our previous study.[5] This observed difference may be attributable to patient demographics and/or regional differences in postoperative management following thyroidectomy. The increased availability of postoperative care protocols for the early detection of hypocalcemia after total thyroidectomy may have also contributed to shorter hospital stays.[29 30] In fact, many studies have reported an increased occurrence of outpatient thyroidectomy with an improved understanding of its safety.[30–33] Our current findings on hospitalization are consistent with these previous studies. In particular, Narayanan *et al*[34] described a low complication and reoperation rate following thyroidectomies in a retrospective study of 1447 thyroidectomy cases between 2006 and 2012. They found that 60.8% of patients were discharged within 6 hours of surgery and 27.7% were discharged within 23 hours of surgery. A small percentage of cases (1.7%) experienced symptomatic hypocalcemia and the majority of these were transient.

Somewhat surprisingly, we found that the need for calcium and/or vitamin D supplementation at discharge was significantly lower among vitamin D-deficient patients compared with vitamin D-sufficient patients. In a meta-analysis of 10 randomized controlled trials, Xing *et al*[35] reported that total thyroidectomy patients provided with calcium and vitamin D supplementation at discharge were at a 79% decreased risk of transient postoperative hypocalcemia compared with those discharged without such supplementation. In another meta-analysis of 3037 total thyroidectomy cases, Sanabria *et al*[36] reported a 25% risk reduction for postoperative hypocalcemia with routine supplementation of calcium and/or vitamin D. Similarly, Arer *et al*[37] described a 32% increase in the incidence of symptomatic hypocalcemia in total thyroidectomy patients given calcium supplementation compared with those without supplementation in a randomized controlled trial of 106 patients. In our study, we observed that only about half of the total thyroidectomy patients were provided with calcium and/or vitamin D supplementation at discharge.

The strengths of this study include the utilization of a large, multi-institutional database over a 9-year span which allowed for a comprehensive analysis of the effect of VDD on hypocalcemia and other postoperative clinical events following total or subtotal thyroidectomy. Our analysis was thorough in that we reported on three commonly

**Table 3** Risk of postoperative hypocalcemia and hospitalization (primary outcomes)

| | Unadjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
|---|---|---|---|---|
| Total calcium (<8 mg/dL) | 3.9 (3.0 to 5.0) | <0.01 | 2.2 (1.6 to 3.1) | <0.01 |
| Corrected calcium (<8 mg/dL) | 2.8 (2.2 to 3.7) | <0.01 | 1.5 (1.1 to 2.1) | 0.02 |
| Hospitalization | 1.3 (1.0 to 1.7) | 0.03 | 1.3 (0.9 to 1.8) | 0.13 |

Adjusted for age, race, urban/rural status, neck dissection, preoperative serum calcium and preoperative serum magnesium.

**Table 4** Postoperative outcomes for sensitivity analysis of patients who had 25-hydroxyvitamin D levels obtained within 90 days of surgery (n=594)

| | n | VDD (≤20 ng/mL) (n=277)<br>Mean (95% CI) or n (%) | n | Non-VDD (>20 ng/mL) (n=317)<br>Mean (95% CI) or n (%) | P value |
|---|---|---|---|---|---|
| Total calcium (mg/dL) | 134 | 8.0 (7.8 to 8.2) | 267 | 8.4 (8.3 to 8.5) | <0.01 |
| Corrected calcium (mg/dL) | 96 | 8.3 (8.1 to 8.4) | 205 | 8.4 (8.3 to 8.5) | 0.10 |
| Ionized calcium (mmol/L) | 72 | 1.1 (1.1 to 1.1) | 112 | 1.1 (1.1 to 1.2) | 0.27 |
| Phosphorus (mg/dL) | 97 | 3.2 (3.0 to 3.4) | 144 | 3.4 (3.3 to 3.5) | 0.15 |
| PTH (pg/mL) | 97 | 36.4 (30.1 to 44.9) | 217 | 29.8 (26.2 to 34.2) | 0.04* |
| Magnesium (mg/dL) | 144 | 1.7 (1.6 to 1.7) | 207 | 1.8 (1.7 to 1.8) | <0.01 |
| Creatinine (mg/dL) | 83 | 0.7 (0.6 to 0.7) | 193 | 0.8 (0.8 to 0.8) | <0.01 |
| Albumin (g/dL) | 176 | 3.7 (3.6 to 3.8) | 217 | 3.8 (3.7 to 3.9) | 0.59 |
| Length of stay, hours | 168 | 34.0 (29.4 to 39.8) | 169 | 30.7 (26.5 to 35.9) | 0.21* |
| Same-day discharge | | 109 (39.4) | | 148 (46.7) | 0.07 |
| Intravenous calcium therapy | | 2 (0.7) | | 6 (1.9) | 0.29 |
| Calcium and/or vitamin D supplement on discharge | | 120 (43.3) | | 187 (59.0) | <0.01 |

