Background: Hypomagnesemia is known to impede hypocalcemia correction. This prospective observational study aimed to evaluate the impact of serum magnesium levels on the development of refractory hypocalcemia, which remains a concerning problem after total thyroidectomy (TT). Subjects and Methods: Consecutive subjects (n = 312; mean age = 38.4 [range: 13–83] years; M:F = 62:250) undergoing TT for benign or malignant thyroid diseases were evaluated for serum corrected-calcium (8.4–10.4 mg/dL), magnesium (1.7–2.4 mg/dL), intact parathormone (iPTH), and 25-hydroxycholecalciferol (25OHD) levels preoperatively, at 48-h and 6-month post-TT. Results: Postoperatively, 98 subjects (31.4%) exhibited transient hypocalcemia, 96 (30.8%) had hypomagnesemia, and 52 (16.7%) had refractory hypocalcemia. Preoperatively, 38 subjects (12.2%) had asymptomatic hypocalcemia and 77 (24.7%) had hypomagnesemia. In multivariate logistic regression analysis, independent risk factors of transient hypocalcemia were hyperthyroidism (odds’s ratio [OR]: 5.6), 48-h iPTH (OR: 3.2), 48-h magnesium (OR: 2.7), preoperative 25OHD (OR: 0.96), and preoperative calcium (OR: 0.5; each analysis, percent calcium decline and 48-h magnesium reliably predicted transient hypocalcemia with a threshold of 10.5% and 1.9 mg/dL, respectively. Area under curve, sensitivity, and specificity were 0.822, 82.7%, and 72.9%; and 0.649 (each analysis, percent calcium decline and 48-h magnesium reliably predicted transient hypocalcemia with a threshold of 10.5% and 1.9 mg/dL, respectively. Conclusion: Serum magnesium below 1.9 mg/dL had 2.7 times higher odds of developing transient hypocalcemia post-TT. Hypomagnesemia and percent calcium decline >10.5% within 48-h post-TT are associated with refractory hypocalcemia, which necessitates correction of both the deficiencies for prompt resolution of symptoms.

Keywords: Hypomagnesemia, magnesium, post-thyroidectomy hypocalcemia, refractory hypocalcemia, thyroidectomy

Introduction

Postoperative hypocalcemia is a common complication after total thyroidectomy (TT), which may be transient (less than 6 months) or permanent.[1] Refractory hypocalcemia, which is resistant to standard intravenous calcium therapy and calcitriol, is an important cause of morbidity, prolonged hospitalization, and readmissions after TT. Hypomagnesemia per se can cause refractory hypocalcemia and impede the correction of hypocalcemia.[2] Post-thyroidectomy hypocalcemia (PH) is commonly attributed to hypoparathyroidism resulting from inadvertent removal of the parathyroid glands or vascularity compromise. Parathyroid hormone (PTH) is the major calcitropic hormone that maintains constant serum calcium (Ca²⁺) levels by increasing calcium mobilization from bone and calcium reabsorption from kidney with any drop in Ca²⁺ levels. Recent evidence reveals that hypomagnesemia produces a state of functional hypoparathyroidism by inhibiting both the PTH secretion from the parathyroid glands as well as the target organ responsiveness.[3]
Although the association of hypomagnesemia with refractory PH is well established, the threshold of serum magnesium level that helps to predict the development of PH remains unknown. Therefore, we conducted this single-center prospective cohort study to evaluate the effects of hypomagnesemia on postoperative hypocalcemia and determine the threshold of serum magnesium levels, which can predict the development of transient hypocalcemia in subjects undergoing TT.

**Subjects and Methods**

Consecutive patients with benign or malignant thyroid disease undergoing first-time TT in the Department of Endocrine Surgery, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai—600003 from July 1st, 2017, to June 31st, 2019, were prospectively studied. This study was done in line with the STROCSS criteria and registered with research registry (UIN: Research Registry 5818). Informed written consent was obtained from all the participants. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional ethics committee (approval no. 18092012) and with the 1964 Helsinki Declaration and later amendments. This article does not contain any studies with animals performed by any of the authors.

