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Original Research

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Abstract

Objective. To optimize and individualize post-thyroidectomy hypocalcemia management.

Study Design. A multicenter prospective cohort study.

Setting. Two tertiary care hospitals.

Subjects and Methods. parathyroid hormone (PTH) was measured preoperatively, then at 1 and 6 hours after surgery. The required doses of calcium and vitamin D were defined as those maintaining the patients asymptomatic and their cCa $\geq$ 2 mmol/L. They were used as an endpoint in a generalized linear mixed effect model (GLIMMEX) aiming to identify the best predictors of these optimal required doses. Models were evaluated by goodness of fit and Receiver Operating Characteristic (ROC) curves.

Results. One hundred and sixty-eight patients were analyzed; 85.1% were female, 49.3% had BMI > 30, and 64% had vitamin D deficiency. Post-thyroidectomy hypocalcemia was found in 25.6%, of whom 18 (41.9%) were symptomatic and received intravenous calcium. First hour percentage of drop in PTH correlated positively with the severity of hypocalcemia ($P < .0001$). The GLIMMIX prediction model for oral calcium requirement was based on first-hour percentage change from preoperative PTH level, preoperative actual PTH, BMI, and thyroid function. The same predictors were identified for vitamin D, except that thyroid function was replaced with vitamin D status. These factors were used to build predictive equations for calcium and vitamin D doses.

Conclusion. Our findings help to optimize management of post-thyroidectomy hypocalcemia by assisting in the early identification of those who are not at risk of hypocalcaemia and by guiding early effective management of those at risk. This may reduce complications and medical cost.

Keywords

post-thyroidectomy hypocalcemia management, calcium, vitamin D, PTH, BMI

Introduction

Hypocalcemia is the most common complication after thyroidectomy and the primary cause of prolonged hospitalization.[1] Previously, we calculated the median hospital stay for hypocalcemic patients (vs non-hypocalcemic) to be 101.0 versus 49.5 hours.[2] This prolonged hospital stay for hypocalcemic patients was required mainly to adjust their calcium and vitamin D doses in order to correct their calcium deficit, based on symptom control and serum calcium level.

There is controversy and a lack of evidence-based guidelines for post-thyroidectomy hypocalcemia management. Several studies recommend providing routine post-thyroidectomy supplementation,[3,4] with calcium and vitamin D, to decrease the incidence and severity of hypocalcemia, while others recommend a selective treatment approach, based on the patients' parathyroid hormone (PTH) and calcium levels, as this would eliminate unnecessary calcium and vitamin D intake that might lead to hypercalcemia and additional unnecessary follow-up assessments, which occurs in at least 58% of patients undergoing thyroidectomy.[5]

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We hypothesized that the severity of parathyroid gland injury, reflected by the magnitude of postoperative PTH level drop, could be considered with other patient biochemical markers and characteristics to derive a calcium and vitamin D supplementation regimen. Accordingly, we conducted this study aiming to predict the optimal calcium and vitamin D doses in post-thyroidectomy hypocalcemia management, based on the patients' perioperative clinical characteristics and biochemical markers.

Materials and Methods

This was a prospective, multicenter standardized protocol conducted over 3 years (November 2009 to November 2012). It was conducted in 2 tertiary care centers, King Fahad Medical City and King Abdulazeez University Hospital in Riyadh–Saudi Arabia. The hypoparathyroidism outcomes and prognosis after 6 months follow-up for the same patients' cohort were presented in a separate paper.[6] Institutional Review Board approval (King Fahad Medical City and King Abdulazeez University Hospital in Riyadh–Saudi Arabia) was obtained before implementing the protocol and data collection. Demographic and clinical data collected were as follows:

- Baseline PTH, vitamin D3 (1.25 dihydroxyvitamin D), corrected calcium (cCa), electrolytes, renal, and thyroid function tests were obtained upon admission.
- First-hour PTH (timed from the patient left the OR) was obtained in the recovery room, while the sixth-hour PTH was obtained in the ward; these were used to plan management.
- Patients at high risk for developing hypocalcemia were defined as those with PTH ≤ 1.7 pmol/L (approximately 15.5 pg/mL, conversion factor is 0.11) regardless of their calcium level; this definition was based on our previous published data, in a similar patients cohort,[2] while hypocalcemic patients were those who had symptoms (eg, circumoral and finger numbness) with or without signs (eg, carpopedal spasm and Chvostek's sign), with associated cCa level ≤ 2 mmol/L (8 mg/dL, conversion factor is 0.25) and normal Mg level.
- Patients considered as high risk for hypocalcemia were started on 1 g Ca carbonate every 8 hours and 0.25 mcg vitamin D once daily, with frequent assessment of symptoms and signs, and cCa level checked every 12 hours.[4]
- Calcium and vitamin D doses were adjusted based on patient's symptoms and to maintain cCa >2 mmol/L, with calcium increased by 1 g/day and vitamin D by 0.25 mcg/day, until cCa reaches >2 mmol/L and patients were symptom free. The amount of calcium and vitamin D given up to this point was defined as the required doses.
- At any point of time if patient developed signs or symptoms of hypocalcemia, STAT cCa and Mg (to exclude and treat concomitant hypomagnesaemia) levels were measured, then 1 or 2 ampules of