$\chi^2$ test for categorical variables, ANOVA for normally distributed variables and likelihood ratio test for exponentially distributed variables.
*Likelihood ratio test.
ANOVA, analysis of variance; PTH, parathyroid hormone; VDD, vitamin D deficiency.

used calcium analytes: total, corrected and ionized serum calcium concentrations. We further analyzed serum calcium concentration both as a continuous and a dichotomized variable. This approach allowed for numerical comparison of serum calcium concentrations between groups as well as assessment of risk associated with VDD in postoperative hypercalcemia.

Elucidating mechanisms through which VDD might result in increased post-thyroidectomy hypocalcemia and increased postoperative morbidity is beyond the scope of this study. Temporary or persistent hypoparathyroidism is widely recognized as a common complication of total thyroidectomy.[1 38–40] Indeed, temporary hypoparathyroidism is observed in approximately 10% of patients after total thyroidectomy, and although postoperative concentrations of PTH did not differ between the two groups in our study, our study was underpowered to demonstrate such a difference.[40] It is also possible that 25-hydroxyvitamin D availability at least partially determines the availability or activity of one of the hormones that are most directly responsible for calcium homeostasis, $1{,}25(OH)_2$ D. In fact, it has been shown that the relationship between 25-hydroxyvitamin D concentrations and $1{,}25(OH)_2$ D is not strictly linear.[41 42] In patients with severe VDD, it has been demonstrated that the formation of $1{,}25(OH)_2$ D may be limited due to lack of substrate, and in such populations a positive correlation between serum 25-hydroxyvitamin D and $1{,}25(OH)_2$ D levels is observed.[43]

Limitations of this study include its retrospective design and findings which show associations rather than causal relationships. Since the possibility for selection bias exists in any observation study, a prospective study of preoperative vitamin D repletion would be beneficial in illuminating the causal effect of VDD on postoperative complications, including hypocalcemia and prolonged hospitalization. Missing postoperative laboratory variables and an inability to assess for the presence or absence of hypocalcemia symptoms were additional limitations of the study. This incompleteness likely highlights the limitations of using the de-identified Health Facts data set for clinical investigation. Furthermore, since the protocol for postoperative care likely varies between the clinics and facilities that are using Cerner's PowerChart interface, the lack of a standardized approach across the USA becomes apparent. As described by Rubin,[44] the missing data likely occurred at random, as opposed to not at random, in this study. As such, the cause of missingness did not induce bias to our estimates, and it is therefore statistically appropriate to proceed with the statistical analysis without accounting for complexities that arise from the missingness. Finally, although there was an imbalance between the groups with respect to the performance of neck dissection, this procedure was more commonly performed in the non-VDD group (table 1). This might be though to favor the occurrence of hypocalcemia in the non-VDD group, but we nevertheless found more hypocalcemia in the VDD group.

In conclusion, preoperative VDD is associated with an increased risk of hypocalcemia and prolonged hospitalization following total thyroidectomy, but it is not associated with an increased risk of subsequent hospitalization. We

**Table 5** Risk of postoperative hypocalcemia and hospitalization (primary outcomes) for the sensitivity analysis of patients who had 25-hydroxyvitamin D levels obtained within 90 days of surgery (n=594)

| | Unadjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
|---|---|---|---|---|
| Total calcium (<8 mg/dL) | 4.3 (3.0 to 6.1) | <0.01 | 2.5 (1.6 to 3.9) | <0.01 |
| Corrected calcium (<8 mg/dL) | 3.1 (2.2 to 4.4) | <0.01 | 1.7 (1.1 to 2.6) | 0.02 |
| Hospitalization | 1.4 (1.0 to 1.9) | 0.07 | 1.0 (0.7 to 1.6) | 0.96 |

Adjusted for age, race, urban/rural status, neck dissection, preoperative serum calcium and preoperative serum magnesium.

recommend that preoperative vitamin D concentrations be determined prior to the performance of total thyroidectomy and that consideration be given to preoperative vitamin D repletion in those who are deficient.

**Contributors** EHEC, FQ, MRB: substantial contribution to the conception or design of the work, acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EA, CL: interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Funding** This study was partially supported by the UNM HSC Clinical & Translational Science Center (NCATS grant #8UL1TR000041).