All the subjects were initially evaluated for complete hemogram, thyroid profile, liver, and renal function tests. Surgical candidates with any of the following: large-volume goiter, pressure symptoms, cytology suspicious for malignancy, indeterminate cytology, retrosternal extension, recurrent/refractory hyperthyroidism, associated ophthalmopathy as well as patients opting surgery for cosmetic and logistic reasons, were included in the study. Subjects with recurrent goiter, concurrent lymphadenectomy, concurrent parathyroid surgery, long-standing medical conditions such as chronic renal and liver diseases, immunosuppression, and those receiving calcium and vitamin D supplementation were excluded.

Serum levels of corrected-calcium, phosphorus, magnesium, intact parathormone (iPTH), and 25-hydroxycholecalciferol (25OHD) were measured preoperatively at the time of diagnosis, 24-h, 48-h, 6-month post-TT, and more tailored to clinical needs. Subjects with hyperthyroidism received Tab. Carbimazole 10–60 mg/day with or without Tab. Propranolol 10–160 mg/day in divided doses, while hypothyroid subjects received supplementary doses of levothyroxine to achieve stable euthyroid state prior to surgery. Classic open TT was performed by the same surgical team as per institutional standards identifying and preserving all the parathyroid glands and laryngeal nerves.

**Laboratory Methods**

Biochemical parameters were determined using automated Roche Cobas e6000 series analyzer, Switzerland. Serum calcium (8.4–10.5 mg/dL) was determined by Arsenazo III method. Serum albumin (3.2–4.8 g/dL) by Bromo-Cresol Green method. Serum magnesium [1.7–2.4 mg/dL] was determined by modified xylidyl blue reaction method. Intact PTH [15–65 pg/mL] was determined by fully automated chemiluminescent immune assay method. The intra-assay and interassay coefficient of variation were 5.8% and 6.4%, respectively. Serum 25OHD (deficiency: <=20 ng/mL; insufficiency: 20–<30 ng/mL; sufficiency: 30–100 ng/mL; toxicity: >100 ng/mL) was determined by fully automated chemiluminescent immune assay method analyzed on Siemens ADVIA Centaur, standardized against isotope dilution-liquid chromatography-tandem mass spectrometry reference methods, as per vitamin D standardization program.

**Definitions**

Hypocalcemia was defined as Ca²⁺ <8.4 mg/dL and/or presence of symptoms and signs including acral or perioral paresthesia, muscle cramps, carpopedal spasm, laryngeal stridor, cardiac arrhythmias, and positive Chvostek and Trousseau sign. Hypomagnesemia was defined as serum magnesium <1.7 mg/dL. Hypoparathyroidism was defined as iPTH less than 10 pg/mL.

Postoperatively, biochemical and symptomatic hypocalcemia were treated with (1) oral calcium carbonate 1–3 g/day; (2) active vitamin D, calcitriol 0.5–2 mcg/day; and (3) intravenous calcium, 10% calcium gluconate at 0.5–2 mg/kg/h as per clinical needs. Vitamin D deficiency was treated with single intramuscular injection of cholecalciferol 600,000 IU 48-h postsurgery or 60,000 IU per-oral weekly for 8 weeks. Refractory hypocalcemia resistant to standard intravenous calcium therapy, in subjects with concurrent hypomagnesemia, was treated with IV magnesium 25–50 mg/kg/day and/or Tab. magnesium oxide 400 mg/day. Asymptomatic hypomagnesemia was not treated.

Subjects received suppressive dose of levothyroxine for differentiated thyroid carcinoma and life-long replacement dose for medullary thyroid cancer and benign histopathology post-TT. During the 6-month follow-up, subjects were reviewed periodically for any clinical evidence of hypocalcemia and treated accordingly.

**Statistical analysis**

Statistical analysis was performed with SPSS statistics, version 20.0, Armonk, NY: IBM Corp. Categorical data were expressed as frequencies (n) and percentage. Continuous data were non-normal (on Kolmogorov–Smirnov test) and expressed as median (interquartile range). Mann–Whitney U test and Spearman’s correlation test were performed. Independent variables significant on univariate analysis were incorporated into multivariate analysis. Multivariate binary logistic regression model was fitted to analyze the determinants of binary outcome variable(s), namely, postoperative hypocalcemia and hypomagnesemia. Receiver-operating characteristic (ROC) curve assessed the relative predictability of variables of interest. Youden index determined the optimal threshold. Results were expressed as odd’s ratio (OR) and...
95% confidence interval (CI). P value < 0.05 was considered statistically significant. The sample size was calculated for 90% powered cohort study with two-sided confidence level of 95%.[1]