intravenous Ca gluconate 10% were given by slow infusion. Subsequently, the oral calcium and vitamin D doses were increased as described previously. All patients with hypomagnesaemia received IV magnesium sulphate or oral magnesium citrate supplement depending on the severity of hypomagnesaemia.

The length of postoperative hospital stay (LOHS; from the time the patient left the operating room until discharged, calculated in hours) and the number of symptoms and signs were documented and considered as markers of severity of hypocalcemia and the response to treatment. Patients with less than total thyroidectomy (unless completion) or with concomitant parathyroidectomy were not enrolled. Patients with chronic renal failure or thyrotoxic osteodystrophy were excluded from the protocol.

Statistical Methods
Sample Size

The study evaluated 168 patients, which based on logistic regression modeling was deemed sufficient to detect a 1.5- to 2-fold likelihood increase in receiving at least 3000 mg of oral calcium and/or 0.5 μg of vitamin D (vs less doses). The ensuing statistical power with these analyses is at least 89% with 5% significance level and attrition rate of at most 7%.

Analysis Methodology

Outcome measures. Oral calcium and vitamin D doses were used as classification variables (each with 3 levels) due to the clustering nature and the sample size considerations of the doses actually given. Oral calcium was consequently grouped as none, up to 3000 mg/day, and more than 3000 mg/day, while vitamin D as none, up to 0.5 μg/day, and more than 0.5 μg/day.

Modeling methodology and selection of model predictors. Given the multinomial nature of the outcome and the presence of 2 centers, a generalized linear mixed effects (GLIMMIX) model was postulated to model the log of the odds (logit) of requiring calcium/vitamin D doses as a function of fixed effects covariates (like postoperative PTH percentage drop, age, thyroid function, and BMI) and the random effect of center. The selection of the model predictors was based on:

- Uni-variant association with the actual need for calcium and vitamin D, using chi-square/Fisher exact, and ANOVA for classificatory and continuous covariates, respectively.
- Statistical significance using an overall 5% test size
- Clinical considerations (factors that are clinically rational to use).

Postoperative PTH was calculated as a percentage change relative to preoperative PTH levels. Further classification of this variable into 3 levels (more than 73% drop, 40% to 73% drop, and below 40% drop) was based on ROC analysis associating actual postoperative PTH percentage of

drop with hypocalcemia (yes/no). Since both 1 and 6 hours postoperative PTH drop yielded similar high areas under the curve (AUC) (0.96), we selected 1-hour postoperative PTH change based on a clinical expediency rationale (ie, earlier intervention for high-risk patient and early discharge for the low-risk patient) to build our models.

Finally the selected predictive models were validated based on (1) the deviance and Pearson goodness-of-fit statistics, which basically relate the *actually* observed probabilities of the final dosages to those *predicted* by the model; (2) other statistical methods, including Akaike's Information Criteria (AIC), Schwartz criterion (SC), and –2 log likelihood test;[7] and (3) Receiver Operating Characteristic (ROC) curves analysis based on model-identified predictors, which are conducted to quantify the ability to discriminate between those who required calcium (or Vitamin D) and those who did not.[8]

Results

One hundred seventy-nine patients were enrolled in the study, of which 11 patients were excluded: 3 had chronic renal failure with secondary hyperparathyroidism (their preoperative PTH was more than 20 pmol/L), and 8 had thyrotoxic osteodystrophy. Consequently, 168 patients were analyzed. Of these, 143 (85.11%) were females, and 25 (14.88%) were males; mean age was 41.8 years (range, 16-79 years). In addition, 49.3% were obese (BMI > 30). One hundred subjects were preoperatively evaluated for vitamin D deficiency; of these 64% had vitamin D deficiency and 18.75% (n = 12 out of 64) had undetectable serum vitamin D. Other clinical characteristics of the patients are summarized in (**Table 1**). One hundred thirty-four (81.21%) patients were recruited in King Fahad Medical City (KFMC) and 34 (20.23%) from King Abdulazeez University Hospitals (KAUH).