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study was approved by the University of New Mexico Human Research Review Committee and deemed as IRB exempt (protocol #14-326).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available.

**ORCID iDs**
Eun Ho Eunice Choi http://orcid.org/0000-0003-2233-4266
Mark R Burge http://orcid.org/0000-0002-3015-3660

## REFERENCES

1 Burge MR, Zeise TM, Johnsen MW, *et al*. Risks of complication following thyroidectomy. *J Gen Intern Med* 1998;13:24–31.
2 Christou N, Mathonnet M. Complications after total thyroidectomy. *J Visc Surg* 2013;150:249–56.
3 Al Qubaisi M, Haigh PI. Hypocalcemia after total thyroidectomy in Graves disease. *Perm J* 2019;23. doi:10.7812/TPP/18-188. [Epub ahead of print: 17 May 2019].
4 Chereau N, Vuillermet C, Tilly C, *et al*. Hypocalcemia after thyroidectomy in patients with a history of bariatric surgery. *Surg Obes Relat Dis* 2017;13:484–90.
5 Alkhalili E, Ehrhart MD, Ayoubieh H, *et al*. Does pre-operative vitamin D deficiency predict postoperative hypocalcemia after thyroidectomy? *Endocr Pract* 2017;23:5–9.
6 Kazaure HS, Zambeli-Ljepovic A, Oyekunle T, *et al*. Severe hypocalcemia after thyroidectomy: an analysis of 7366 patients. *Ann Surg* 2019. doi:10.1097/SLA.0000000000003725. [Epub ahead of print: 05 Dec 2019].
7 Kirkby-Bott J, Markogiannakis H, Skandarajah A, *et al*. Preoperative vitamin D deficiency predicts postoperative hypocalcemia after total thyroidectomy. *World J Surg* 2011;35:324–30.
8 Liu RH, Razavi CR, Chang H-Y, *et al*. Association of hypocalcemia and magnesium disorders with thyroidectomy in commercially insured patients. *JAMA Otolaryngol Head Neck Surg* 2020;146:237–46.
9 Macefield G, Burke D. Paraesthesiae and tetany induced by voluntary hyperventilation. increased excitability of human cutaneous and motor axons. *Brain* 1991;114(Pt 1B):527–40.
10 Mrowka M, Knake S, Klinge H, *et al*. Hypocalcemic generalised seizures as a manifestation of iatrogenic hypoparathyroidism months to years after thyroid surgery. *Epileptic Disord* 2004;6:85–7.
11 Hochman HI, Mejlszenkier JD. Cataracts and pseudotumor cerebri in an infant with vitamin D-deficiency rickets. *J Pediatr* 1977;90:252–4.
12 Sheldon RS, Becker WJ, Hanley DA, *et al*. Hypoparathyroidism and pseudotumor cerebri: an infrequent clinical association. *Can J Neurol Sci* 1987;14:622–5.
13 Armelisasso C, Vaccario ML, Pontecorvi A, *et al*. Tonic-clonic seizures in a patient with primary hypoparathyroidism: a case report. *Clin EEG Neurosci* 2004;35:97–9.
14 Graff AT, Miller FR, Roehm CE, *et al*. Predicting hypocalcemia after total thyroidectomy: parathyroid hormone level vs. serial calcium levels. *Ear Nose Throat J* 2010;89:462–5.
15 Barstow C, Braun M. Electrolytes: calcium disorders. *FP Essent* 2017;459:29–34.
16 Noureldine SI, Genther DJ, Lopez M, *et al*. Early predictors of hypocalcemia after total thyroidectomy: an analysis of 304 patients using a short-stay monitoring protocol. *JAMA Otolaryngol Head Neck Surg* 2014;140:1006–13.
17 Pike JW, Christakos S. Biology and mechanisms of action of the vitamin D hormone. *Endocrinol Metab Clin North Am* 2017;46:815–43.
18 Goltzman D, Mannstadt M, Marcocci C. Physiology of the Calcium-Parathyroid Hormone-Vitamin D axis. *Front Horm Res* 2018;50:1–13.
19 Toniato A, Boschin IM, Piotto A, *et al*. Thyroidectomy and parathyroid hormone: tracing hypocalcemia-prone patients. *Am J Surg* 2008;196:285–8.
20 Fleet JC. The role of vitamin D in the endocrinology controlling calcium homeostasis. *Mol Cell Endocrinol* 2017;453:36–45.
21 Carvalho GBde, Giraldo LR, Lira RB, *et al*. Preoperative vitamin D deficiency is a risk factor for postoperative hypocalcemia in patients undergoing total thyroidectomy: retrospective cohort study. *Sao Paulo Med J* 2019;137:241–7.