**Results**

Out of 353 subjects prospectively studied, 312 subjects with a mean age of 38.4 years (range: 13–83 years), comprising 62 (19.9%) male and 250 (80.1%) female patients, were included in the analysis as shown in Figure 1. Subjects with (1) Graves’ disease who had spontaneous remission (n = 3) or radioactive iodine therapy (n = 16), (2) concurrent lymphadenectomy (n = 9) on intraoperative detection of lymph node metastasis, and (3) those (n = 13) lost in the follow-up of 16.9 (5.7) months were excluded. Preoperatively, 38 subjects (12.2%) had asymptomatic biochemical hypocalcemia and 77 (24.7%) hypomagnesemia. Postoperatively, 31.4% (n = 98) exhibited hypocalcemia, 16.7% (n = 52) refractory hypocalcemia, 30.8% (n = 96) hypomagnesemia, and 15.7% (n = 49) exhibited concurrent hypocalcemia and hypomagnesemia. The incidence of transient hypocalcemia in subjects with hyperthyroidism was 45.7% (42/92), while the incidence was 20.9% (46/220) among euthyroid subjects undergoing TT. About 26 subjects (8.3%) had undetectable 24-h iPTH levels, despite stringent adherence to collection, analysis, and interpretation protocols. At 6-month post-TT, 29 subjects were hypocalcemic. Demographics and clinical profile of subjects under study were tabulated [Table 1].

**Transient postoperative hypocalcemia**

Subjects exhibiting transient hypocalcemia (group A; n = 98) were compared with eucalcemic cohorts (Group B; n = 214) not exhibiting hypocalcemia post-TT. On multivariate analysis [Table 2], the independent risk factors for transient hypocalcemia were low levels of preoperative TSH (OR: 5.6; P < 0.001), preoperative calcium (OR: 0.5; P < 0.001), preoperative 25OHD (OR: 0.9; P = 0.015), 48-h magnesium (OR: 2.7; P = 0.001), 48-h iPTH (OR: 3.2; P = 0.001), increased operative duration (OR: 2.9; each P < 0.001), and percent decline of calcium (OR: 1.3; P < 0.001) through 48-h post-TT.

In ROC analysis [Figures 2 and 3], the reliable predictors for postoperative hypocalcemia were 48-h calcium, percent decline of calcium, and 48-h magnesium with a threshold of 7.9 mg/dL, 10.5%, and 1.9 mg/dL, respectively. The area under ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for 48-h calcium were 0.962 (95% CI: 0.938–0.988), 93.87%, 93.92%, 87.61%, and 97.1%, respectively. AUC, sensitivity, specificity, PPV, and NPV for percent calcium decline were 0.830 (95% CI: 0.781–0.879), 82.7%, 72.9%, 58.27%, and 90.17%. AUC, sensitivity, specificity, PPV, and NPV for 48-h magnesium were 0.649 (95% CI: 0.578–0.720; each P < 0.001), 68.4%, 63.1%, 45.8%, and 81.3%, respectively. The AUC values for percent decline of magnesium and iPTH were 0.573 (95% CI: 0.500–0.645; P = 0.040) and 0.596 (95% CI: 0.525–0.666; P = 0.036), respectively.

**Postoperative hypomagnesemia**

Subjects exhibiting postoperative hypomagnesemia (n = 96) were compared with normomagnesemic cohorts (n = 216; age = 37 (18) years; male: female = 42:174). Univariate and multivariate analysis are given in Table 3. In multivariate binary logistic regression model, independent risk factors for postoperative hypomagnesemia were low levels of TSH (OR: 2.1; P = 0.029), preoperative magnesium (OR: 0.04; P < 0.001), 48-h calcium (OR: 2.5; P = 0.007), and 48-h iPTH (OR: 2.1; P = 0.035).

There was no significant difference between the groups with respect to age, gender, and thyroid hormone levels. Transient
hypoparathyroidism was seen in more than two-third of subjects exhibiting hypomagnesemic hypocalcemia and refractory hypocalcemia. The slope of magnesium correlated well with the slope of calcium ($r = 0.290; P < 0.001$) and iPTH ($r = 0.177; P = 0.002$).

Thus, the power of this cohort study at 95% confidence level was 99.87% with continuity correction for the current dataset including 98 subjects in group A (hypocalcemic group) and 214 cohorts in group B (eucalcemic group) having 50% and 22% risk of postoperative hypomagnesemia (risk ratio = 2.3), respectively, after TT.

