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Clinical and Biochemical Predictors of Postoperative Hypocalcemia Following Thyroidectomy

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Abstract

Background: Post-thyroidectomy hypocalcemia is an important complication which can be caused by either temporary or permanent hypofunction of the parathyroids. Identification of patients with increased risk can help monitor and treat them at an early stage. Objective: To determine clinical, operative and biochemical risk factors for postoperative hypocalcemia in patients undergoing surgery for thyroidectomy in Al-Zuhoor Private Hospital and Tikrit Teaching Hospital, Iraq. Study Methods: The number of 100 adult patients undergoing thyroidectomy between January 2023 and January 2025 will be used for this hospital-based cohort study. Demographic, operating and biochemical data will be mined from reliable records. The prospective definition of postoperative hypocalcemia is used in analysis; it is defined as having a calcium below 8.5 mg/dL or the calcium threshold determined in the approved postoperative protocol. The only times that group comparisons and multivariable logistic regression and ROC analysis should be used is when there is observed data to support it. Results: The figures in the working tables are provided for illustration only and do not represent actual study results and should not be interpreted as such. Conclusions: There are a number of candidate predictors that seem clinically plausible such as extent of surgery, early postoperative PTH, calcium and magnesium levels, and vitamin D status; however, these associations and the predictive power of these variables can only be determined after analysis of the actual data set.

Keywords: Thyroidectomy; Hypocalcemia; Parathyroid Hormone; Vitamin D; Predictive Factors.

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Introduction

Thyroidectomy is a common surgical procedure utilized in the treatment of a variety of benign thyroid problems, multinodular goiter, Graves' disease, suspicious thyroid nodules, and thyroid malignancies. The surgical technique and the perioperative management have improved and thyroid surgery is now considered a relatively safe procedure, but still there are complications that are relevant to the clinical situation. Of these complications, hypocalcemia is of special importance as it may lead to a neuromuscular syndrome that can prolong hospital stays, necessitate further treatment and lead to emergency readmission in some cases [1,2].

When the function of the parathyroid glands is compromised during the thyroid surgical procedure, it is commonly seen as postoperative hypocalcemia. These small glands are in the thyroid area and control calcium levels by producing parathyroid hormone (PTH) [3]. Surgery, ischemia, accidental removal or trauma to the parathyroid glands can lead to a decrease in PTH secretion. Thus, there may be a period of hypocalcemia in the early postoperative phase. Incidence is reported to vary between studies due to variations in surgical technique, animal, laboratory, sampling time, and definition of biochemical and symptomatic hypocalcemia [4].

Some factors have been previously suggested as predictors of development of hypocalcemia after surgery. Alqahtani et al conducted a systematic review that showed multiple clinical and biochemical parameters and perioperative PTH are relevant predictors [5]. Qin et al. conducted a meta-analysis that showed that total thyroidectomy was associated with hypoparathyroidism, hypomagnesemia, vitamin D deficiency, and thyroid malignancy [6]. This study suggests that surgery-induced calcium imbalance is complex and cannot be reliably determined by any single parameter.

Perioperative biochemical evaluation is thus a significant part of perioperative risk assessment. Serum calcium should be measured in conjunction with serum albumin to detect calcium abnormalities, and when available, to measure the biologically active calcium is more direct. PTH levels taken immediately after surgery can help determine the parathyroid function prior to the lowest calcium concentration. Also, magnesium is important since magnesium deficiency may affect PTH secretion and action. Moreover, 25(OH)D levels may be useful for a characterization of vitamin D status, but not all studies have found them to have a clear-cut predictive value of their own [7,8]. Objectives of the study: To find the incidence of postoperative hypocalcemia among 100 patients undergoing thyroidectomy at the two hospitals between January 2023 and January 2025.The second objective is to determine the relationship between clinical, surgeon-specific and biochemical parameters and the development of hypocalcemia after surgery and develop independent predictors with suitable statistical analysis.

Materials and Methods

Study design and setting

It is a cohort study in which patients who underwent thyroidectomy from January 2023 to January 2025 in Al-Zuhoor Private Hospital and Tikrit Teaching Hospital in Iraq were followed up at the hospital. The targeted number of patients to be included in the study is 100 patients.

