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DOES PREOPERATIVE VITAMIN D DEFICIENCY PREDICT POSTOPERATIVE HYPOCALCEMIA AFTER THYROIDECTOMY?

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Abstract

Introduction: Postoperative hypocalcemia is frequent after total thyroidectomy. The role of preoperative vitamin D levels in the pathogenesis of this condition has not been studied under the most current guidelines for evaluation of the role of vitamin D in calcium homeostasis. We hypothesized that patients with preoperative vitamin D deficiency are more likely to suffer from postoperative hypocalcemia, thereby requiring prolonged hospitalization.

Methods: A retrospective chart review of patients undergoing total thyroidectomy at the University of New Mexico Hospital between 2005 and 2014 was performed. Patients who underwent parathyroidectomy were excluded. The study included 30 patients who had a 25-hydroxyvitamin D levels obtained within 12 months before surgery.

Results: 12 patients with vitamin D deficiency (VDD; 25-hydroxyvitamin D ≤ 20 ng/ml) were compared to 18 patients without vitamin D deficiency (Non-VDD; 25-hydroxyvitamin D > 20 ng/ml). The mean nadir postoperative ionized calcium concentration was lower in the VDD group (0.99±0.10 vs. 1.06±0.06 mmol/l, p=0.04) (Ref Range = 1.15–1.27 mmol/l), as was the postoperative concentration of phosphorus (3.48±0.60 vs. 4.17±0.84 mg/dl, p=0.03). VDD patients had a longer length of stay (4.3±4.4 vs. 1.7±1.5 days, p=0.03). Three patients in the VDD group required intravenous calcium for treatment of symptomatic hypocalcemia, but none of the Non-VDD patients required this intervention (p=0.054).

Conclusions: Preoperative vitamin D deficiency is associated with an increased risk of postoperative hypocalcemia and a prolonged length of stay in patients undergoing total thyroidectomy. Vitamin D replacement before thyroidectomy may improve postsurgical outcomes in vitamin D deficient patients.

Keywords

thyroidectomy; surgical complications; hypocalcemia; vitamin D deficiency

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Introduction

Hypoparathyroidism and hypocalcemia after thyroidectomy is a known complication that can lead to prolonged length of hospital stay, increased numbers of biochemical tests, and need for medical treatment, all of which increase costs (1,2). The risk of this phenomenon ranges between 3–30% (3). Identified predictors of postoperative hypocalcemia following thyroidectomy include perioperative parathyroid hormone (PTH) level, preoperative vitamin D concentration, inadvertent parathyroid gland excision and/or auto-transplantation, the specialty of the surgeon performing the operation, Grave's Disease, and female sex (2,4). The impact of vitamin D deficiency (VDD) on the overall incidence and severity of post-thyroidectomy hypocalcemia remains uncertain, but risk factors for VDD can be readily recognized (4,5). The aim of this study is to investigate whether VDD, as defined by the current guidelines of the Endocrine Society (25-hydroxyvitamin D < 20 ng/ml) is associated with increased postoperative hypocalcemia and prolonged hospital stay after total thyroidectomy (6).

Study Methods

This study was approved by the University of New Mexico Human Research Review Committee. A retrospective chart review of all patients who underwent total thyroidectomy at our institution between 2005 and 2015 was performed. Inclusion criteria included performance of total thyroidectomy and attainment of a documented 25-hydroxyvitamin D level within 12 months preoperatively. Exclusion criteria included the presence of chronic kidney disease and/or the performance of intentional parathyroidectomy during the same operation.

Vitamin D levels in the form of 25-hydroxycalciferol were measured using High Performance Liquid Chromatography and Tandem Mass Spectrometry (HPLC-MS) with a coefficient of variation of 5% (TriCore Laboratories ®, Albuquerque, NM, USA). Ionized calcium was determined using an ion-sensitive electrode methodology with the Roche 9180 Electrolyte analyzer (Mannheim, Germany) and a coefficient of variation of 2.4%.

Patient demographics, indication for surgery, operative findings, surgical pathology results, pre- and postoperative biochemical laboratory results, and clinical outcomes were compared. Continuous variables are expressed as mean ± standard deviation (SD) and compared using the unpaired Student's t-test. Categorical variables were reported as frequencies and compared using *chi-square* or Fisher's exact test.