**Table 1: Demographics and clinical profile of subjects under each category**

| Parameters                        | Total cases | Transient hypocalcemia | Postoperative hypomagnesemia | Hypomagnesemic hypocalcemia | Refractory hypocalcemia |
|-----------------------------------|-------------|------------------------|------------------------------|-----------------------------|-------------------------|
| Frequency ($n$); percentage (%)   | 312 (100%)  | 98 (31.4%)             | 96 (30.8%)                   | 49 (15.7%)                  | 52 (16.67%)            |
| Age in years                      |             |                        |                              |                             |                         |
| ≤45 years                         | 213 (68.3%) | 66 (67.3%)             | 67 (69.8%)                   | 33 (67.3%)                  | 35 (67.3%)             |
| >45 years                         | 99 (31.7%)  | 32 (32.7%)             | 29 (30.2%)                   | 16 (32.7%)                  | 17 (32.7%)             |
| Gender                            |             |                        |                              |                             |                         |
| Male                              | 62 (19.9%)  | 20 (20.4%)             | 20 (20.8%)                   | 9 (18.4%)                   | 10 (19.2%)             |
| Female                            | 250 (80.1%) | 78 (79.6%)             | 76 (79.2%)                   | 40 (81.6%)                  | 42 (80.2%)             |
| Thyroid profile                   |             |                        |                              |                             |                         |
| Thyrotoxic                        | 92 (29.5%)  | 52 (53.7%)             | 42 (43.8%)                   | 25 (51%)                    | 25 (48.1%)             |
| Euthyroid                         | 220 (70.5%) | 46 (46.9%)             | 54 (56.3%)                   | 24 (49%)                    | 27 (51.9%)             |
| Vitamin D deficiency*             |             |                        |                              |                             |                         |
| Present                           | 168 (53.8%) | 60 (61.2%)             | 57 (59.3%)                   | 33 (67.3%)                  | 36 (69.2%)             |
| Absent                            | 144 (46.2%) | 38 (38.8%)             | 39 (40.7%)                   | 16 (32.7%)                  | 16 (30.8%)             |
| Preoperative hypocalcemia         |             |                        |                              |                             |                         |
| Present                           | 38 (12.2%)  | 24 (24.5%)             | 16 (16.7%)                   | 16 (32.7%)                  | 31 (63.3%)             |
| Absent                            | 274 (87.8%) | 74 (75.5%)             | 80 (83.3%)                   | 33 (67.3%)                  | 18 (36.7%)             |
| Preoperative hypomagnesemia       |             |                        |                              |                             |                         |
| Present                           | 77 (24.7%)  | 36 (36.7%)             | 62 (64.6%)                   | 31 (63.3%)                  | 31 (59.6%)             |
| Absent                            | 235 (75.3%) | 62 (63.3%)             | 34 (35.1%)                   | 18 (36.7%)                  | 21 (40.4%)             |
| Postoperative hypocalcemia        |             |                        |                              |                             |                         |
| Present                           | 98 (31.4%)  | 98 (100%)              | 49 (51%)                     | 49 (100%)                   | 52 (100%)              |
| Absent                            | 214 (68.6%) | Nil                    | 47 (49%)                     | Nil                         | Nil                    |
| Postoperative hypomagnesemia      |             |                        |                              |                             |                         |
| Present                           | 96 (30.8%)  | 49 (50%)               | 96 (100%)                    | 49 (100%)                   | 49 (94.2%)             |
| Absent                            | 216 (69.2%) | 49 (50%)               | Nil                         | Nil                         | 3 (5.8%)               |
| Transient hypoparathyroidism†      |             |                        |                              |                             |                         |
| Present                           | 131 (42%)   | 52 (53.1%)             | 49 (51%)                     | 32 (65.3%)                  | 34 (65.4%)             |
| Absent                            | 181 (58%)   | 46 (46.9%)             | 47 (49%)                     | 17 (34.7%)                  | 18 (34.6%)             |

*Serum 25-hydroxycholecalciferol vitamin D <20 ng/mL; †intact parathormone <10 pg/mL.

