

Original Research Article

The utility of serum 25-hydroxyvitamin D in predicting post-thyroidectomy hypocalcemia in thyrotoxic subjects: a single-center cohort study

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ABSTRACT

Background: The role of preoperative vitamin D deficiency as a predictor of post-thyroidectomy hypocalcemia in thyrotoxic subjects is controversially reported. This prospective cohort study determined the utility of serum 25-hydroxyvitamin D (25OHD) levels in predicting transient hypocalcemia in thyrotoxic and euthyroid patients undergoing total thyroidectomy (TT).

Methods: Subjects with new-onset hyperthyroidism (n=97; age=median (Inter-Quartile Range); 38 (18) years; M:F=25:72) and age; sex-matched euthyroid cohorts (n=231; age=37 (18) years; M:F=40:191) undergoing TT were evaluated for serum corrected-calcium, intact parathormone and 25OHD levels at baseline, 48-hour and 6-months post-TT, p value <0.05 was considered significant.

Results: The incidence of transient hypocalcemia in thyrotoxic subjects was 58.8% (57/97) versus 22.5% (52/179) in euthyroid cohorts. In receiver operating characteristic analysis predicting transient hypocalcemia for the test-variable preoperative 25OHD, the area under curve (AUC) among euthyroid subjects was 0.725 (95% CI: 0.641-0.809; p<0.001) with a threshold of 17.6 ng/mL with sensitivity and specificity of 65.4% and 64.2% respectively. In thyrotoxic subjects, the AUC was 0.573 (95% CI: 0.452-0.694; p=0.222) with poorer predictability and was less than that of euthyroid subjects.

Conclusions: Preoperative 25OHD below 17.6 ng/ml was reliable in predicting transient postoperative hypocalcemia in euthyroid subjects though with a limited sensitivity and specificity but unreliable in thyrotoxic subjects undergoing TT.

Keywords: Euthyroid, Hyperthyroidism, Postoperative hypocalcemia, Thyroidectomy, Thyrotoxicosis, 25-hydroxycholecalciferol, Vitamin D deficiency

INTRODUCTION

Thyroid surgery is the most common endocrine surgery performed worldwide. Total thyroidectomy (TT) has emerged as the procedure of choice for thyroid malignancy as well as many benign toxic goitre and non-toxic multinodular goitre with compression symptoms, in

order to avoid recurrence and revision surgery.¹ "Postoperative hypocalcemia is" remove comma and add is, a common complication after TT, which may be transient or permanent (>6 months) and is increasingly seen with this radical technique.^{2,3} Hypocalcemia varies from an asymptomatic biochemical abnormality to a life-threatening tetany, depending on the duration, severity,

and rapidity of development. In particular, thyrotoxic subjects exhibited higher rates of transient and permanent post-thyroidectomy hypocalcemia (PH) compared to euthyroid subjects. The most important cause of transient hypocalcemia is functional hypoparathyroidism, resulting from surgical trauma and devascularization of parathyroid gland and hence impaired secretion of parathormone hormone, which is the major calciotropic hormone. Vitamin D is the other major hormone involved in calcium regulation and therefore, Vitamin D deficiency (VDD), a potentially correctable factor was extensively investigated for its role in the development of post-thyroidectomy hypocalcemia. The previous studies had variable results owing to wide variation in prevalence of VDD as it is latitude-specific and population based.⁴⁻¹⁰ Few high-level evidences are available regarding the impact of VDD on PH in our region. Moreover, there is no consensus regarding the threshold of vitamin D levels predisposing to the development of post-thyroidectomy hypocalcemia in thyrotoxic subjects.

Therefore, we conducted this cohort study to determine the utility of 25-hydroxyvitamin D (25OHD) in predicting the development of transient hypocalcemia in thyrotoxic and euthyroid subjects undergoing TT in southern India.

METHODS

Consecutive patients undergoing first-time total thyroidectomy in the Department of Endocrine Surgery, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai- 600003 (Latitude: 13.08° N, 80.27° E) from July 2017 to December 2019 were prospectively studied after obtaining Institutional ethics committee approval (No.18092012). Informed written consent obtained from all participants. The study was conducted in accordance with the Helsinki declaration and its later amendments. None of the procedures in the study involved animals.