Of the 168 evaluable patients, 43 (25.59%) were considered as a high-risk group for hypocalcemia (based on their sixth-hour PTH) and were prescribed oral calcium; 19 (44.18%) received up to 3000 mg/day and 24 (55.81%) received more than 3000 mg/day. Of these 43 high-risk patients, 18 (41.86%) developed symptoms with/without signs and thus received intravenous calcium gluconate (1-2 g) at least once to manage their acute clinical manifestations. On the other hand, 23 (53.48%) of those 43 patients were discharged on vitamin D up to 0.5 µg/day, 17 (39.53%) were discharged on more than 0.5 µg/day, and 3 (7%) did not receive their vitamin D due to a protocol violation and thus they were excluded from the final model analysis. None of these patients returned to the emergency room or the clinic with hypocalcemia symptoms. None of them required increase in the discharged calcium or vitamin D doses in the subsequent outpatients follow-up visits. One hundred twenty-five (74.40%) were characterized as low risk for hypocalcemia and thus did not require calcium or vitamin D supplement. None of our patients developed postoperative seroma or hematoma, which might consider as rare causes of post-thyroidectomy hypocalcemia. Furthermore, none of them had post-thyroidectomy low serum calcium level with normal PTH level.

Table 1. Clinical Characteristics of Studied Patients.

Characteristics	Number (%)	Total
Type of surgery		168
1. Total thyroidectomy (TT)	121 (72.0)	
2. TT + unilateral neck dissection	5 (2.9)	
3. TT + bilateral neck dissection	5 (2.9)	
4. TT + central neck	3 (1.7)	
5. Completion thyroidectomy	31 (18.4)	
6. Completion + unilateral neck dissection	1 (0.6)	
7. Completion + bilateral neck dissection	2 (1.2)	
Thyroid pathology		162
1. Multi-nodular goiter	53 (32.71)	
2. Papillary thyroid carcinoma	66 (40.74)	
3. Follicular thyroid carcinoma	2 (1.23)	
4. Medullary thyroid carcinoma	1 (0.61)	
5. Hurthle cell adenoma	7 (4.32)	
6. Follicular adenoma	6 (3.70)	
7. Hashimoto's thyroiditis	17 (10.49)	
8. Graves' disease	1 (0.61)[a]	
9. Lymphocytic thyroiditis	7 (4.32)	
10. Large B-cell lymphoma	2 (1.23)	
Clinically classification of thyroid function		168
1. Normal	123 (73.21)	
2. Hypothyroidism	41. (24.40)	
3. Hyperthyroidism	4 (2.38)[a]	
Body Mass Index (BMI) kg/m^2		152
1. Under weight (< 19)	2 (1.32)	
2. Normal (19-25)	26 (17.11)	
3. Overweight (25-30)	49 (32.24)	
4. Obese (>30)	38 (25.00)	
5. Severely obese (>35)	37 (24.34)	

[a]Notice that hyperthyroid patients are few because any hyperthyroid patients with concomitant thyrotoxic osteodystrophy were excluded.

The mean, standard deviation, and median length of hospital stay (in hours) for patients at low risk of hypocalcemia versus those at high risk of hypocalcemia were 33.5 ± 24.6, 24 (17, 150) versus 94.7 ± 69.3, 68.5 (20, 312).

Model-based Determination of the Required Optimal Dose

Oral calcium. Best GLIMMIX selected prediction model was based on 1-hour percentage change of PTH, preoperative PTH value, BMI, and thyroid function status (**Table 2**). The model indicates that the required dose is largely driven by a 1-hour percentage PTH drop and BMI while adjusting for preoperative PTH and thyroid function. **Figure 1A** depicts the model-based relationship between the required calcium dose and each of BMI and 1-hour percentage PTH drop.

Vitamin D. The GLIMMIX model retained the same covariates as those for the calcium dose with the omission of thyroid function and the addition of preoperative vitamin D status.

Table 2. Final GLIMMIX Model for Optimal Prediction of Required Oral Calcium Doses.

| Factor	Odds Ratio Estimates	95% CI	P Value
Drop of 1 hr PTH by 73% or more to require up to 3 g/day[a]	107.4	15.52 to 743.94	<.0001
Drop of 1 hr PTH by 73% or more to require more than 3 g/day[a]	288.3	31.00 to >999.99	<.0001
BMI (for one unit change difference)	1.1	1.00 to 1.197	.046
Preoperative PTH (for 1 unit change difference)	0.7	0.52 to 1.02	.067
Not hyperthyroidism (ie, hypo- and euthyroidism)[b,c]	0.1	0.01 to 2.23	.169
Model Fit Statistics: AIC = 151.307, SC = 187.192, −2 Log L = 127.307, and likelihood ratio P = < .0001			