22 Eismontas V, Slepavicius A, Janusonis V, *et al*. Predictors of postoperative hypocalcemia occurring after a total thyroidectomy: results of prospective multicenter study. *BMC Surg* 2018;18:55.
23 Falch C, Hornig J, Senne M, *et al*. Factors predicting hypocalcemia after total thyroidectomy - A retrospective cohort analysis. *Int J Surg* 2018;55:46–50.
24 Cheah WK, Arici C, Ituarte PHG, *et al*. Complications of neck dissection for thyroid cancer. *World J Surg* 2002;26:1013–6.
25 Kim WW, Chung S-H, Ban EJ, *et al*. Is preoperative vitamin D deficiency a risk factor for postoperative symptomatic hypocalcemia in thyroid cancer patients undergoing total thyroidectomy plus central compartment neck dissection? *Thyroid* 2015;25:911–8.
26 Griffin TP, Murphy MS, Sheahan P. Vitamin D and risk of postoperative hypocalcemia after total thyroidectomy. *JAMA Otolaryngol Head Neck Surg* 2014;140:346–51.
27 Cherian AJ, Ponraj S, Gowri S M, *et al*. The role of vitamin D in post-thyroidectomy hypocalcemia: Still an enigma. *Surgery* 2016;159:532–8.
28 Deffain A, Scipioni F, De Rienzo B, *et al*. Preoperative vitamin D levels do not relate with the risk of hypocalcemia following total thyroidectomy. A cohort study. *Minerva Chir* 2019;74:14–18.
29 Nahas ZS, Farrag TY, Lin FR, *et al*. A safe and cost-effective short hospital stay protocol to identify patients at low risk for the development of significant hypocalcemia after total thyroidectomy. *Laryngoscope* 2006;112:906–10.
30 Lee DJ, Chin CJ, Hong CJ, *et al*. Outpatient versus inpatient thyroidectomy: a systematic review and meta-analysis. *Head Neck* 2018;40:192–202.
31 Segel JM, Duke WS, White JR, *et al*. Outpatient thyroid surgery: safety of an optimized protocol in more than 1,000 patients. *Surgery* 2016;159:518–23.
32 Reinhart HA, Snyder SK, Stafford SV, *et al*. Same day discharge after thyroidectomy is safe and effective. *Surgery* 2018;164:887–94.
33 Snyder SK, Hamid KS, Roberson CR, *et al*. Outpatient thyroidectomy is safe and reasonable: experience with more than 1,000 planned outpatient procedures. *J Am Coll Surg* 2010;210:575–82. 582–584.
34 Narayanan S, Arumugam D, Mennona S, *et al*. An evaluation of postoperative complications and cost after short-stay thyroid operations. *Ann Surg Oncol* 2016;23:1440–5.
35 Xing T, Hu Y, Wang B, *et al*. Role of oral calcium supplementation alone or with vitamin D in preventing post-thyroidectomy hypocalcaemia: a meta-analysis. *Medicine* 2019;98:e14455.
36 Sanabria A, Rojas A, Arevalo J. Meta-analysis of routine calcium/vitamin D3 supplementation versus serum calcium level-based strategy to prevent postoperative hypocalcaemia after thyroidectomy. *Br J Surg* 2019;106:1126–37.
37 Arer IM, Kus M, Akkapulu N, *et al*. Prophylactic oral calcium supplementation therapy to prevent early post thyroidectomy hypocalcemia and evaluation of postoperative parathyroid hormone levels to detect hypocalcemia: a prospective randomized study. *Int J Surg* 2017;38:9–14.
38 Asari R, Passler C, Kaczirek K, *et al*. Hypoparathyroidism after total thyroidectomy: a prospective study. *Arch Surg* 2008;143:132–7. discussion 138.
39 Ritter K, Elfenbein D, Schneider DF, *et al*. Hypoparathyroidism after total thyroidectomy: incidence and resolution. *J Surg Res* 2015;197:348–53.
40 Khan MI, Waguespack SG, Hu MI. Medical management of postsurgical hypoparathyroidism. *Endocr Pract* 2011;17(Suppl 1):18–25.
41 Institute of Medicine, Food and Nutrition Board. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academy Press, 2010.
42 Lips P. Relative value of 25(OH)D and 1,25(OH)2D measurements. *J Bone Miner Res* 2007;22:1668–71.
43 Dobnig H, Pilz S, Scharnagl H, *et al*. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;168:1340–9.
44 Rubin DB. Inference and missing data. *Biometrika* 1976;63:581–92.