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Original Article

Risk Factors for Hypocalcemia Following Total Thyroidectomy: A Retrospective Cohort Study

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Abstract

Background. Hypocalcaemia is the most frequent complication of total thyroidectomy. Reported incidences vary widely, from 15% to more than 60% for transient hypocalcaemia and from 0.2% to 10% for permanent hypoparathyroidism, and the risk factors that drive this variation remain incompletely defined. **Objectives.** To determine the incidence of post-operative hypocalcaemia after total thyroidectomy at a Libyan tertiary teaching hospital and to identify the clinical, operative and pathological factors associated with its development. **Materials and Methods.** We conducted a retrospective cohort study of consecutive patients aged 16 years or older who underwent total thyroidectomy at Tobruk Medical Center between January 2016 and December **2020**. Pre-operative, intra-operative and tumour-related variables were abstracted from electronic medical records and histopathology reports. Hypocalcaemia was defined as an albumin-corrected total serum calcium below 8.0 mg/dL or an ionised calcium below 4.0 mg/dL recorded at any point during the index admission. Groups were compared using the chi-squared or Fisher exact test for categorical variables and the Student t-test or Mann-Whitney U test for continuous variables, followed by univariable and multivariable logistic regression. **Results.** Of 337 patients who underwent total thyroidectomy during the study period, 290 had complete post-operative calcium follow-up and constituted the analysis cohort. Median age was 47 years; 223 patients (76.9%) were women. Thyroid carcinoma was the operative indication in 219 patients (75.5%). Post-operative hypocalcaemia occurred in 37 patients (12.8%). On univariable analysis, intra-operative parathyroid gland injury (OR 2.49, 95% CI 1.11-5.59), drain placement (OR 2.40, 95% CI 1.19-4.87), concomitant lymph node dissection (OR 2.45, 95% CI 1.20-4.90) and operative time exceeding 2.5 hours (OR 2.00, 95% CI 1.03-4.19) were each associated with hypocalcaemia. In the multivariable model, only parathyroid gland injury remained independently associated with the outcome (adjusted OR 3.68, 95% CI 1.65-8.21; p = 0.001). No patient receiving pre-operative levothyroxine developed hypocalcaemia (0 of 34); because this zero cell produced complete separation, the association is reported descriptively rather than modelled. **Conclusions.** Intra-operative parathyroid gland injury was the only independent risk factor for hypocalcaemia after total thyroidectomy in this cohort. Because such injury is recognised by the operating surgeon at the time of the procedure, it identifies intra-operatively a subgroup of patients who may benefit from closer post-operative calcium monitoring and earlier supplementation.

Keywords. Hypocalcaemia; Hypoparathyroidism; Thyroidectomy; Thyroid cancer; Parathyroid glands.

Introduction

Differentiated thyroid carcinoma is the most common endocrine malignancy, and its recorded incidence has risen substantially over the past two decades. Much of this rise is attributed to increased detection of small, indolent tumours through the widespread use of neck ultrasonography rather than to a true increase in clinically significant disease [1,2].

Total thyroidectomy remains the standard operative treatment for most patients with differentiated thyroid carcinoma and for a substantial proportion of patients with benign multinodular or toxic goitre [3]. When performed by high-volume surgeons, mortality is negligible and morbidity is low; however, complication rates rise appreciably when the procedure is undertaken in lower-volume settings [3].

Post-operative hypocalcaemia, arising principally from transient or permanent hypoparathyroidism, is the most frequent complication of the operation. Transient hypocalcaemia is reported in 15% to 30% of patients in most series, with some cohorts describing incidences above 60%, whereas permanent hypoparathyroidism occurs in

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0.2% to 10% [4,5]. Even when transient, hypocalcaemia delays recovery, prolongs hospital stay and generates additional biochemical monitoring and supplementation [4]. Factors that have been variably associated with its development include female sex, extrathyroidal tumour extension, central compartment lymph node dissection, prolonged operative time, intra-operative blood loss, obesity and failure to identify or inadvertent injury of the parathyroid glands [5].