Abbreviations: GLIMMIX, generalized linear mixed model, PTH; parathyroid hormone, BMI; body mass index; AIC, Akaike's Information Criteria; SC, Schwartz criterion; 2 Log L, = −2 log likelihood criteria.
[a]Compared to a PTH drop by less than 40%, no drop or an increase in PTH.
[b]Even its individual P value is insignificant, but it makes the model more solid and accurate.
[c]Thyroid function status was defined according to the patient clinical condition into "hyperthyroidism, hypothyroidism and euothyroidism."
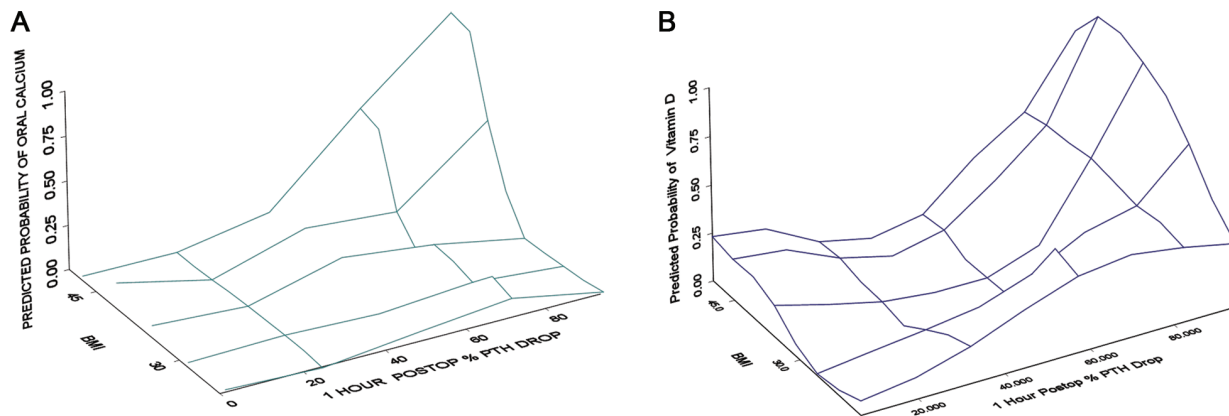
Figure 1. (A) The relation between percentage of PTH drop "y-axis," BMI "x-axis," and the probability of requiring oral calcium supplement "z-axis." (B) PTH drop "y-axis," BMI "x-axis," and the probability to need higher oral vitamin D doses "z-axis."

Table 3 delineates the primary dependency of the required dose on 1-hour PTH percentage drop and BMI, adjusting for the covariates in the model. **Figure 1B** demonstrates this functional dependency by illustrating how the probability of requiring a higher dose of vitamin D increases as a result of greater percentage drop in PTH and increase in BMI.

Model-based Calculations of the Required Doses

Table 4 specifies the general prediction equation given the model-based respective coefficients, which does not contain center random effect since it did not show any statistically significant association with the outcomes. The equation calculates the probability for required calcium or vitamin D dose categories. These probabilities can then be used to aid the clinical determination of the calcium and vitamin D dosing. In **Figure 2** we chose specific examples for the covariates in the model and graphically represented them.

Association between Postoperative PTH Change and Severity of Hypocalcemia

Figure 3A illustrates the positive dependence between 1-hour PTH percentage drop and number of symptoms and signs ($P < .001$), which indicates that patients with symptoms or signs had significantly greater PTH drop than those without symptoms. **Figure 3B** depicts the positive relationship between length of hospital stay and 1 hour postoperative PTH drop ($P < .001$). Those with more than 73% PTH drop required significantly longer hospital stay (to control his or her symptoms and calcium level).

Model Validations

For optimum doses of calcium and vitamin D, the resulting values of AIC and SC (**Tables 2** and **3**) based on contrasting the model with intercept only versus intercept with covariates, indicated adequacy of each predictive model (both P-values of the likelihood ratios <.0001). **Figure 4** shows the ROC analysis for both models.

Discussion

PTH levels and the status of other biochemical variables have been studied for their ability to predict hypocalcemia risk; however, controversy persists regarding the optimal time to measure PTH and the most accurate test standards

Table 3. Final GLIMMIX Model for Optimal Prediction of Required Vitamin D Doses.