Selection of subjects

Group A/thyrotoxic group

Surgical candidates with new-onset overt hyperthyroidism were included. Diagnosis was based on suppressed Thyroid Stimulating Hormone (TSH) below reference range with or without elevated free thyroid hormone levels. Indications for surgery were: large volume goitre, non-compliance/resistance to antithyroid drugs, suspicion for malignancy in cytology or sonography, planning pregnancy, presence of moderate/severe Graves' ophthalmopathy and logistic reasons including patient's preference for surgery.

Group B/ euthyroid subjects

Age and sex-matched euthyroid patients with benign thyroid nodule/s having compression symptoms or

malignant thyroid disease who are surgical candidates were included. All the subjects were evaluated for TSH (0.35-4.5 mIU/l), free thyroxine (0.8-2.2 ng/dl), liver and renal function tests. Subjects with revision surgery, concomitant neck dissection, intentional parathyroidectomy, associated medical conditions including chronic renal or hepatic disorder, malignancy, immunosuppression, uncontrolled diabetes and those with calcium and vitamin D supplements were excluded.

Preoperatively, thyrotoxic patients received antithyroid drug, Tab. Carbimazole 10-60 mg/day and propranolol 10-160 mg/day in divided doses until stably euthyroid. Under general anesthesia, classic total thyroidectomy was performed by the same surgical team as per institutional standards identifying and preserving all the parathyroid glands and both the external branch of superior laryngeal and recurrent laryngeal nerves on either side. Blood samples were collected for preoperative 25OHD at the time of diagnosis and categorized as severe deficiency<10, deficiency=10-19.9, insufficiency=20-29.9, sufficiency=30-100 ng/ml. Serum 25-OHD was measured in Siemens ADVIA Centaur using fully automated chemiluminescent immune assay method standardized against isotope dilution-liquid chromatography-tandem mass spectrometry reference methods as per vitamin D standardization programme. Serum corrected-calcium (8.5-10.4 mg/dl) and intact Parathormone (iPTH) (12-65 pg/ml) were measured with automated analyzer, Roche eCobas 6000 series, Switzerland at baseline, 24-hour, 48-hour post-surgery and as per clinical needs.

In the postoperative recovery phase, clinical signs and symptoms of hypocalcemia including perioral and acral numbness, cramps, carpopedal spasm, laryngeal stridor, bronchospasm, cardiac arrhythmia, seizures, Chvostek and Trousseau signs were monitored. Patients with clinically evident hypocalcemia or corrected calcium <8 mg/dl received Tab. Calcium carbonate 0.5-2g/day±Cap. Calcitriol (active vitamin D) 0.25-1 mcg/day and 10% intravenous calcium gluconate 0.5-2 mg/kg/day for resistant hypocalcemia. Subjects with vitamin D deficiency or insufficiency received high dose cholecalciferol single intramuscular injection of 6 lakh units, or per oral 60,000 IU/week for 4-12 weeks tailored to individual needs.

In the follow up, Tab. Thyroxine sodium in replacement dose for benign or medullary thyroid cancer while suppressive doses were administered for differentiated thyroid cancer.

Statistical analysis

SPSS software version 20.0, IBM Incorp, was used for statistical analysis. Categorical data was expressed as percentage and frequency. Continuous data which was normal and non-normal on Shapiro Wilk's normality test were expressed as mean (Standard deviation) and median

(Inter-Quartile Range: IQR) respectively. Chi-square test, Mann Whitney U test and Multinomial regression tests were performed where appropriate. The results were expressed as Odds ratio (OR) with 95% confidence interval (95% CI). Receiver Operating Characteristic (ROC) determined the diagnostic accuracy of the test-variable 25OHD in predicting transient hypocalcemia. Youden index determined the optimal “cut-off” value. The area under ROC curve (AUC) with values closer 1 indicates better predictability and those closer to 0.5 indicates poorer predictability. P value<0.05 was considered statistically significant.