Study population

Adult patients who have had thyroid surgery within the period and had adequate information in their records for diagnosis of calcium status after surgery will be eligible for the study. Total thyroidectomy was performed in all patients in the study. Standardization of the extent of surgery was done to minimize procedural variability and to allow clinical and biochemical variables to be assessed as predictors of postoperative hypocalcemia. To determine factors contributing to hypocalcemia, serum calcium levels and other biochemical parameters were measured postoperatively.

Exclusion criteria may be pre-existing hypocalcemia due to another cause, history of hypoparathyroidism before surgery, advanced chronic kidney disease (CKD) which could affect calcium regulation, previous parathyroid surgery, or inadequate records to assess the primary outcome.

Data collection

The following recorded on a standardized case-record form: Age, Sex, indication for surgery, relevant co-morbidities, previous thyroid treatment, medications, and previous calcium or vitamin D supplementation. The operative variables included procedure type, procedure duration, specimen weight, lymph node

dissection, parathyroid identification and preservation, and suspected parathyroid injury, as well as the presence of auto transplantation, and inadvertent parathyroid removal. Calcium and PTH levels available, symptoms present, calcium or vitamin D therapy, hospital stay, re-admission and evidence of continued hypocalcemia at follow-up after surgery.

Definition of postoperative hypocalcemia

The primary outcome defined as album-corrected total serum calcium < 8.5mg/dL (2.12mmol/L) unless other validated end point is defined by the participating laboratories and approved protocol. This definition shall be strictly adhered to. Any hypocalcemia expressed by symptoms noted separately and documentation of its symptoms including perioral tingling, distal paresthesia's, muscle cramps, or tetany with low calcium. Transient and persistent hypocalcemia differentiated based on an established recovery period, and a recovery documented. The diagnosis of hypoparathyroidism didn't make by a single early postoperative calcium level.

Biochemical sampling

Preoperative measurements and postoperative sampling at about 4–6 hours, 24 hours, and 48 hours is a preferred protocol. Intact PTH levels performed before surgery and preferably within 4-6 hours after surgery. Measurement times need to be taken from the records. When available, the concentration of calcium (Ca) ion may be added, especially when the total calcium (Ca) is difficult to interpret because of changes in albumin or acid-base status.

Measured parameters and laboratory equipment

Table 1 presents categories of equipment – not instruments used at the two hospitals. Fill in the laboratory specific analyzer manufacturer, model, assay kit and reference interval for each laboratory as they appear in the laboratory records prior to submission. Surgical equipment can include any combination of the following: a standard operating table and lights, thyroidectomy instruments, electrosurgical or energy-based vessel-sealing devices, and suction/irrigation, an anesthesia work station, patient monitoring equipment, and specimen containers.

Table 1. Parameters, sampling schedule, units, and laboratory methods planned for data extraction.

Parameter	Timing	Unit / recording	Suitable method or equipment
Age and sex	Preoperative	Years; categories	Medical records
Thyroid diagnosis	Preoperative	Diagnostic category	Clinical records, imaging, histopathology
Type of thyroidectomy	Intraoperative	Procedure category	Operative report
Operative duration	Intraoperative	Minutes	Operative/anesthesia records
Parathyroid status	Intraoperative	Preserved/injured/autotransplanted/removed/unknown	Operative report
Total serum calcium	Pre/postoperative	mg/dL or mmol/L	Automated chemistry analyzer
Serum albumin	Pre/postoperative where available	g/dL or g/L	Automated chemistry analyzer
Corrected calcium	Calculated	mg/dL or mmol/L	Validated calculation from calcium and albumin
Ionized calcium	When available	mmol/L	Blood-gas analyzer or ion-selective electrode
Intact PTH	Preoperative	pg/mL or assay-specific unit	Automated

	and early postoperative		immunoassay analyzer
Magnesium	Pre/postoperative where available	mg/dL or mmol/L	Automated chemistry analyzer
Phosphate	Pre/postoperative where available	mg/dL or mmol/L	Automated chemistry analyzer
25-hydroxyvitamin D	Preoperative where available	ng/mL or nmol/L	Immunoassay or validated LC-MS/MS
Renal function	Preoperative where available	Creatinine; eGFR	Chemistry analyzer and validated equation
TSH and free T4	Preoperative if indicated	Laboratory-specific units	Automated immunoassay analyzer
Histopathology	Postoperative	Benign/malignant and diagnosis	Histopathology laboratory
Symptoms and treatment	Postoperative	Clinical status, drug/dose	Clinical examination and medication chart
Length of stay/readmission	Postoperative	Days; yes/no	Hospital records