Factor	Odds Ratio Estimates	95% CI	P Value
Drop of 1 hr PTH by 73% or more to require upto 0.5 μg/day[a]	209.3	14.66 to >999.99	<.0001
Drop of 1 hr PTH by 73% or more to require more 0.5 μg/day[a]	113.0	9.88 to >999.99	<.0001
BMI (for 1 unit change difference)	1.1	1.013 to 1.28	.030
Preoperative PTH (for 1 unit change difference)[b]	1.1	0.95 to 1.38	.146
Preoperative vitamin D status (if deficiency)[b]	1.7	0.23 to 12.26	.602

Model Fit Statistics: AIC = 96.307, SC = 126.035, −2 Log L = 72.307, and likelihood ratio $P \leq 0.0001$

Abbreviations: GLIMMIX, generalized linear mixed model; PTH, parathyroid hormone; BMI, body mass index; AIC, Akaike's Information Criteria; SC, Schwartz criterion; −2 Log L = −2 log likelihood criteria.
[a]Compared to a PTH drop by less than 40%, no drop, or an increase in PTH.
[b]Even their individual P values are insignificant, but they make the model more solid and accurate.

Table 4. General Equations for Predicted Probabilities of Required Calcium and Vitamin D Doses, Based on the GLIMMIX Model.

The probability of the recommended dosage = $\frac{e^{yi}}{1+e^{yi}}$
  Definitions:
  i^{th} patient (specific patient under consideration)
  For the jth calcium dosage: j = 1 "for calcium dosage up to 3000 mg/day," 2 "for calcium dosage more than 3000 mg/day";
  let $y_i = \alpha_j + \beta_j(\% \text{ PTH drop})_i + \pi_j(\text{Thyroid function status})_i + \theta_j(BMI)_i + \omega_j(\text{preop PTH})_i$
  For the jth vitamin D dosage: j = 1 "for Vitamin D dosage up to 0.5 μg/day," 2 "for vitamin D dosage more than 0.5 μg/day";
  let $y^i = \alpha_j + \beta_j(\% \text{ PTH drop})_i + \tau_j(\text{Pre op Vitamin D status})_i + \theta_j(BMI)_i + \omega_j(\text{preop PTH})_i$

e = the base for the natural logarithm; y^i = logit(P)=log(P/1-P)= log of odds of being prescribed calcium (or vitamin D). P is the probability of calcium (or vitamin D).
α_j = intercept for the jth dosage; β_j, π_j, τ_j, θ_j, and ω_j are the model-determined coefficients for the respective covariates of percentage of PTH drop, thyroid function status, preoperative vitamin D status, BMI, and preoperative PTH.

and cutoff values.[9] Furthermore, the relationship between PTH values and the severity of hypocalcaemia or the optimal therapeutic calcium and vitamin D doses required to resolve the condition have not been clearly defined.