RESULTS

Out of 359 patients enrolled in the study, a total of 328 patients who underwent TT were eligible for analysis. Thyrotoxic subjects who had remission with antithyroid drug/ radioactive iodine therapy (n=16), those with lesser resection including hemithyroidectomy and isthmectomy (n=3), concomitant neck dissection (n=9) for intraoperative detection of lymphnode metastasis and those with incomplete calcium and iPTH values (n=3) were excluded.

Table 1: Comparison of thyrotoxic and euthyroid cohorts undergoing total thyroidectomy.

| Parameters | Thyrotoxic group Median (IQR; min-max) n=97 | Euthyroid group Median (IQR; min-max) n=231 | P value |
|---------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------|
| Age (years) | 38 (18; 17-66) | 37 (17; 13-83) | 0.489 |
| Male:Female | 25:72 | 40:191 | 0.214 |
| Free Thyroxine (ng/dl) | 2.5 (2.9; 0.6-10.6) | 1.3 (0.3; 0.9-2.1) | 0.043 |
| Thyroid stimulating hormone (mIU/l) | 0.005 (0.007; 0.001-0.3) | 2.6 (1; 0.4-5.3) | <0.001 |
| Baseline serum calcium (mg/dl) | 9 (1.2; 5.8-12.4) | 9.3 (0.7; 6.4-11.6) | 0.005 |
| 48-hour serum calcium (mg/dl) | 7.8 (1.3; 4.5-11.8) | 8.5 (1.1; 5.6-11.0) | <0.001 |
| Baseline serum intact parathormone (pg/ml) | 30.1 (36.2;1.2-184) | 26 (23.5; 1-83.8) | 0.220 |
| 48-hour serum intact parathormone (pg/ml) | 13.2 (23.3; 0.01-82.1) | 11.5 (16.6; 0.01-199) | 0.038 |
| Baseline serum 25-hydroxy vitamin D (ng/ml) | 18 (11.6; 3-55) | 19.2 (11.5; 3-61.7) | < 0.001 |

IQR = Inter-quartile range

Table 2: Multinomial logistic regression model fitted for the analysis of determinants of transient post-thyroidectomy hypocalcemia.

| Independent variable | Thyrotoxic group | | Euthyroid group | |
|-------------------------|------------------|-----------------------------------------|-----------------|-----------------------------------------|
| | P value | Odds ratio (95% Confidence Interval) | P value | Odds ratio (95% Confidence Interval) |
| Age (years) | 0.907 | | 0.367 | |
| Gender | 0.749 | | 0.211 | |
| Preoperative calcium | 0.894 | | 0.001 | 3.9 (1.5-9.9) |
| 25OHD severe deficiency | 0.137 | | 0.001 | 4.4 (4.5-431.6) |
| 25OHD deficiency | 0.285 | | 0.064 | |
| 25OHD insufficiency | 0.051 | | 0.081 | |
| 48-hour Parathormone | 0.008 | 3.7 (1.4-9.8) | 0.005 | 9.4 (2.6-34.4) |

25OHD= 25-hydroxycholecalciferol.

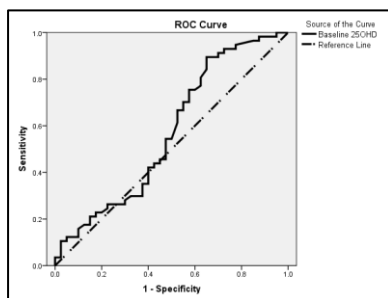


Figure 1: Receiver operating characteristic analysis showing preoperative 25-hydroxycholecalciferol predicting post-thyroidectomy hypocalcemia in thyrotoxic subjects.

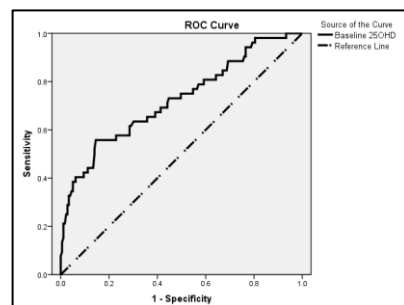


Figure 2: Receiver operating characteristic analysis showing preoperative 25-hydroxycholecalciferol predicting post-thyroidectomy hypocalcemia in euthyroid subjects.