Corrected calcium calculation

A very simple approximation for when both total calcium is measured in mg/dL and the albumin is measured in g/dL: Corrected calcium (mg/dL) = measured calcium + 0.8 × (4.0 − albumin). Measurement of direct ionized calcium is preferred, if clinically indicated and available. This formula should be used only with the same units.

Statistical analysis

The data put into a validated spreadsheet and then analyzed in IBM SPSS Statistics 22. Continuous variables summarized as the mean + or – SD if approximately normally distributed or median and IQR if skewed, and tested for distribution. Categorical variables reported as frequencies and percentages.

Patients divided into hypocalcemia group and no-hypocalcemia group. Independent-samples t-test or Mann–Whitney U test used for continuous variables for group comparisons, and the chi-square test used for categorical variables depending on the data type. Independent predictors assessed by multivariable logistic regression, with adjusted odds ratios and 95% confidence intervals. Area under the curve and confidence intervals used to evaluate discrimination with receiver operating characteristic (ROC) analysis. A two-sided p value < 0.05 used as a cut-off.

Results

Baseline demographic and clinical characteristics

Table 2 provides an example of the 100 participants that included in the baseline profile. Here, the population's mean age is 42.6 ± 13.8 years and 68.0% of the population were women. The proportion of benign thyroid disease was more than malignant (72.0% versus 28.0%).

Table 2. Illustrative baseline demographic and clinical characteristics of the planned cohort (n = 100); values require verification.

Variable	Result (n = 100)
Age, years, mean ± SD or median (IQR)	42.6 ± 13.8
Female, n (%)	68 (68.0%)
Male, n (%)	32 (32.0%)
Benign thyroid disease, n (%)	72 (72.0%)
Thyroid malignancy, n (%)	28 (28.0%)
Multinodular goiter, n (%)	46 (46.0%)
Graves' disease, n (%)	10 (10.0%)
Thyroiditis, n (%)	16 (16.0%)
Diabetes mellitus, n (%)	12 (12.0%)
Preoperative vitamin D deficiency, n (%)	39/86 (45.3%)
Preoperative hypocalcemia, n (%)	5/94 (5.3%)

Surgical characteristics

The following illustrative operative characteristics were summarized in the table below. The thyroid procedure most commonly performed is total thyroidectomy (64.0%) followed by central neck dissection (18.0%). Suspected parathyroid injury (9.0%) and incidental parathyroid removal (6.0%).

Table 3. Illustrative operative characteristics and parathyroid-related variables (n = 100); values require verification.

Operative variable	Result (n = 100)
Total thyroidectomy, n (%)	64 (64.0%)
Near-total thyroidectomy, n (%)	8 (8.0%)
Subtotal thyroidectomy, n (%)	12 (12.0%)
Completion thyroidectomy, n (%)	6 (6.0%)
Central neck dissection, n (%)	18 (18.0%)
Lateral neck dissection, n (%)	7 (7.0%)
Operative duration, minutes	108 (IQR 85–140)
Parathyroid glands identified/preserved, n (%)	3–4 glands in 78 (78.0%)
Suspected parathyroid injury, n (%)	9 (9.0%)
Parathyroid autotransplantation, n (%)	11 (11.0%)
Incidental parathyroid removal, n (%)	6 (6.0%)
Malignancy on histopathology, n (%)	28 (28.0%)

Perioperative biochemical parameters

The perioperative biochemical values are shown in illustrative form in table 4. A decrease in mean total calcium from 9.18mg/dL preoperatively to 8.42mg/dL at 24 hours, along with a decrease in mean early postoperative PTH.