Among the published selective supplementation approaches, Tunbridge Wells (Hospital) protocol,[10] based on laboratory assessments (calcium and phosphate levels), revealed inconsistent management of post-thyroidectomy patients, and attempts to implement this protocol in other institutions met with limited success.[11] On the other hand, Wiseman et al,[12] Cayo et al,[13] and Raffaelli et al[14] developed their post-thyroidectomy hypocalcemia management protocols based on allocating the patients into different groups, based on their actual postoperative PTH levels, and supplementing each group with different calcium and vitamin D doses. Wiseman et al[12] developed an algorithm based on different 3- and 1-hour post-thyroidectomy PTH cutoffs. Cayo et al[13] randomized their patients into 2 groups based on their next day early morning PTH value (above or below 10 pg/ml), and Raffaelli et al[14] developed a treatment protocol by dividing the patients into three groups based on their 4-hour postoperative PTH and the first postoperative day serum calcium levels.
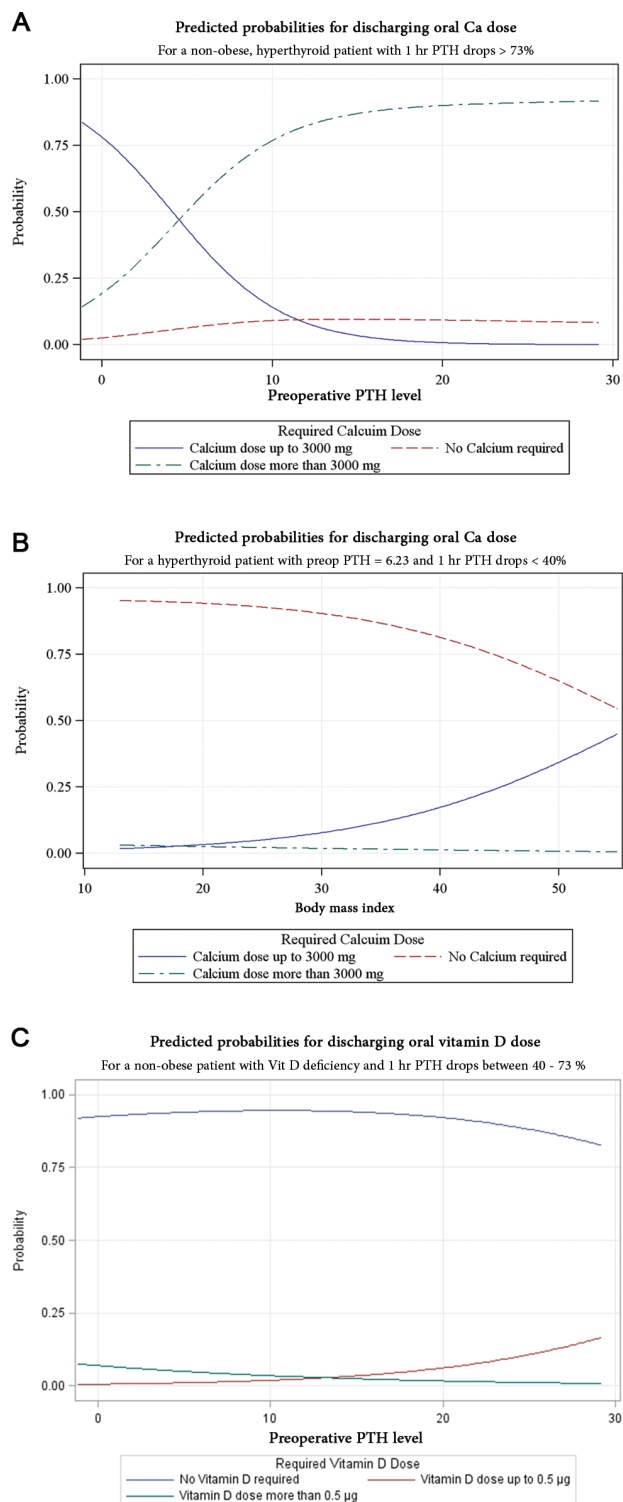
None of the aforementioned studies incorporated the perioperative percentage change in PTH (as a key factor) or take into account the multivariant prediction approach (eg, using BMI, thyroid function status, and vitamin D status) in their dose selection strategies. These factors may not play a role in developing hypocalcemia per se, and the postoperative PTH drop remains the main cause, yet these factors have a significant impact on the patient response to treatment, as we show here, and adding them to the evaluation and dose prediction process improves the management plan and the outcome prediction.

Based on our previous published data, the implementation of this study protocol[2] reduced the median length of hospital stay for low-risk patient by 54.8% (from 49.5 to 24 hours). The median length of hospital stay for the high-risk group dropped by 32.1% (from 101.0 to 68.5 hours), which emphasize on the importance of early preempt management of these patients. We previously calculated the single PTH measurement cost (US$2.6) and the estimated cost of bed utilization (US$23 per hour), in our institute.[2] These numbers clearly reflect the tremendous amount of cost saving that can be achieved by using a protocol based on PTH measurements versus routine or imperial calcium supplementation.

Why Perioperative PTH Percentage Drop and Not the Actual PTH Level?

Most of the published literature[12-14] on post-thyroidectomy hypocalcemia management was based on some cutoff points of postoperative actual PTH values. In our protocol-derived

A

Predicted probabilities for discharging oral Ca dose
For a non-obese, hyperthyroid patient with 1 hr PTH drops > 73%

(graph: Probability vs Preoperative PTH level)

Required Calcium Dose
— Calcium dose up to 3000 mg   - - - No Calcium required
— · — Calcium dose more than 3000 mg

B

Predicted probabilities for discharging oral Ca dose
For a hyperthyroid patient with preop PTH = 6.23 and 1 hr PTH drops < 40%

(graph: Probability vs Body mass index)

Required Calcuim Dose
— Calcium dose up to 3000 mg   - - - No Calcium required
— · — Calcium dose more than 3000 mg

C

Predicted probabilities for discharging oral vitamin D dose
For a non-obese patient with Vit D deficiency and 1 hr PTH drops between 40 - 73 %

(graph: Probability vs Preoperative PTH level)

Required Vitamin D Dose
— No Vitamin D required   — Vitamin D dose up to 0.5 µg
— Vitamin D dose more than 0.5 µg

Figure 2. Models simulation examples: (A) and (B) for oral calcium doses, while (C) for vitamin D. The required doses for each patient will be the highest dose probability predicted by the model.

model we elected to use perioperative 1 hour PTH percentage change for the following reasons:

(1) PTH percentage change does quantify the *magnitude of change* in PTH between preoperative and

postoperative and thus *longitudinally* reflects more information about the clinical state of the patient.

