The role of vitamin D in post-thyroidectomy hypocalcemia: Still an enigma

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Background. *There is conflicting evidence regarding the role of vitamin D deficiency in the development of post-thyroidectomy hypocalcemia. Recent reports show postoperative parathormone (PTH) is unreliable in predicting post-thyroidectomy hypocalcemia in vitamin D deficient patients. We conducted this study to analyze the role of vitamin D status in the development of post-thyroidectomy hypocalcemia and to evaluate its effect on the predictability of PTH as a marker for post-thyroidectomy hypocalcemia.*
Method. *A retrospective review of prospectively collected data of patients undergoing thyroidectomy between August 2007 to September 2013 (*$n = 150$*) was performed. Results of preoperative calcium, albumin, vitamin D, PTH and postoperative calcium, albumin, and PTH were collated. Patients were divided into 2 groups based on their vitamin D status: group A, vitamin D* $\geq$ *20 ng/mL and group B, vitamin D* $<$ *20 ng/mL.*
Results. *Vitamin D deficiency was present in 80 (53.3%) patients and post-thyroidectomy hypocalcemia developed in 67 (44.7%). The incidence of postoperative hypocalcemia was similar in both the groups (48.6% and 41.3%, respectively). Vitamin D status was not associated with the development of post-thyroidectomy hypocalcemia (*$P = .23$*). Postoperative PTH of* <8 *pg/mL was strongly associated with the development of hypocalcemia in both the groups (*$P = .0002$ *and .0045, respectively). The area under the receiver operator characteristic curve in group B (0.68) was less than in group A (0.76;* $P = .41$*).*
Conclusion. *The majority of patients were vitamin D deficient in this cohort, but this did not increase the risk of post-thyroidectomy hypocalcemia, nor did it interfere with the predictability of PTH as a marker of post-thyroidectomy hypocalcemia. (Surgery 2016;159:532-8.)*

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TOTAL THYROIDECTOMY has evolved as the treatment of choice for most malignant and many benign thyroid disorders. However, complete thyroid resection is significantly complicated by parathyroid dysfunction and hypocalcemia, influencing the duration of postoperative hospital stay. Factors implicated as the cause/risk factor for the development of post-thyroidectomy hypocalcemia include age of the patient, gender, parathyroid gland injury/autotransplantation, reoperative surgery, extent of surgery, locally advanced thyroid cancers, presence of hyperthyroidism, hemodilution and magnesium deficiency.[1-8] Of these causes, parathyroid injury/ischemia is the most common.[9] Postoperative parathormone (PTH) level measured intraoperatively or on the same day of surgery has been shown to be an accurate marker to predict the development of postoperative hypocalcemia.[10-15] Recent literature has evaluated the role of vitamin D deficiency in post-thyroidectomy hypocalcemia with variable results.[16-23] Further, a few studies have demonstrated that the accuracy of PTH to predict postoperative hypocalcemia is affected by low vitamin D levels.[24,25]

In India, vitamin D deficiency is common and therefore assumes importance as a factor that could influence post-thyroidectomy management; however, it remains unclear whether or not low vitamin D level is a risk for development of

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post-thyroidectomy hypocalcemia.[26-28] The objectives of this study were to document the prevalence of vitamin D deficiency in patients undergoing thyroidectomy, evaluate the role of vitamin D status in the development of post-thyroidectomy hypocalcemia, and determine whether the accuracy of PTH as a predictor of post-thyroidectomy hypocalcemia is affected by vitamin D levels.

METHODS

This study was conducted at a tertiary hospital in South India. After approval by the institutional review board and ethics committee, a retrospective analysis of prospectively collected data of patients undergoing total thyroidectomy with or without neck dissection between August 2007 and June 2009 (n = 100) and October 2012 and September 2013 (n = 50) was performed. The estimation of preoperative vitamin D levels is not performed routinely at our institution. To evaluate the role of vitamin D in post-thyroidectomy hypocalcemia, vitamin D levels were estimated in a previous unpublished study, from August 2007 to June 2009 (n = 100). A further study was performed between October 2012 to September 2013 (n = 50) to evaluate the risk factors for post-thyroidectomy hypocalcemia; preoperative vitamin D levels was 1 factor analyzed. The setting, inclusion/exclusion criteria, blood sample collection, and analysis and discharge protocol for both studies were identical, although performed in different time periods.