Table 4. Illustrative perioperative biochemical measurements by sampling time; denominators and values require verification.

Parameter	Preoperative	4–6 h post-op	24 h post-op	48 h post-op
Total calcium (mg/dL)	9.18 ± 0.36	8.61 ± 0.49	8.42 ± 0.52	8.55 ± 0.48
Corrected calcium (mg/dL)	9.22 ± 0.34	8.64 ± 0.48	8.46 ± 0.51	8.59 ± 0.47
Ionized calcium (mmol/L), if available	1.19 ± 0.05	1.10 ± 0.07	1.08 ± 0.08	1.10 ± 0.07

Intact PTH (pg/mL)	42.8 ± 16.5	18.6 ± 10.2	—	—
Magnesium (mg/dL)	1.96 ± 0.18	1.82 ± 0.21	1.79 ± 0.22	1.84 ± 0.20
Phosphate (mg/dL)	3.42 ± 0.48	3.71 ± 0.55	3.86 ± 0.61	3.72 ± 0.56
Albumin (g/dL)	4.02 ± 0.31	3.78 ± 0.32	3.72 ± 0.33	3.76 ± 0.32

Incidence and clinical presentation of hypocalcemia

The primary outcome and clinical manifestations reported as shown in table 5. 29 of 100 patients (29.0%) were considered to have biochemical hypocalcemia and 12 patients (12.0%) were considered as having biochemical hypocalcemia and were also considered as having symptoms. These are not incident estimates, but simulations. Prospectively defined mutually exclusive categories of symptoms are not necessarily mutually exclusive within the same patient; no aggregate of symptom-specific percentages is possible unless they are mutually exclusive.

Table 5. Illustrative incidence and clinical presentation of postoperative hypocalcemia; values require verification.

Outcome	Result
Total participants, n	100
Biochemical postoperative hypocalcemia, n (%)	29 (29.0%)
No postoperative hypocalcemia, n (%)	71 (71.0%)
Symptomatic hypocalcemia, n (%)	12 (12.0%)
Perioral tingling/numbness, n (%)	8 (8.0%)
Distal paresthesia, n (%)	7 (7.0%)
Muscle cramps or tetany, n (%)	4 (4.0%)
Intravenous calcium treatment, n (%)	5 (5.0%)
Oral calcium and/or active vitamin D, n (%)	29 (29.0%)
Readmission related to hypocalcemia, n (%)	2 (2.0%)
Persistent hypocalcemia at defined follow-up, n (%)	2 (2.0%)

Comparison between outcome groups

A representative comparison of the patients based on their hypocalcemia status after surgery is shown in Table 6. In this example, total thyroidectomy, central neck dissection, lower early postoperative PTH, lower preoperative vitamin D, lower postoperative magnesium and longer operative duration are displayed as being associated with hypocalcemia, at the unadjusted level.

Table 6. Illustrative comparison of clinical and biochemical variables by postoperative hypocalcemia status; p-values require recalculation.

Variable	Hypocalcemia group	No-hypocalcemia group	p-value
Age, years	44.1 ± 13.5	42.0 ± 13.9	0.49
Female sex, n (%)	23 (79.3%)	45 (63.4%)	0.12
Total thyroidectomy, n (%)	25 (86.2%)	39 (54.9%)	0.004
Central neck dissection, n (%)	10 (34.5%)	8 (11.3%)	0.006
Preoperative corrected calcium, mg/dL	9.16 ± 0.35	9.24 ± 0.34	0.29
Preoperative PTH,	41.2 ± 15.8	43.5 ± 16.8	0.53

pg/mL			
Early postoperative PTH, pg/mL	10.8 ± 5.7	21.8 ± 9.5	<0.001
Preoperative 25-hydroxyvitamin D, ng/mL	18.1 ± 7.0 (n=25)	24.7 ± 9.1 (n=61)	0.002
Postoperative magnesium, mg/dL	1.68 ± 0.17	1.86 ± 0.20	<0.001
Operative duration, minutes	135 ± 38	105 ± 31	<0.001

Independent predictors and predictive performance

Table 7An illustrative multivariable model is presented, Table 8 and Figure 1 An illustrative ROC performance is presented.