(2) The predictive ability of the model was significantly improved by using PTH percentage change as opposed to the actual postoperative PTH values.

It is clinically meaningful and statistically reassuring (from the model building perspective) that 1-hour PTH percentage change, which is a model-based significant predictor of the required doses of calcium and vitamin D, is also significantly correlated with the clinical endpoint of symptoms and signs as well as length of hospital stay (both reflective of severity of post-thyroidectomy hypocalcemia).

We selected 2 cutoff values for percentage of PTH drop to be used in our statistical model: upper limit = 73% and lower limit = 40%. These cutoff points were found to provide an optimal balance between positive and negative predictive values. Both upper and lower limits produce, respectively, high sensitivity and specificity levels. Above the upper limit of 73% drop, sensitivity was 97.5% and specificity was 85.8%. Similarly, the lower limit of 40% had specificity of 92% and sensitivity of 85%. Accordingly, 97.5% of patients with PTH percentage of drop of more than 73% will likely to be hypocalcemic. Conversely, 92% of patients with PTH drop of less than 40% are expected to be normocalcemic. Sands et al[15] found that 1 hour postoperative PTH drop of 70% or more is a reliable predictor for patients at risk of developing hypocalcemia (91% sensitivity and 98% specificity). Chapman et al[16] found that patients with a greater than 44% PTH drop from preoperative to 6-hour postoperative are very likely to develop hypocalcemia (100% sensitivity and 53.8% specificity).

Our final model for vitamin D dosage concurred with the fact that vitamin D deficiency leads to secondary hyperparathyroidism,[17] as it clearly demonstrated that the need for vitamin D was primarily driven by PTH drop ($P < .0001$). Despite worldwide disparities in prevalence of vitamin D deficiency,[18,19] it was substantially high in our study sample (64%) compared, for instance, with healthy Western Canadians[18] (34%) and an adult Australian population[19] (31%). This, in turn, may explain the notably high proportion (24%) of patients with baseline PTH more than 7 pmol/L, in spite of excluding those with secondary hyperparathyroidism due to chronic renal failure. This fact played a significant role in our selection of percentage of change in perioperative PTH (as opposed to the actual postoperative PTH) together with preoperative PTH in our predictive statistical model.