Blood samples. Preoperative blood samples were collected for calcium, albumin, creatinine, 25 hydroxy vitamin D (vitamin D) and PTH. Postoperative PTH and albumin was checked only on the morning after surgery (postoperative day 1) and calcium was checked each postoperative day until the patient was discharged. The biochemical estimation of serum calcium and albumin were performed using photometric method (modular P800 automated analyzer; Roche, Nutley, NJ), intact PTH was estimated by chemiluminescence (Adiva centaur centre; Siemens, Pleasanton, CA), and serum vitamin D by electrochemiluminescence (Roche).

Definitions. Thacher et al[29] classified vitamin D status in their review article on vitamin D insufficiency as vitamin D optimal (>20 ng/dL), vitamin D insufficient (10–20 ng/ml) and vitamin D deficient (<10 ng/mL). Based on this, definition our patients were divided into 2 groups, those with vitamin D $\geq$ 20 ng/mL were defined as vitamin D sufficient (group A), whereas those with vitamin D < 20 ng/mL as vitamin D deficient (group B). Patients who were detected to be vitamin D deficient prior to surgery did not receive routine vitamin D supplements/replacements preoperatively or postoperatively. Patients with albumin-corrected serum calcium <8.0 mg/dL with or without clinical features of hypocalcemia were defined as being hypocalcemic.

Discharge protocol. Normocalcemic patients were discharged on the day after the operation (postoperative day 1), whereas hypocalcemic patients received elemental calcium and active vitamin D (calcitriol) supplementation as per the department's post-thyroidectomy hypocalcemia treatment protocol (Table I). These patients were discharged when a stable or increasing trend of corrected serum calcium was documented.

Statistical analysis. Data were analyzed to derive the mean along with standard deviation for the normal data and the median along with ranges for non-normal data. Categorical data were summarized using frequency along with percentages. Independent t test and Mann–Whitney U test were used to compare the continuous variables among both groups depending on the nature of the data. Chi square test was used to evaluate the association between the variables. Receiver operator characteristic curve (ROC) was constructed and the area under the ROC was compared between both groups. Hypocalcemia being a binary outcome variable logistic regression was performed for univariate and multivariate analysis. All analyses were performed using STATA 13.1 I/C.

RESULTS

There were 150 patients who were included in the study. Among them, 104 (69.3%) were female and 46 (30.7%) male. The mean age was 43.85 ± 12.68 years. The type of operations performed included total thyroidectomy in 120 (80%), total thyroidectomy plus central lymph node dissection plus modified radical neck dissections in 20 (13.3%), total thyroidectomy plus central lymph node dissection alone in 8 (5.3%), and completion thyroidectomy in 2 (1.3%). All neck dissections performed were therapeutic. Vitamin D sufficiency (group A, vitamin D $\geq$ 20 ng/mL) was seen in 70 patients (46.7%) and vitamin D deficiency (group B, vitamin D < 20 ng/mL) was seen in 80 patients (53.3%). Among the group B patients, severe deficiency (<10 ng/mL) was seen in 19 patients (23.8%). Post-thyroidectomy hypocalcemia developed in 67 of 150 patients (44.7%). There were 3 patients with normal serum corrected calcium who developed mild hypocalcemic symptoms (occasional perioral

Table I. Postthyroidectomy hypocalcemia management protocol

Corrected serum calcium (mg/dL)	*Signs (Chvostek's/ Trousseau)*	*Symptoms (perioral/extremity paresthesia and tingling, spontaneous carpel/pedal spasm)*	*Treatment*
<8.0	No	No	Calcium carbonate 1 g twice daily
<8.0	Yes	No	Calcium carbonate 1 g thrice daily and Calcitriol 0.25 μg once daily
<8.0	Yes/no	Yes (mild)	Calcium carbonate 1 gm thrice daily and Calcitriol 0.25–0.5 μg twice daily
		Yes (Severe)	Add to above infusion of 50 mL of 10% calcium gluconate in 500 mL of 5% dextrose infused at 1 mL/kg/h until asymptomatic

Table II. Comparing the demographic and biochemical characteristics of patients belonging to groups A and B