Table 7. Illustrative multivariable logistic regression for postoperative hypocalcemia; estimates require recalculation from verified data.

Candidate predictor	Adjusted OR	95% CI	p-value
Early postoperative PTH	0.91	0.86–0.96	0.001
Preoperative vitamin D status	1.72	0.62–4.77	0.30
Total thyroidectomy	2.68	0.88–8.16	0.083
Central neck dissection	2.21	0.72–6.80	0.166
Postoperative magnesium	0.24	0.07–0.82	0.023
Parathyroid injury/removal	2.93	0.63–13.62	0.17

Table 8. Illustrative receiver operating characteristic (ROC) performance of selected biochemical predictors; estimates require recalculation.

Predictor	AUC	95% CI	Cut-off	Sensitivity	Specificity
Early postoperative PTH	0.86	0.77–0.95	≤12 pg/mL	79%	82%
Postoperative corrected calcium	0.81	0.72–0.90	<8.5 mg/dL	76%	78%
Preoperative vitamin D	0.66	0.53–0.79	<20 ng/mL	64%	61%

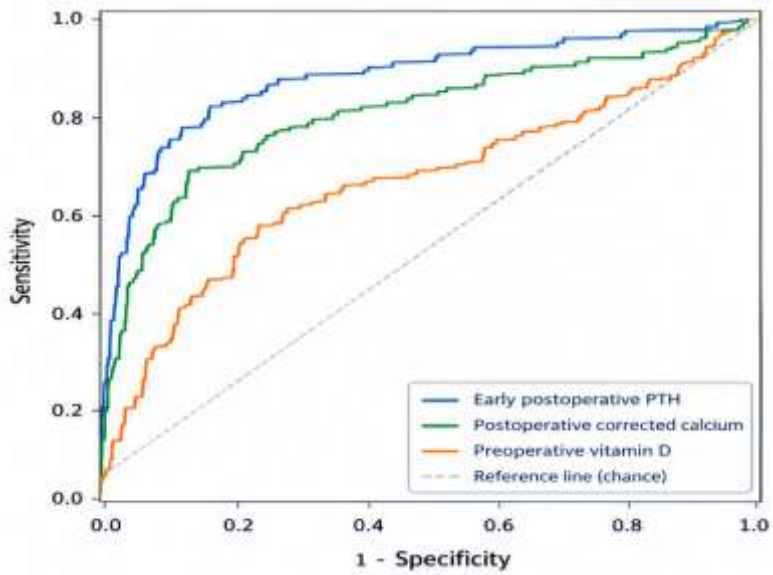


Figure 1. Receiver operating characteristic (ROC) curves for early postoperative PTH, postoperative corrected calcium, and preoperative 25-hydroxyvitamin D. Generate curves only from verified patient-level data and report AUCs with 95% confidence intervals; identify whether cut-offs were prespecified or data-derived.

Discussion

Results from any incidence estimate should be considered within the context of the operational definition, the timing of blood sampling, the type of surgery performed and the type of hypocalcemia treated (biochemical versus symptomatic). Edafe et al. found 115 observational studies, reporting a median incidence of transient hypocalcemia of 27% (IQR, 19-38%) and a median incidence of permanent hypocalcemia of 1% (IQR, 0-3%) [9]. A second systematic review and meta-analysis by Qin et al. found 1.96% (95% CI, 0.8–3.1%) of pooled patients with permanent, and 24.92% (95% CI, 21.5–28.3%) with transient, hypocalcemia, and noted that studies were heterogeneous [6]. These estimates are for illustrative purposes and should not be used in place of incidence based on the current cohort. The final manuscript must also differentiate between transient biochemical hypocalcemia and symptomatic events and/or persistent hypoparathyroidism.