Data describing this complication in North African surgical practice are scarce, and local incidence and risk profiles may differ from those reported in the high-volume Western and East Asian centres that dominate the literature. We therefore reviewed our institutional experience with total thyroidectomy to determine the incidence of post-operative hypocalcaemia and to identify the clinical and operative characteristics associated with it.

Material and Method

Study design and setting

This was a retrospective cohort study conducted at Tobruk Medical Center, a tertiary teaching hospital in Tobruk, Libya. The electronic medical records of all patients who underwent total thyroidectomy between January 2016 and December **2020** were reviewed. The study is reported in accordance with the STROBE statement for observational research.

Participants

Patients aged 16 years or older who underwent total thyroidectomy for any indication were eligible. Patients were excluded if they were younger than 16 years, had documented pre-operative hypocalcaemia or hypoparathyroidism, or underwent concurrent parathyroid surgery. Patients without a recorded post-operative serum calcium measurement were excluded from the outcome analysis; the number excluded on this basis and a comparison of their baseline characteristics with those of the analysed cohort are reported in the Results.

Variables

Pre-operative variables. Age, sex, pre-operative thyroid functional status (euthyroid, hypothyroid on levothyroxine, or hyperthyroid), previous neck surgery and comorbid conditions.

Intra-operative variables. Operative indication, total operative time, estimated intra-operative blood loss above 200 mL, performance of concomitant lymph node dissection, drain placement, annual thyroidectomy volume of the operating surgeon, and the intra-operative status of the parathyroid glands (identified, inadvertently injured, or auto-transplanted). Inadvertent parathyroid injury was defined as glandular devascularisation or excision recognised by the operating surgeon and recorded in the operative note, or the incidental identification of parathyroid tissue within the thyroidectomy specimen on histopathological examination.

Tumour-related variables. Tumour size, histological subtype, pathological stage, lymph node metastasis, capsular invasion, lymphovascular and perineural invasion, and locoregional or distant spread.

Outcome definition

The primary outcome was post-operative hypocalcaemia, defined as an albumin-corrected total serum calcium below 8.0 mg/dL or an ionised calcium below 4.0 mg/dL recorded at any point during the index admission. Calcium sampling followed routine ward practice rather than a fixed research protocol, so the timing of measurement was not standardised across the cohort; this is addressed in the Limitations. Where paired total and ionised measurements were discordant, the value within the reference range was adopted. Symptomatic hypocalcaemia was recorded as perioral or acral paraesthesia or a positive Chvostek or Trousseau sign, and calcium and vitamin D supplementation was prescribed on clinical grounds by the treating team. Biochemical follow-up did not extend beyond discharge, so transient and permanent hypoparathyroidism could not be distinguished; the outcome reported here should be understood throughout as early post-operative hypocalcaemia.

Statistical analysis

Categorical variables are presented as absolute frequencies and percentages. Continuous variables are presented as mean with standard deviation where normally distributed and as median with interquartile range otherwise; normality was assessed using the Shapiro-Wilk test. Groups were compared using the Student t-test or the Mann-Whitney U test for continuous variables and the chi-squared test, or the Fisher exact test where expected cell counts were below five, for categorical and ordinal variables.

Patients with no recorded post-operative calcium result were excluded rather than imputed, so the outcome was analysed on a complete-case basis. For covariates, missing values affected fewer than 15% of records for any single variable and were replaced by the modal value for categorical and ordinal variables and by the mean or median for continuous variables according to their distribution. Single imputation of this kind does not propagate the uncertainty introduced by the missing values, and the resulting confidence intervals should therefore be read as marginally narrower than they would be under multiple imputation.

Associations with post-operative hypocalcaemia were quantified as odds ratios with 95% confidence intervals derived from univariable logistic regression. Variables with $p < 0.10$ on univariable analysis, together with age and sex, were entered into a multivariable logistic regression

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model; given 37 outcome events, the model was restricted to a maximum of three covariates in order to maintain at least ten events per variable. Model fit was assessed with the Hosmer-Lemeshow test and discrimination with the area under the receiver operating characteristic curve.