Primary study end points were postoperative concentrations of calcium, phosphorus, and total length of stay. Secondary outcomes included the use of intravenous calcium for the treatment of hypocalcemia and the need for calcium and/or calcitriol supplementation at the time of discharge. Oral calcium carbonate, starting at 2500 mg three times daily, is routinely prescribed during the postoperative period following total thyroidectomy at our institution. Symptomatic hypocalcemia (tetany or incipient tetany) and very low calcium levels (< 7.0 mg/dl) are typically treated with intravenous calcium in addition to oral calcium and calcitriol supplementation.

Results

Three hundred and forty-eight patients underwent total thyroidectomy during the study period, but only 41 patients had a measured preoperative 25-hydroxyvitamin D level obtained within 12 months prior to surgery. The mean time interval between Vitamin D measurement and surgery was 137 ± 92 days. Eleven patients were excluded due to a history of chronic kidney disease or concomitant parathyroidectomy, leaving 30 patients for final data analysis. Patients were divided into two groups based on preoperative vitamin D levels: those with vitamin D deficiency (VDD; n=12) who had vitamin D levels ≤ 20 ng/ml, and those without vitamin D deficiency (Non-VDD; n=18) who had vitamin D levels > 20 ng/ml. The mean vitamin D concentration in the VDD group was 16.8±3.6 ng/ml, and it was 33.0±9.7 ng/ml in Non-VDD patients. Four of 12 patients (33%) in the vitamin D deficient group were receiving vitamin D repletion therapy at the time of surgery.

As shown in Table 1, the male to female distribution between the two groups was similar (p=0.53). There was no difference between the two groups with respect to age (49±15 vs. 47±11 years, p=0.65) or body mass index (BMI) (30.7±7.2 vs. 32.9±18.2 kg/m^2, p=0.68). The indication for surgery, surgical pathology (benign vs. malignant), and thyroidectomy specimen weight didn't differ between the two groups. The rates of performing neck dissection (25% vs. 28%, p=0.52) and parathyroid auto-transplantation (25% vs. 17%, p=0.45) were also similar. The time of the year (by season) when the surgery was performed also did not differ (p=0.14).

As shown in Table 2, the nadir postoperative ionized calcium concentrations were significantly lower in the VDD group (0.99±0.10 vs. 1.06±0.06 mmol/l, p=0.04). Nadir phosphorus concentrations were also lower in the VDD group (3.48±0.60 vs. 4.17±0.84 mg/dl, p=0.03). No difference was found in the postoperative PTH concentrations (35±29 vs. 30±30 pg/ml, respectively, p=0.69). The proportion of patients experiencing a 50% or greater drop in postoperative PTH concentrations was also similar (33% vs. 39%, p=0.5). The concentrations of postoperative serum creatinine, blood urea nitrogen (BUN), and serum albumin were similar in both groups.

Four patients in the VDD group and three patients in the non-VDD experienced postoperative complications (33% vs. 17%, p=0.39). However, hypocalcemia was the main reason for prolonged length of stay in three out of four patients experiencing complications in the VDD group (75%), and in the non-VDD group, only one patient had hypocalcemia resulting in prolonged length of stay (33%).

Intravenous calcium therapy for hypocalcemia was required for three patients in VDD group, while none received it in the non-VDD group (p=0.054). The proportion of patients requiring calcium and/or calcitriol supplements at the time of discharge was similar (50% vs 28%, respectively, p=0.19), and the frequency of patients discharged on calcitriol also did not differ between the two groups (17% in VDD vs. 6% in non-VDD, p=0.54). The total length of hospital stay was significantly longer in the VDD group as compared with the Non-VDD group (4.3±4.4 vs 1.7±1.5 days, p=0.03). No patient developed permanent hypoparathyroidism.

Discussion

This retrospective study demonstrates that preoperative vitamin D deficiency is associated with an increased risk of hypocalcemia and prolonged length of stay after total thyroidectomy. In addition, a lower concentration of phosphorus was observed in patients with VDD. Vitamin D deficiency may cause hypophosphatemia by decreasing gastrointestinal phosphate absorption and/or by causing secondary hyperparathyroidism, resulting in increased urinary phosphate excretion (7). These findings support previous studies that have identified a correlation between VDD and hypocalcemia. In a prospective study of 35 patients, Tripathi, et al., showed that patients with vitamin D concentrations less than 20 ng/ml were more likely to develop postoperative hypocalcemia (6).