**Figure 3:** Receiver-operating characteristic curve demonstrating the rate of change of calcium, magnesium, and iPTH (intact parathormone) at 48 h after total thyroidectomy

**DISCUSSION**

In the present study, the incidence of transient postoperative hypocalcemia after TT was 31.4% (98/312). Although the incidence of permanent hypocalcemia was relatively high at 9% (29/312), it was well within the reported incidence of up to 12.1%. Subjects with hyperthyroidism exhibited higher rates of transient hypocalcemia (45.7% vs. 20.9%) compared to euthyroid subjects undergoing TT, which is consistent with prior reports. Subjects with hyperthyroidism had 5.6 times higher odds of developing PH. Other independent risk factors for transient hypocalcemia were preoperative vitamin D deficiency, prolonged operative duration, transient hypoparathyroidism, and rapid decline of calcium within 48-h post-TT. The aforementioned findings corroborated with published reports. In addition, subjects exhibiting postoperative hypomagnesemia had 2.7 times higher odds of developing transient PH. Recent studies emphasized on the role of hypomagnesemia in the development and progression of PH, which supports our observation. Magnesium modulates calcium homeostasis by acting as partial agonist at Ca$^{2+}$-sensing receptor which mediates the following: (1) Ca$^{2+}$ absorption or reabsorption, (2) PTH synthesis and secretion, (3) sensitivity of target organs to PTH, and (4) synthesis of 1,25(OH)$_2$ vitamin D. Moreover, hypomagnesemia per se can induce hypokalemia, neuromuscular irritability, tetany, seizures, tachyarrhythmia, and can cause resistant hypocalcemia, refractory to standard calcium therapy. Rude et al. showed that intravenous administration of magnesium in hypomagnesemia-induced hypocalcemia produces a twofold rise in PTH levels within
a minute after injection and restores serum calcium levels. Magnesium therapy thus facilitates prompt resolution of symptoms, which is refractory to standard IV calcium therapy. In agreement with this finding, we observed that 49 subjects with concurrent hypomagnesemia and hypocalcemia and remaining 3 subjects with refractory hypocalcemia required both calcium and magnesium therapy for resolution of symptoms.

The AUC of 0.96 (which is nearly 1) indicates that serum 48-h calcium can accurately predict the clinically relevant transient hypocalcemia at a cutoff value of 7.9 mg/dL and remains the gold standard of care. The AUC value of 0.649 indicates that 48-h magnesium can reliably predict postoperative hypocalcemia at a threshold of 1.9 mg/dL, though with a limited sensitivity and specificity. Although significant, the AUC for percent decline of magnesium and iPTH were closer to 0.5 and indicate poorer predictability.

The simultaneous fall of Ca\(^{2+}\) below 7.9 mg/dL, magnesium below 1.9 mg/dL, and percent calcium decline >10.5% improved the accuracy of predictability of severe PH at 48-h post-TT. To the best of our knowledge, our study is the first to define cutoff value to predict refractory hypocalcemia after TT. Interestingly, our study has revealed that serum magnesium even in the lower level of reference range from 1.7 to 1.9 mg/dL was associated with the development of PH. Recently, Wang et al.\(^{[17]}\) reported that serum magnesium within

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**Table 2:** Comparison of subjects exhibiting postoperative hypomagnesemia with those not exhibiting hypomagnesemia. Univariate and multivariate analysis for the determinants of transient hypocalcemia