It is not clinically surprising that our final statistical model included, besides percentage PTH change as a ''key predictor,'' BMI, thyroid function, and vitamin D status as potential predictors of oral calcium needs. Although it did not reach statistical significance, adjusting for thyroid function and vitamin D significantly improved the model's predictability. Our findings support the importance of knowing the concomitant vitamin D status to guide post-thyroidectomy hypocalcemia management. This could be clinically rationalized by the fact
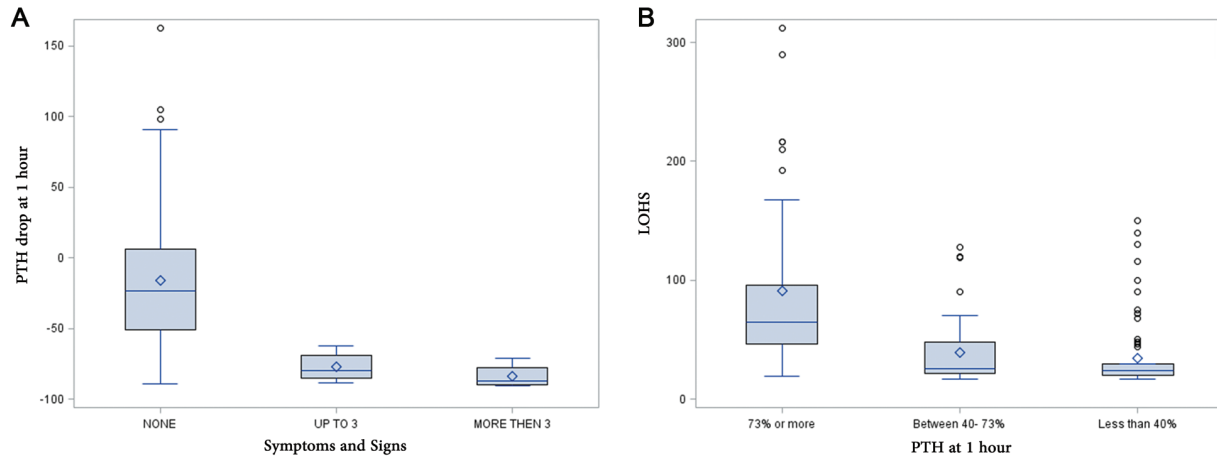
Figure 3. Boxplots of (A): Distribution of postoperative percentage PTH change by number of symptoms and signs and (B): Length of hospital stay (hours) by distributional cut points of postoperative PTH drop.
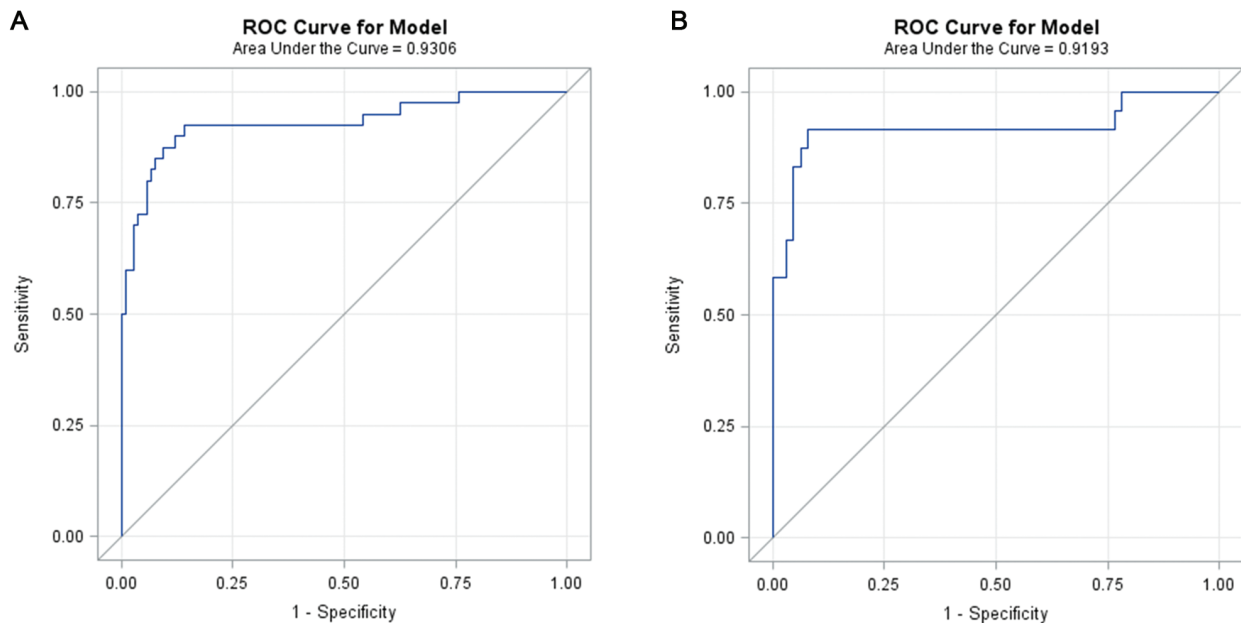
Figure 4. ROC curves validation for the model-identified predictors. (A) Area under the curve for the calcium model equal 0.93, (B) area under the curve for the vitamin D model equal 0.92. Both show excellent predictive ability.

that vitamin D is a key factor for calcium absorption.[20] Therefore, knowing baseline vitamin D status plays a crucial role in management of those patients. On the other hand, it was found that hyperthyroidism[21] may decrease calcium absorption, which might explain why this group requires relatively more calcium doses even if they do not exhibit the picture of thyrotoxic ostyodystrophy. In our model, obese patients will require more calcium and vitamin D doses to correct their calcium than patients with lower BMI, which can be explained by the fact that obese patients tend to have more vitamin D insufficiency, probably due to the decrease in the bioavailability of vitamin D3 from cutaneous and dietary sources.[22]

A potential limitation of this study is the lack of external validation of the models, which needs to be undertaken in a future study.

In conclusion, factors that affect both oral calcium and vitamin D requirements are percentage of perioperative PTH change, preoperative PTH level, BMI, preoperative thyroid function, and preexisting vitamin D status. Implementation of this model will assist in early identification of those who are not at risk of hypocalcaemia and thus allow early discharge. Additionally, the model also obviates unnecessary supplementation of calcium and vitamin D and guides early effective and optimal management of those at risk of hypocalcemia, therefore avoiding them suffering

from frequent hypocalcemia symptoms, signs, and complications and ultimately reducing the health care expenses including the hospitalization cost.

Author Contributions

Saleh F. Al-Dhahri, study design, data collection, and writing the manuscript; **Mohamed Mubasher**, statistics and writing the manuscript; **Fida Al-Muhawas**, data collection, patients follow-up, and reviewed the manuscript; **Mohammed Alessa**, data collection, patients follow-up, and reviewed the manuscript; **Rayan S. Terkawi**, data collection, patients follow-up, and reviewed the manuscript; **Abdullah S. Terkawi**, study design, data collection, and writing the manuscript.

Disclosures

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