Variable	*Group A vitamin D ≥ 20 (n = 70)*	*Group B vitamin D < 20 (n = 80)*	P *value*
Age in years (mean ± SD)	45.0 ± 12.6	42.8 ± 12.7	.29
Gender			.37
Male	52.2% (*n* = 24)	47.8% (*n* = 22)	
Female	44.2% (*n* = 46)	55.8% (*n* = 58)	
Vitamin D			Not applicable
Mean ± SD	27.9 ± 6.6	13.5 ± 4.8	
Range	20–45.1	4–19.8	
Preoperative calcium (mean ± SD)	8.7 ± 0.4	8.7 ± 0.5	.93
Preoperative PTH			.37
mean ± SD	56.5 ± 29.0	60.6 ± 31.3	
Range	18.1–143	7.10–164	
Postoperative D1 calcium (mean ± SD)	8.0 ± 0.7	8.0 ± 0.6	.96
Postoperative D2 calcium (mean ± SD)	8.2 ± 0.7	8.2 ± 0.8	.90
Postoperative PTH			.71
Mean ± SD	18.96 ± 18.4	19.7 ± 18.8	
Range	0.1–85	0.3–91	
Incidence of postoperative hypocalcemia (Ca < 8), *n* (%)	34 (48.57)	33 (41.25)	.37
Decrease in PTH preoperative vs postoperative (%)	64.3	64.3	.90

D1, Day 1; *D2*, day 2; *PTH*, parathyroid hormone; *SD*, standard deviation.

tingling) only on postoperative day 1 with subsequent resolution spontaneously. Therefore, these 3 patients were not considered to be hypocalcemic.

Demographic and biochemical characteristics. The demographic and biochemical characteristics of patients belonging to group A and B are compared in Table II. There was no difference in the mean preoperative calcium values ($P = .93$), preoperative PTH values ($P = .37$), postoperative calcium values on days 1 and 2 ($P = .96$ and .90 respectively), and postoperative PTH values ($P = .71$) between the groups. The rate of postthyroidectomy hypocalcemia and the mean percentage fall in PTH (preoperative versus postoperative), in both the groups were similar. Nineteen patients were severely vitamin D deficient (<10 ng/mL). Among them, 9 patients (47.4%) developed postoperative hypocalcemia. Neither the presence of vitamin D deficiency nor the presence of severe vitamin D

Table III. Preoperative and postoperative PTH

Biochemical variable	*Group A: vitamin D ≥ 20* (n = *70)*			*Group B: vitamin D < 20* (n = *80)*		
	Ca ≥ 8 mg/dL (n = *36)*	*Ca < 8 mg/dL* (n = *34)*	P *value*	*Ca ≥ 8 mg/dL* (n = *47)*	*Ca < 8 mg/dL* (n = *33)*	P *value*
Preoperative PTH	54.1 ± 25.2	58.95 ± 32.8	.74	60.6 ± 32.3	60.6 ± 30.4	.98
Postop PTH	25.1 ± 18.1	12.4 ± 16.6	.0002	24.2 ± 19.8	13.3 ± 15.4	.005
Decrease in PTH preoperative vs postoperative (%)	53	76.3	.0004	55.9	76.3	.003

PTH, Parathyroid hormone.

deficiency affected the rate of development of postoperative hypocalcemia (P = .37 and .80, respectively).

Postoperative PTH accuracy. Table III compares the preoperative and postoperative PTH in group A versus group B. This table also compares the groups with regard to the presence or absence of hypocalcemia. A significant association was seen between postoperative PTH and hypocalcemia in both the groups (P = .002 and .004, respectively). The fall in postoperative PTH in hypocalcemic patients compared with the normocalcemic patients in both the groups was also significant (P = .004 and .003, respectively).

Vitamin D deficiency and postoperative PTH. A ROC curve was plotted for both the groups to assess the accuracy of PTH as a marker for the development of post-thyroidectomy hypocalcemia (Fig 1). The area under the curve for group A and B were 0.76 and 0.68, respectively (P = .41).

Risk factors for hypocalcemia. The details of univariate analysis performed are shown in Table IV. Age and gender did not have an effect on post-thyroidectomy hypocalcemia (P = .42 and .15, respectively). Patients with postoperative PTH < 8 were at a 5.08 (95% CI, 2.48–10.44) times higher risk of developing postoperative hypocalcemia than those with postoperative PTH ≥8 (P < .001).

Ten patients were hyperthyroid. Among them there were 6 patients with Graves' disease, 2 toxic multinodular goiters and 2 autonomously functioning toxic nodules. Six of the 10 hyperthyroid patients (60%) developed postoperative hypocalcemia, 5 of whom were patients with Graves' disease. Surprisingly hyperthyroidism was not significantly associated with the development of post-thyroidectomy hypocalcemia (P = .32).