Pre-operative hypothyroidism was associated with a zero outcome cell (0 of 34 patients), producing complete separation. The maximum-likelihood odds ratio is therefore not estimable and is not reported; the association is presented descriptively and tested with the Fisher exact test. A two-sided p-value below 0.05 was considered statistically significant. Analyses were performed using **SPSS20.0**.

Ethical considerations

The study protocol was reviewed and approved by the institutional research ethics committee of Tobruk Medical Center **(3588)**. Given the retrospective design and the exclusive use of anonymised records, the requirement for individual informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Result

A total of 337 patients underwent total thyroidectomy during the study period. Forty-seven patients (13.9%) had no recorded post-operative serum calcium result and were excluded, leaving 290 patients in the analysis cohort (Figure 1). The possibility that these exclusions were not independent of the outcome cannot be ruled out and is addressed in the Limitations.

The median age of the analysed cohort was 47 years, and 223 patients (76.9%) were women. Most patients were euthyroid before surgery; 34 (11.7%) were receiving levothyroxine for previously diagnosed hypothyroidism and 25 (8.6%) had biochemical hyperthyroidism. The commonest operative indication was well-differentiated thyroid carcinoma in 219 patients (75.5%), followed by goitre in 31 (10.7%) and thyroiditis in 15 (5.2%). Baseline and operative characteristics are summarised in Table 1.

Table 1. Baseline and operative characteristics of the analysis cohort (n = 290)

Characteristic	n	%
Median age, years	47	—
Age > 60 years	68	23.4
Female sex	223	76.9
Male sex	67	23.1
Pre-operative hypothyroidism (on levothyroxine)	34	11.7
Pre-operative hyperthyroidism	25	8.6
Indication: thyroid carcinoma	219	75.5
Indication: goitre	31	10.7
Indication: thyroiditis	15	5.2
Indication: other	25	8.6
Concomitant lymph node dissection	76	26.2
Operative time > 2.5 h	97	33.4
Estimated blood loss > 200 mL	14	4.8
Parathyroid gland(s) identified intra-operatively	273	94.1
Parathyroid gland injury	74	25.5
Parathyroid gland auto-transplantation	19	6.6
Drain placement	83	28.6

IQR, interquartile range.

Incidence of hypocalcaemia

Post-operative hypocalcaemia developed in 37 of 290 patients (12.8%). All affected patients were symptomatic, with manifestations ranging from perioral paraesthesia to positive Chvostek and Trousseau signs, appearing 8 to 12 hours after surgery.

Univariable analysis

Table 2 compares patients who developed hypocalcaemia with those who remained normocalcaemic. Lymph node invasion (40.5% versus 21.3%; p = 0.010), concomitant lymph node dissection (43.2% versus 23.7%; p = 0.010), operative time exceeding 2.5 hours (48.6% versus 31.2%; p = 0.030), intra-operative parathyroid gland injury (43.2% versus 22.9%; p = 0.008) and drain placement (45.9% versus 26.1%; p = 0.008) were all significantly more frequent among patients who developed hypocalcaemia. Pre-operative levothyroxine therapy was recorded in 34 normocalcaemic patients and in no hypocalcaemic patient (p = 0.018, Fisher exact test). Hypocalcaemia occurred in 32 of 219 patients operated on for thyroid carcinoma (14.6%), 2 of 31 with goitre (6.5%) and 2 of 15 with thyroiditis (13.3%); these differences were not statistically significant (p = 0.097, 0.265 and 0.945, respectively). Neither parathyroid gland identification nor auto-transplantation was associated with the outcome.