Group A included 97 patients with new-onset hyperthyroidism with the median age of 38 years (range: 17-66 years) including 25 male and 72 female subjects. Group B included age- and sex-matched euthyroid cohorts (n=231) comprising 40 male and 191 female subjects with median age of 37 years. The incidence of postoperative transient hypocalcemia in thyrotoxic patients was 58.8% (57/97) compared to 22.5% (52/179) in euthyroid cohorts undergoing TT ($p<0.001$). There was no significant difference between group A and group B across the categories of preoperative 25OHD severe deficiency (15.5% vs. 12.6%), deficiency (37.1% vs. 41.6%), insufficiency (33% vs. 33.3%) and sufficiency (14.4% vs. 12.6%), $p=0.813$. In group A vs. group B analysis (Table 1), thyrotoxic patients had significantly reduced preoperative 25OHD ($p<0.001$), preoperative calcium ($p=0.005$), 48-hour calcium ($p<0.001$) and elevated 48-hour iPTH ($p=0.038$) compared to euthyroid cohorts. Multinomial logistic regression model was fitted (Table 2) for the analysis of determinants of outcome variable, transient hypocalcemia. In group A, independent risk factor was 48-hour iPTH (OR: 3.7, $p=0.008$). In group B, the independent risk factors of transient hypocalcemia were preoperative 25OHD severe deficiency (OR: 44.1, $p=0.001$), preoperative calcium (OR: 9.4, $p=0.001$) and 48-hour iPTH (OR: 3.9, $p=0.005$).

ROC analysis

In group A subjects, the area under the ROC curve (Figure 1) predicting transient hypocalcemia for the test-variable preoperative 25OHD was 0.573 (95% CI: 0.452-0.694; $p=0.222$) and optimal threshold could not be computed. Whereas, in euthyroid cohorts (Figure 2), preoperative 25OHD reliably predicted transient hypocalcemia with AUC of 0.725 (95% CI: 0.641-0.809; $p<0.001$) at an optimal cut-off value of 17.6 ng/mL. Sensitivity and specificity were 65.4% and 64.2%. Positive predictive value and negative predictive value was 34.6% and 86.5% respectively.

DISCUSSION

Hyperthyroidism is associated with higher rate and severity of postoperative hypocalcemia compared to euthyroid subjects undergoing TT.^{11,12} The phenomenon of hungry bone resulting from remineralization of bone loss associated with thyrotoxicosis induced osteoporosis is implicated as an important cause of post-thyroidectomy hypocalcemia.¹³⁻¹⁷ Hence, Vitamin D, which is an independent predictor of bone health and a potentially correctable factor was extensively studied for its role in the development of PH in thyrotoxic subjects. However, the results are variable owing to; geographic variation in vitamin D deficiency prevalence; the lack of uniformity in the utilization of 25OHD vs. 1, 25-dihydroxycholecalciferol for assessment of vitamin D status; differences in the assay method and cut-off values for defining the reference range. This single-center

prospective study addressed these issues and utilized serum 25-hydroxycholecalciferol, which is the major circulating form and the most reliable marker for assessment of vitamin D status. The severity of hypovitaminosis D was categorized as insufficiency, deficiency and severe deficiency in accordance with the Endocrine Society clinical practice guidelines.¹⁸ The risk of development of PH in each category among thyrotoxic subjects was compared and contrasted with age- and sex-matched euthyroid cohorts.

The present study demonstrated higher rates of transient hypocalcemia in thyrotoxic patients compared to euthyroid cohorts undergoing total thyroidectomy (58.8% vs. 22.5%), which is consistent with published reports.¹⁹⁻²⁴ Although the mean levels of preoperative 25OHD was significantly diminished in thyrotoxic subjects compared to euthyroid cohorts, there was no significant difference in the percent prevalence across the categories of severe deficiency, deficiency and insufficiency between the two groups. In multinomial regression analysis, the major determinant of PH in thyrotoxic group was low levels of 48-hour iPTH (OR: 3.7) and 25OHD even in the category of severe deficiency failed to impact the development of transient hypocalcemia.