Patients who underwent total thyroidectomy or completion thyroidectomy alone were grouped together (n = 122) and compared with those who underwent total thyroidectomy with central/lateral neck dissection (n = 28) to assess if the extent of surgery impacts the development of post-thyroidectomy hypocalcemia. Extent of surgery did not impact the development of post-thyroidectomy hypocalcemia (P = .83). Vitamin D levels were also not associated with the development of postoperative hypocalcemia (P = .23). Because univariate analysis showed no association of age, gender, hyperthyroidism, extent of surgery, and vitamin D status with hypocalcemia, multivariate analysis was not performed.

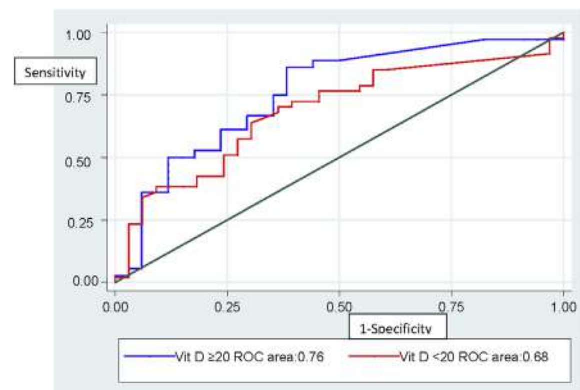

Fig. Comparison of the receiver operator characteristic curve (ROC) between groups A and B (P = .41).

Vitamin D status and severity of postoperative hypocalcemia. The mean duration of temporary hypocalcemia in group B was 4.21 ± 2.81 days and that in group A was 2.61 ± 1.52 days (P = .02). Hence, temporary hypocalcemia lasted significantly longer in the vitamin D–deficient group than in the vitamin D–sufficient group.

The dose of calcium/active vitamin D supplements received by hypocalcemic patients was not recorded during the period August 2007 to June 2009. Thus, comparing the requirements of these supplements between both the groups was not possible.

Table IV. Comparison of postoperative hypocalcemia with postoperative PTH, vitamin D, hyperthyroid state and extent of surgery

Group (n = *150*)	*Univariate analysis*	
	Odds ratio (95% CI)	P *value*
Postoperative PTH		<.001
<8 (*n* = 67)	5.08 (2.48, 10.44)	
≥8 (*n* = 83)	Reference group	
Vitamin D	1.02 (0.98, 1.06)	.23
Hyperthyroid		.32
Present (*n* = 10)	1.94 (0.52, 7.18)	
Absent (*n* = 140)	Reference group	
Extent of surgery		.84
CT/TT (*n* = 122)	Reference group	
TT + CLND/TT + CLND + MRND (unilateral/bilateral) (*n* = 28)	1.09 (0.47, 2.38)	

CLND, Central lymph node dissection; *CT*, completion thyroidectomy; *MRND*, modified radical neck dissection; *PTH*, parathyroid hormone; *TT*, total thyroidectomy.

Six patients developed permanent hypoparathyroidism and all 6 patients were vitamin D sufficient.