| Parameter                      | Hypomagnesemia (n=96) Median (IQR)* | Eumagnesemia (n=214) Median (IQR)* | Univariate P | Multivariate P | Odd’s ratio (95% CI) |
|-------------------------------|-------------------------------------|------------------------------------|--------------|----------------|---------------------|
| Age in years                  | 37.5 (17)                           | 37 (16)                            | 0.665        | 0.978          |                     |
| Male: female                  | 20.78                               | 42.172                             | 0.760        | 0.270          |                     |
| Free tetraiodothyronine (ng/dL) | 1.9 (1.6)                           | 1.4 (0.7)                          | <0.001       | 0.562          |                     |
| Thyroid stimulating hormone (mIU/L) | 0.016 (2.5)                       | 2.5 (1.4)                          | <0.001       | <0.001         | 5.64 (3.01-10.57)   |
| Intraoperative time period (min) | 2.4 (0.4)                           | 1.9 (0.3)                          | <0.001       | <0.001         | 2.89 (1.91-4.14)    |
| Baseline calcium (mg/dL)      | 8.9 (1.3)                           | 9.3 (0.7)                          | <0.001       | <0.001         | 0.54 (0.39-0.76)    |
| 48-h calcium (mg/dL)          | 7.1 (1.2)                           | 8.6 (0.9)                          | <0.001       |               |                     |
| Baseline phosphorous (mg/dL)  | 4.1 (1.5)                           | 4.1 (1.0)                          | 0.134        |               |                     |
| 48-h Phosphorous (mg/dL)      | 4.4 (2.4)                           | 4.2 (1.2)                          | 0.596        |               |                     |
| Baseline magnesium (mg/dL)    | 1.9 (0.7)                           | 2.0 (0.4)                          | 0.017        | 0.381          |                     |
| 48-h Magnesium (mg/dL)        | 1.7 (0.7)                           | 1.9 (0.4)                          | 0.001        | 0.001          | 2.66 (1.47-4.83)    |
| Baseline parathormone (pg/mL) | 24.4 (30)                           | 28.6 (25.4)                        | 0.948        |               |                     |
| 48-h Parathormone (pg/mL)     | 9.3 (12)                            | 13.9 (18)                          | 0.003        | 0.001          | 3.21 (1.66-6.21)    |
| Baseline 25-OH vitamin D (ng/mL) | 16.9 (12.2)                         | 20 (12.5)                          | <0.001       | 0.015          | 0.96 (0.28-0.99)    |
| Percent decline calcium (%)   | 18.2 (15.9)                         | 5.9 (10.2)                         | <0.001       | <0.001         | 1.28 (1.20-1.36)    |

*IQR=Interquartile range

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**Table 3:** Comparison of subjects exhibiting postoperative hypomagnesemia with those not exhibiting hypomagnesemia. Univariate and multivariate analysis for the determinants of postoperative hypomagnesemia

| Parameter                      | Hypomagnesemia (n=96) Median (IQR)* | Eumagnesemia (n=216) Median (IQR)* | Univariate P | Multivariate P | Odd’s ratio (95% CI) |
|-------------------------------|-------------------------------------|------------------------------------|--------------|----------------|---------------------|
| Age in years                  | 36.5 (17)                           | 37 (18)                            | 0.763        | 0.992          |                     |
| Male: female                  | 20.76                               | 42.174                             | 0.311        | 0.089          |                     |
| Free tetraiodothyronine (ng/dL) | 1.8 (1.1)                           | 1.4 (0.7)                          | 0.058        |               |                     |
| Thyroid stimulating hormone (mIU/L) | 1.6 (2.7)                           | 2.4 (1.7)                          | <0.001       | 0.029          | 2.14 (1.08-4.23)    |
| Baseline calcium (mg/dL)      | 9.3 (1.1)                           | 9.2 (0.7)                          | 0.911        |               |                     |
| 48-h Calcium (mg/dL)          | 7.9 (1.8)                           | 8.5 (1.1)                          | <0.001       | 0.007          | 2.49 (1.28-4.84)    |
| Baseline phosphorous (mg/dL)  | 4.2 (1.3)                           | 4.1 (1)                            | 0.465        |               |                     |
| 48-h Phosphorous (mg/dL)      | 3.9 (1.9)                           | 4.4 (1.4)                          | 0.031        | 0.054          |                     |
| Baseline magnesium (mg/dL)    | 1.5 (0.6)                           | 2.2 (0.3)                          | <0.001       | <0.001         | 0.04 (0.02-0.09)    |
| 48-h Magnesium (mg/dL)        | 1.2 (0.4)                           | 2 (0.3)                            | <0.001       |               |                     |
| Baseline parathormone (pg/mL) | 24.8 (33.4)                         | 27.4 (24.7)                        | 0.281        |               |                     |
| 48-h Parathormone (pg/mL)     | 9.2 (14)                            | 13 (17.6)                          | 0.007        | 0.035          | 2.14 (1.06-4.35)    |
| Baseline 25-OH vitamin D (ng/mL) | 7.4 (14.2)                           | 19.6 (10.8)                        | 0.026        | 0.740          |                     |
| Percent decline calcium (%)   | 13.4 (15.8)                         | 17.1 (12.7)                        | <0.001       | 0.029          | 1.06 (1.01-1.11)    |

*IQR=Interquartile range
the reference range from 0.66 to 0.74 mmol/L was associated with an increased risk of PH (OR: 4.6; 95% CI: 2.1–10.4), which is in support of our observation. Recent evidence have shown that the downward trend of magnesium levels through 48 h after TT correlated highly with the development of hypocalcemia.\textsuperscript{[18,19]}