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Table 2. Univariable comparison of patients who developed post-operative hypocalcaemia and those who did not (n = 290)

Variable	Normocalcaemia n = 253 (87.2%)	Hypocalcaemia n = 37 (12.8%)	p
Age > 60 years	60 (23.7)	8 (21.6)	0.770
Female sex	199 (78.6)	24 (64.9)	0.063
Pre-operative hypothyroidism	34 (13.4)	0 (0)	**0.018**
Pre-operative hyperthyroidism	21 (8.3)	4 (10.8)	0.611
Indication: thyroid carcinoma	187 (73.9)	32 (86.5)	0.097
Indication: goitre	29 (11.5)	2 (5.4)	0.265
Indication: thyroiditis	13 (5.1)	2 (5.4)	0.945
Lymph node invasion	54 (21.3)	15 (40.5)	**0.010**
Lymph node dissection	60 (23.7)	16 (43.2)	**0.010**
Operative time > 2.5 h	79 (31.2)	18 (48.6)	**0.030**
Estimated blood loss > 200 mL	12 (4.7)	2 (5.4)	0.861
Parathyroid gland identification	238 (94.1)	35 (94.6)	0.891
Parathyroid gland auto-transplantation	18 (7.1)	1 (2.7)	0.311
Parathyroid gland injury	58 (22.9)	16 (43.2)	**0.008**
Drain placement	66 (26.1)	17 (45.9)	**0.008**

Data are n (%). p-values in bold are statistically significant at the 0.05 level. The p-values for the three operative-indication rows were recalculated from the counts shown, the submitted version having assigned a single value to two rows.

Multivariable analysis

Results of the univariable and multivariable logistic regression models are shown in Table 3. Intra-operative parathyroid gland injury was the only variable independently associated with post-operative hypocalcaemia (adjusted OR 3.68, 95% CI 1.65-8.21; p = 0.001). Drain placement was significant on univariable analysis but not after adjustment (adjusted OR 1.88, 95% CI 0.89-3.96; p = 0.097). Lymph node dissection and prolonged operative time were also significant on univariable analysis but were not retained in the final model, which was restricted to four covariates in order to preserve an acceptable ratio of outcome events to variables.

Table 3. Univariable and multivariable logistic regression for factors associated with post-operative hypocalcaemia

Variable	OR	95% CI	p	aOR	95% CI	p
Age > 60 years	0.89	0.39–2.04	0.779	—	—	—
Age (per year)	—	—	—	0.99	0.97–1.02	0.692
Female sex	0.50	0.24–1.05	0.067	—	—	—
Pre-op hyperthyroidism	1.34	0.43–4.14	0.611	1.49	0.45–4.85	0.507
Lymph node invasion	2.51	1.22–5.17	0.012	—	—	—
Lymph node dissection	2.45	1.20–4.99	0.014	—	—	—
Operative time > 2.5 h	2.09	1.04–4.19	0.039	—	—	—
Parathyroid gland injury	2.49	1.11–5.59	0.027	3.68	1.65–8.21	0.001
Drain placement	2.40	1.19–4.87	0.014	1.88	0.89–3.96	0.097

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval. A dash indicates that the variable was not entered into that model. The multivariable model comprised age, pre-operative hyperthyroidism, parathyroid gland injury and drain placement. Univariable estimates for age over 60 years, female sex, pre-operative hyperthyroidism, lymph node invasion, lymph node dissection and operative time were derived from the counts in Table 2; the univariable p-values for parathyroid gland injury and drain placement were derived from the reported odds ratios and confidence intervals. All should be checked against the source dataset. Pre-operative hypothyroidism is not shown because complete separation (0 of 34 events) rendered the odds ratio non-estimable; the univariable association was p = 0.018 by Fisher exact test.

Discussion

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In this single-centre retrospective cohort of 290 patients undergoing total thyroidectomy, early post-operative hypocalcaemia occurred in 12.8%, and intra-operative parathyroid gland injury was the only factor independently associated with the outcome after adjustment.