DISCUSSION

Vitamin D level and postoperative hypocalcemia. Thyroidectomy is evolving into a day-case procedure.[30] The presence of transient hypocalcemia postoperatively lengthens the duration of hospital stay. Therefore, there is increased interest in the identification of risk factors for the development of post-thyroidectomy hypocalcemia. PTH has been shown to be a strong predictor of hypocalcemia and is in popular use currently. However, vitamin D deficiency has been claimed to influence postoperative hypocalcemia and interfere with the accuracy of PTH prediction, ostensibly by causing a secondary hyperparathyroidism and false elevation of PTH. Vitamin D deficiency is highly prevalent in India and therefore a cause for concern.[27,28,31] It was seen in 80 of 150 patients (53.33%) in this study. Its role in the development of post-thyroidectomy hypocalcemia is debatable. A positive role of vitamin D deficiency for the development of post-thyroidectomy hypocalcemia has been proposed by some authors.[19-21,24] These authors hypothesize that, in patients with parathyroid ischemia/injury, the parathyroid gland is unable to secrete PTH and hence the maintenance of calcium homeostasis is dependent on the vitamin D level as vitamin D increases the intestinal calcium absorption. In vitamin D–deficient patients, this mechanism of increased calcium absorption is impaired; hence, these patients are prone to developing hypocalcemia.[19,21] This hypothesis may explain our finding of significantly increased duration of temporary hypocalcemia among vitamin D–deficient patients (P = .02). In contrast, others have shown that vitamin D status is not related to the development of post-thyroidectomy hypocalcemia.[17,18,32] Further, Nhan et al have reported a protective effect of vitamin D deficiency for hypocalcemia. They opine that the secondary hyperparathyroidism caused by vitamin D deficiency results in the ability of the parathyroid gland to secrete more PTH and thus protect against the development of postoperative hypocalcemia.[22] We found no relationship between vitamin D deficiency and post-thyroidectomy hypocalcemia (P = .368). The cause of hypocalcemia after total thyroidectomy is mainly owing to trauma/ischemia to the parathyroid gland resulting in hypoparathyroidism. PTH regulates 1-α-hydroxylase in the kidney, which is the enzyme that converts 25 hydroxyvitamin D to its biologically active form 1,25 dihydroxyvitamin D. Thus, an explanation for the lack of association between vitamin D deficiency and post-thyroidectomy hypocalcemia is that the hypoparathyroidism results in decreased conversion of 25 hydroxyvitamin D to 1,25 dihydroxyvitamin D, regardless of the amount of 25 hydroxyvitamin D available.

Postoperative PTH as a marker for post-thyroidectomy hypocalcemia. Postoperative PTH level as an accurate marker for the development of post-thyroidectomy hypocalcemia has been well-established.[10,11,13,15,33] We report a similar finding with postoperative PTH cutoff of <8 pg/mL. When comparing the area under the ROC curve for both groups, a decrease in the area under the curve for group B as compared with group A (0.76 vs 0.68) was seen, but this was not significant (P = .407). Hence, vitamin D deficiency did not affect the accuracy of postoperative PTH to predict hypocalcemia in this cohort. This is contradictory to the findings of other authors, who have shown that postoperative PTH is not a reliable marker in predicting postoperative hypocalcemia in patients with vitamin D deficiency.[24,25] Pradeep et al[24] in a study of 203 patients undergoing thyroidectomy reported the presence of secondary hyperparathyroidism in the group with vitamin D deficiency, their preoperative PTH (60.35 ± 16.06) was significantly higher than in the vitamin D–sufficient group (22.4 ± 7.12; P = .0001). They also report a higher postoperative PTH in the vitamin D deficient group (16 ± 9.77) compared with the vitamin D–sufficient group (7.13 ± 1.79) among hypocalcemic patients. They concluded that secondary hyperparathyroidism influences the postoperative PTH level in vitamin D–deficient patients and hence it is not a reliable predictor for hypocalcemia in this subset of patients. In the present study, the mean preoperative PTH was similar in both the groups (56.48 ± 29.04 in group A and 60.61 ± 31.34 in group B; $P = .37$). Therefore, our finding of the accuracy of postoperative PTH to predict post-thyroidectomy hypocalcemia not being affected by vitamin D deficiency may be attributed to the absence of secondary hyperparathyroidism in this cohort.

LIMITATIONS

Data for this study were entered prospectively in 2 different time periods and have been analyzed retrospectively. Information regarding the dose of calcium/active vitamin D supplements received by hypocalcemic patients was incomplete; therefore, comparing the requirements of these supplements between the groups was not possible. Hence, the effect of vitamin D status on the intractability of postoperative hypocalcemia could not be assessed. Data on number of parathyroid glands preserved and the number autotransplanted during surgery were incomplete. Consequently, its impact on postoperative hypocalcemia could not be estimated.

In conclusion, vitamin D deficiency is common, present in the majority of this cohort (53.33%). Temporary hypocalcemia post-thyroidectomy was seen in 67 patients (44.66%). Age, gender, extent of surgery, hyperthyroidism, and vitamin D deficiency were not associated with the development of post-thyroidectomy hypocalcemia ($P = .42$, .15, .83, .32, and .23, respectively). The duration of temporary hypocalcemia among vitamin D–deficient patients was significantly longer than among the vitamin D sufficient patients ($P = .02$). The need for preoperative and/or postoperative supplementation to decrease the severity of postoperative hypocalcemia in this subset of patients needs to be further studied. Postoperative PTH is not affected by the vitamin D status of the patient ($P = .41$).

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