The concentrations of vitamin D used to define vitamin D deficiency, as well as the calcium concentrations employed to define hypocalcemia, are not consistent between studies (Table 3). Nhan, et al., compared patients with low vitamin D to patients with adequate vitamin D levels, and the low vitamin D groups in that study included patients with both vitamin D insufficiency (25-hydroxyvitamin D ≤ 28 ng/ml) and deficiency (25-hydroxyvitamin D less than 14 ng/ml), and no difference in the incidence of postoperative hypocalcemia was demonstrated (8). Al-Khatib and colleagues performed multivariate analysis on 213 patients undergoing total and completion thyroidectomy and showed that VDD, defined as serum 25-hydroxyvitamin D level < 25 nmol/l (10 ng/ml), and low PTH levels, were independent predictors of postoperative hypocalcemia (9).

More recently, Falcone and colleagues described a large retrospective study of 264 total or completion thyroidectomies performed within the University of Virginia Health System between 2007 and 2011 (10). Serum 25-hydroxyvitamin D levels were obtained within 21 days of surgery, and an unspecified number of patients received vitamin D repletion therapy prior to surgery. Mean 25-hydroxyvitamin D levels in this study were 25±12 ng/ml. In their analysis, the investigators found no relationship between preoperative vitamin D concentrations and postoperative hypocalcemia, but lower 25-hydroxyvitamn D levels did predict the need for postoperative calcitriol therapy. This analysis, however, was performed as a multivariate logistic regression, and no direct comparison was made between patients with preoperative vitamin D deficiency and those without. In contrast to the Falcone, et al. study, we were able to detect a significant difference in postoperative ionized calcium concentrations despite a small study group using a widely accepted definition of vitamin D deficiency, possibly because we prospectively identified the direct comparison vitamin D deficient patients to non-deficient patients as a critical study endpoint. A summary of studies comparing the risk of postoperative hypocalcemia in relation to vitamin D levels is shown in Table 3.

The correlation between VDD and length of hospital stay has been less extensively studied. In a larger study of 166 total thyroidectomies from the United Kingdom, vitamin D was not only associated with higher risk of postoperative hypocalcemia, but also longer median length of stay (i.e.- 2 days vs. 1 day) (11). A meta-analysis of 115 observational studies in 2014 showed that preoperative vitamin D levels were predictive of postoperative hypocalcemia, but an effect on the length of stay was not demonstrated (4). Alhefdhi, et al.,

published a meta-analysis of randomized controlled trials examining the preoperative administration of vitamin D or its metabolites, and/or calcium supplementation, in preventing postoperative hypocalcemia in patients undergoing thyroidectomy regardless of their vitamin D status. In nine studies with 2,285 patients, they found a significant decrease in postoperative hypocalcemia among patients who received routine preoperative supplementation of calcium or vitamin D. This benefit was enhanced with the combined administration of both supplements, although a beneficial effect of supplementation on the total length of stay was reported in only two of the nine studies (12). While those two studies demonstrated a decreased length of stay with preoperative supplementation irrespective of patients' vitamin D concentrations, our study is the first to specifically link preoperative VDD with a prolonged length of hospitalization after thyroidectomy, as well as adhering to current clinical guidelines regarding the classification of vitamin D deficiency as a 25-hydroxyvitamin D concentration ≤ 20 ng/ml (13).

Elucidating the mechanism through which vitamin D deficiency might result in increased post-thyroidectomy hypocalcemia and increased postoperative morbidity is difficult and largely speculative. The most logical potential mechanism for these observations is to invoke temporary or persistent hypoparathyroidism (either absolute or relative), which is widely recognized as a common complication of total thyroidectomy (2,14–16). 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 under-powered to demonstrate such a difference (16). It is also possible that 25-hydroxyvitamin D availability at least partially determines the availability or activity of one of the hormones that is most directly responsible for calcium homeostasis, 1,25-dihydroxyvitamin D. In fact, it has been shown that the relationship between 25-hydroxyvitamin D concentrations and 1,25-dihydroxyvitamin D is not strictly linear (17,18). In patients with severe vitamin D deficiency, it has been demonstrated that the formation of 1,25-dihydroxyvitamin D may be limited because of lack of substrate, and in such populations, a positive correlation between serum 25-hydroxyvitamin D and 1,25-dihdroxyvitamin D levels is observed (19).