The present study constructed ROC curve to assess the diagnostic accuracy of 25OHD in predicting transient hypocalcemia. In ROC analysis, classifiers that give curves to the top left corner indicates better performance and curves closer to 45-degree diagonal has less accurate results. In thyrotoxic subjects, ROC curve for the test-variable 25OHD was closer to the reference diagonal and indicates poor performance. Moreover, AUC of 0.5 has poor predictability. Thus, our study observed that preoperative 25OHD was unreliable in predicting transient hypocalcemia in thyrotoxic subjects.

In contrast, preoperative 25OHD reliably predicted transient hypocalcemia in euthyroid subjects at optimal cut-off value of 17.6 ng/mL. The sensitivity and specificity were 65.4% and 64.2% respectively, though with limited PPV of 34.6%. A PPV of 34.6% implies that 65.4% of subjects would be wrongly diagnosed with false positive results. Additionally, multivariate analysis revealed that independent risk factors for PH were preoperative calcium (OR: 9.4), 48-hour iPTH (OR: 3.9) and severe 25OHD deficiency (OR: 44.1) in euthyroid subjects. Therefore, euthyroid subjects with severe 25OHD deficiency had 44-fold increased likelihood to develop transient hypocalcemia post-TT compared to 25OHD sufficient group. Hence, correction of severe vitamin D deficiency and associated hypocalcemia preoperatively in this subset of euthyroid subjects will decrease the occurrence of PH and facilitate early safe discharge. Several meta-analysis and randomized controlled trails have reported that prophylactic calcium and vitamin D supplementation facilitates same-day discharge post-TT.²⁵⁻²⁹ Literature evidences have

implicated hungry bone syndrome (HBS) as an important cause of PH in thyrotoxic subjects in addition to surgically induced functional hypoparathyroidism.³⁰⁻³² Hungry bone phenomenon is characterized by profound and prolonged hypocalcemia along with hypomagnesemia and hyperphosphatemia with concomitant elevation of parathyroid hormone usually 72- to 96-hours after TT and is due to rapid remineralization of bone loss associated with thyrotoxic osteodystrophy. Thus, the significantly diminished 48-hour calcium and elevated 48-hour iPTH post-TT in thyrotoxic subjects compared to euthyroid group in the present study is corroborative of HBS. Michie et al had reported that higher rates of PH cannot be solely explained by functional hypoparathyroidism and showed that HBS is the mechanism of post-thyroidectomy hypocalcemia in thyrotoxic subjects. In a previous report, we have shown that HBS occurred exclusively in thyrotoxic subjects undergoing TT and correlated with the severity of bone demineralization.^{13,17} Furthermore, the author has shown in the previously published reports that the radical technique of TT was associated with higher rates of PH in thyrotoxic subjects and facilitates rapid recovery of bone mineral density.^{33,34} Moreover, 25OHD levels were not different in subjects exhibiting and not exhibiting PH among thyrotoxic subjects. Recently, Manzini et al had reported that decreased preoperative vitamin D levels did not predict PH, which is in keeping with our observation.⁸

Limitations

As vitamin D deficiency is latitude- and ethnicity-based, some of our observation could have been caused by characteristics specific to our population. The present study has not evaluated the bone mineral density nor its correlation with the severity of thyrotoxicosis and development of PH. Moreover, serum magnesium, alkaline phosphatase and other bone turnover markers which are potential predictors of PH in thyrotoxicosis were not included.

CONCLUSION

Serum 25OHD had limited utility in predicting transient hypocalcemia in thyrotoxic patients undergoing TT. However, preoperative 25OHD below 17.6 ng/mL was a reliable predictor of transient post-thyroidectomy hypocalcemia in euthyroid subjects, though with a limited sensitivity and specificity. Euthyroid patients with severe vitamin D deficiency had 44-fold increased likelihood of developing PH compared to 25OHD sufficient patients. Preoperative Calcium and vitamin D therapy in these patients at risk of PH will facilitate early safe discharge.

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