The etiology for hypomagnesemia after TT seems to be multifactorial.\textsuperscript{[3]} Prolonged surgery and larger volume of intravenous fluid administration could cause hemodilution and extravasation of electrolyte and proteins, leading to transient fall in the serum levels of calcium, magnesium, phosphorous, and sodium. Also, expansion of extracellular fluid volume inhibits tubular reabsorption of magnesium and precipitates further fall in magnesium levels. Additionally, bone hunger associated with hyperthyroidism, vitamin D deficiency, or hypercalcitoninemia is known to cause influx of calcium, magnesium, and phosphorous into the hungry bones.\textsuperscript{[16,10,20]} All these factors could have contributed to the rapid decline in calcium and magnesium seen after TT, which in turn can worsen surgically induced hypoparathyroidism and further exacerbate refractory hypocalcemia. Corroborating with this finding, we observed that the slope, that is, the rate of fall of magnesium level, correlated linearly with the slope of calcium and iPTH. Moreover, hyperthyroidism, postoperative hypocalcemia, and hypoparathyroidism were independently associated with postoperative hypomagnesemia. Therefore, the acute fall in magnesium and subsequent inhibition of PTH release could be the plausible explanation for aparathyroidism and further exacerbate refractory hypocalcemia. A few studies have previously demonstrated this correlation between rate of change of calcium, magnesium, and iPTH in subjects exhibiting hypomagnesemic hypocalcemia syndrome post-TT.\textsuperscript{[1]} Similar studies on Indian subjects have reported an association of hypomagnesemia with PH but were inadequately powered.\textsuperscript{[21,22]} Cherian et al. had reported preoperative hypomagnesemia in 24% of cases, which is similar to our observation. However, contradictory to our results, the authors could not demonstrate a relationship between hyperthyroidism and hypomagnesemia, probably owing to the small sample size.

The study has certain limitations. Of 96 subjects with postoperative hypomagnesemia, only 49 subjects exhibiting hypomagnesemic hypocalcemia syndrome needed intravenous magnesium and calcium therapy for resolution of symptoms of refractory hypocalcemia. The study could not provide clear explanation for the absence of symptoms or the need for magnesium correction in the remaining subjects with postoperative hypomagnesemia. It is probable that this reflects the effect rather than the cause as majority of this subset had preexisting hypomagnesemia (62/96) as given in Table 1. The study may contain confounders or other factors not included in the analysis, which could have caused this observation. Second, relatively high permanent hypocalcemia at 6-month post-TT may reflect prolonged lag time required for complete regain of parathyroid function and warrants evaluation after 1 year. Third, in order to uncover the true incidence of hypocalcemia and hypomagnesemia post-TT, preoperative deficiency was not corrected, which is ethically unsound. Also, subjects receiving prior calcium and vitamin D supplements were excluded. In contrary, nutritional supplementation is a contemporary practice in the developed countries, and therefore, our results cannot be generalized. Finally, differences in the ethnicity, vitamin D status, dietary habits, and the latitude specific to our geographic region may have contributed to some of our observations. Therefore, we recommend a worldwide multi-centric randomized controlled trial (RCT) for evaluation of magnesium therapy in refractory hypocalcemia post-TT.

**Conclusion**

In summary, the study demonstrated postoperative hypocalcemia in 31.4%, postoperative hypomagnesemia in 30.8%, refractory hypocalcemia in 16.7%, and concurrent hypomagnesemia and hypocalcemia in 15.7% of cases after TT. Monitoring of both serum calcium and magnesium will help to prospectively identify subjects at risk of developing PH. The decline of serum 48-h magnesium below 1.9 mg/dL, that is, even in the lower level of reference range (1.7–2.4 mg/dL), had 2.7 times higher odds of developing transient PH. Hypomagnesemia with concurrent decline of serum calcium below 7.9 mg/dL and percent calcium decline >10.5% within 48 h after surgery was associated with the development of refractory hypocalcemia, particularly in subjects with hyperthyroidism undergoing TT. Correction of both hypomagnesemia and hypocalcemia is necessary for prompt resolution of symptoms of refractory hypocalcemia after TT. The role of magnesium therapy in selective subjects at high risk of refractory hypocalcemia after TT merits further evaluation in RCT.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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