The limitations of our study include its retrospective design, the relatively small number of patients, the relatively long interval between the determination of vitamin D status and thyroid surgery, and the single-site setting of the study. Nevertheless, we found both a statistically and clinically significant relationship between VDD and postoperative hypocalcemia, as well as between VDD and a prolonged length of hospitalization. Clearly, the optimal formula for preoperative vitamin D and/or calcium supplementation, supplement dosages, and duration of treatment have not been elucidated, and standards of care regarding these important topics have not yet been established.

Conclusions

Preoperative vitamin D deficiency (VDD) is associated with increased occurrence of postoperative hypocalcemia and a prolonged length of hospital stay following total thyroidectomy. Screening for VDD in all patients preoperatively, as well as aggressive

treatment of patients with documented preoperative vitamin D deficiency, is indicated for all patients undergoing total thyroidectomy.

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Abbreviations:

VDD	Vitamin D deficient
Non-VDD	Non-Vitamin D deficient
PTH	Parathyroid Hormone
HPLC-MS	High Performance Liquid Chromatography and Mass Spectrometry
BMI	Body Mass Index

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Table 1.

Patient demographics and clinical characteristics.

Variable	VDD (n=12)	Non-VDD (n=18)	P-value
Sex: Male	2	2	
Female	10	16	0.53
Age (years)	49 ± 15	47 ± 11	0.65
BMI (kg/m^2)	30.7 ± 7.2	32.9 ± 18.2	0.68
Preoperative Vitamin D (ng/ml)	16.8 ± 3.6	33 ± 9.7	< 0.001
Preoperative Serum Calcium (mg/dl)	9.1 ± 0.67	9.4 ± 0.42	0.42
Preoperative Diuretic Use	1/12 (8%)	2/18 (5%)	0.53
Preoperative Use of Proton Pump Inhibitors	4/12 (33%)	2/18 (11%)	0.18
Indication for Thyroidectomy:			
Hyperthyroidism	1	0	
Compression symptoms	1	2	0.45
Suspicious nodule	10	16	
Surgical Pathology:			
Malignant	10	14	0 54
Benign	2	4	
Season of Surgery:			
Winter	1	2	
Spring	2	5	0.14
Summer	7	3	
Autumn	2	8	
Thyroid weight (grams)	21.1 ± 7.6	34.6 ± 37.2	0.25
Performance of neck dissection	3/12 (25%)	6/18 (33%)	0.47
Parathyroid Auto-transplantation	3/12 (25%)	3/18 (17%)	0.45

Table 2.

Postoperative results and outcomes.

Postoperative Results	VDD (n=12)	Non-VDD (n=18)	P-value
Nadir Postoperative Ionized Calcium (mmol/l)	0.99 ± 0.10	1.06 ± 0.06	0.04
Nadir Postoperative Phosphorus (mg/dl)	3.48 ± 0.60	4.17 ± 0.84	0.03
Preoperative PTH (pg/ml)	53 ± 35	52 ± 38	0.92
Postoperative PTH (pg/ml)	35 ± 29	30 ± 30	0.69
Magnesium (mEq/l)	1.8 ± 0.22	1.9 ± 0.21	0.57
Creatinine (mg/dL)	0.72 ± 0.23	0.85 ± 0.40	0.3
Albumin (g/dL)	3.9 ± 0.7	4.0 ± 0.4	0.44
Intravenous Calcium Therapy	3/12 (25%)	0/18 (0%)	0.06
Calcium and Vitamin D Supplement on Discharge	6/12 (50%)	5/18 (28%)	0.19
Total Length of Stay (days)	4.3 ± 4.4	1.7 ± 1.5	0.03

Table 3.

Summary of studies comparing the risk of postoperative hypocalcemia in relation to vitamin D levels.

Study	25-hydroxyvitamin D Levels for Comparison	Results
Tripathi, et al. 2014 (6)	≤ 20 ng/ml vs. > 20ng/ml	Increased risk of hypocalcemia in deficient group.
Kirby-Bott, et al. 2011 (7)	< 10 ng/ml vs. 10–20 ng/ml vs. > 20ng/ml	Increased risk of hypocalcemia in < 10 ng/ml group 1 compared to the > 20ng/ml group.
Nhan, et al. 2012 (8)	≤ 28 ng/ml vs. > 28 ng/ml	No difference in postoperative hypocalcemia.
Falcone, et al. 2015 (11)	Not applicable; multivariate logistic regression	Pre-operative 25-hydroxyvitamin D did not predict postoperative hypocalcemia, but did predict the need for postoperative calcitriol therapy.