PTH is biologically plausible as an early predictor, since compromise of the parathyroid gland could result in a reduction of secretion of parathyroid hormone before a nadir would be reached in the serum calcium [10]. Edafe et al. named perioperative PTH as an important biochemical predictor [9] while Baldassarre and colleagues' systematic review of the included studies also identified the most consistent statistically significant predictor to be perioperative PTH [11]. This would support the pattern of hypocalcemia, which was observed, of a lower PTH in the early stages. However, the level of association, independent effect and optimum threshold needs to be determined from the specific cohort. The levels of PTH that are acceptable depend on the type of assay being used and the time of day the test is drawn; therefore, a value (e.g., 12 pg/mL) should not be stated as being universally accepted or be validated without local analysis and validation.

Calcium, magnesium, and vitamin D. Serial calcium is useful to quantify the severity and time of the onset of calcium deficiency after surgery [12]. Total calcium levels should be utilized in conjunction with albumin, while ionized calcium may be better used in specific patients where there is difficulty in interpretation due to protein binding and/or acid–base disturbances. A meta-analysis of 23 studies has identified some factors that are associated with postoperative hypocalcemia: hypomagnesemia and hypovitaminosis D preoperatively [13]. Physiological relevance: Mg deficiency may result in impaired PTH secretion and peripheral action of PTH. Vitamin D deficiency may lead to a decrease in calcium absorption and/or diminish the calcium reserve before surgery, but its independent predictive power is different among cohorts. It is essential to think about these variables together and in conjunction with effect estimates and confidence intervals, since the variables are not necessarily independently predictive.

Candidates to be studied as predictors include the extent of resection, central or lateral neck dissection or preservation of parathyroid tissue [14]. Dissection of total thyroidectomy may provide an increased risk of

vascular compromise and accidental removal of parathyroids. Lalitha et al. found that a correlation exists between transient hypocalcemia and inadvertent removal of parathyroid glands, parathyroid auto transplantation, Graves' disease and female gender [15]. Kim et al. determined that central lymph-node dissection, thyroid malignancy, vitamin D deficiency and low postoperative PTH level are other risk factors for transient hypocalcemia [16]. If the differences noted in the illustrative examples in the total thyroidectomy and central neck dissection variables are observed in the verified database, they should be considered as unadjusted associations and should be discussed in the context of these differences; if present, independent effects should be shown in the multivariable model. The precision may be limited with relatively few outcome events, particularly for rare operative complications, with 100 participants.

A locally validated risk-stratification process including early PTH, calcium and selected operating parameters may help to identify the level of postoperative monitoring and/or the necessity for supplemental calcium. The American Thyroid Association has released a statement about post-operative hypoparathyroidism with the aim of standardizing post-operative hypoparathyroidism diagnosis, prevention and management [17]. However, the estimates of the ROC for the current cohort should only be considered as exploratory until validated within the current cohort and ideally confirmed in an independent cohort. Treatment pathway is not implied by the values in this draft, but should be consistent with local protocols and clinician assessment.

Strengths and limitations. The two-hospital setting is introduced, as well as the planned integration of clinical, operative and biochemical variables will enable the locally relevant information. Until the tables in this manuscript can be replaced or substantiated with patient-level data, however, it is not possible to draw substantive conclusions. Limited precision for multivariable modelling and ROC estimates may be achieved from a sample of 100 patients. The drawbacks are the absence of laboratory results, variability in the timing of the sample, assay differences and/or variations in the surgical approach in hospitals, incomplete documentation of parathyroid status, selection bias and remaining confounding. Where this is a retrospective study, these should be clearly identified. Observational associations cannot be used to establish cause and effect. Standardization of sampling and external data validation in future multi-center studies would be helpful.

Conclusion

Post-thyroidectomy hypocalcemia is an important postoperative complication and should be promptly diagnosed and managed. In the literature, early postoperative PTH, serial calcium levels, magnesium levels, preoperative vitamin D levels and surgical factors such as extent of thyroid resection, neck dissection, parathyroid injury etc. are potential factors in risk assessment. In the current manuscript, however, the numbers shown are only illustrative and do not directly reflect the incidence of hypocalcemia or the predictive value of each variable in the study population. A definitive conclusion should be written only when the records of all eligible patients have been reviewed, missing data and sampling times have been recorded, planned comparisons are conducted and a parsimonious multivariable model is performed. If verified, these estimates may help in the local postoperative monitoring; at present, however, no clinical recommendation for cohorts is justified.

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