The incidence observed here is at the lower end of the published range. A systematic review and meta-analysis of 115 observational studies reported a median incidence of permanent post-thyroidectomy hypoparathyroidism of approximately 1%, with transient hypocalcaemia substantially more frequent [5]. Our comparatively low figure is notable given that more than 75% of our patients were operated on for malignancy and more than a quarter underwent concomitant lymph node dissection, both of which are recognised risk factors. Two explanations warrant consideration. First, the absence of routine post-discharge biochemical surveillance means that mild or late-presenting hypocalcaemia may have gone undetected; consistent with this, every hypocalcaemic patient in our cohort was symptomatic, whereas other series report that more than half of affected patients are asymptomatic [7,8]. Second, the exclusion of 47 patients without post-operative calcium results may have introduced selection bias in either direction.

Female sex and older age have both been proposed as risk factors for post-thyroidectomy hypocalcaemia [5]. In our cohort, hypocalcaemia was in fact numerically more frequent among men than women (13 of 67, 19.4%, versus 24 of 223, 10.8%), although this difference did not reach statistical significance ($p = 0.063$). This runs counter to pooled data, in which female sex carried an odds ratio of 2.28 (95% CI 1.53 to 3.40) for transient hypocalcaemia [5], and should be interpreted cautiously given the small number of male patients in our cohort and the absence of adjustment for operative extent.

The influence of intra-operative parathyroid gland identification on subsequent hypocalcaemia remains contested. Some authors report that failure to identify the glands is associated with both transient [9,10] and permanent [11] hypoparathyroidism, whereas others have found that identification itself is associated with a higher risk, presumably because glands that are actively sought are more likely to be handled and devascularised [12]. In our cohort, neither identification nor auto-transplantation was associated with the outcome. Injury, by contrast, was strongly and independently associated with hypocalcaemia in both univariable and multivariable models. The direction and magnitude of this association are consistent with pooled data, in which inadvertent parathyroid excision carried an odds ratio of 1.90 (95% CI 1.31 to 2.74) for transient hypocalcaemia [5]. This is the most clinically actionable finding of the study: parathyroid injury is recognised by the operating surgeon at the time it occurs, and it therefore provides an immediate intra-operative signal that a given patient warrants intensified post-operative calcium monitoring and, potentially, pre-emptive supplementation.

None of the 34 patients receiving pre-operative levothyroxine developed hypocalcaemia. We deliberately refrain from interpreting this as evidence of a protective effect. A zero outcome cell of this kind produces complete separation in logistic regression, and any odds ratio generated from it is a numerical artefact rather than a valid estimate. The finding is hypothesis-generating at most and requires replication in a larger cohort using an analytical method suited to sparse data, such as Firth penalized or exact logistic regression.

Hypocalcaemia has been reported to be more common after thyroidectomy for Graves' disease or diffuse toxic goitre [13], and thyrotoxicosis of recent onset has been identified as a predictor in prospective data [7]. Only 4 of our 25 hyperthyroid patients developed hypocalcaemia, and hyperthyroidism was not associated with the outcome in either model; our cohort was, however, underpowered to detect an effect of this magnitude.

Surgeon procedural volume is a well-established determinant of complications after thyroidectomy [5,10]. Our cohort reflects the combined practice of several lower-volume and a small number of higher-volume surgeons, and case allocation between them was not randomised. We did not have sufficient case numbers per surgeon to analyse this factor reliably, and it should therefore be regarded as an unmeasured confounder rather than as a variable the study has addressed.

Limitations

This study has several limitations. Its retrospective, single-centre design limits generalisability and precludes control of unmeasured confounding. There was no standardised surgical protocol across operators. Most importantly, biochemical follow-up did not extend beyond the immediate post-operative period, so transient and permanent hypoparathyroidism cannot be distinguished and the true burden of permanent hypoparathyroidism in this population remains unknown. Parathyroid hormone was not measured, which precludes confirmation of a hypoparathyroid mechanism in individual patients. Forty-seven eligible patients were excluded for lack of calcium data, raising the possibility of selection bias. Finally, the modest number of outcome events constrained the multivariable model and left the study underpowered to detect associations of small or moderate size.

Conclusion

Early hypocalcaemia occurred in 12.8% of patients after total thyroidectomy at our institution. Intra-operative parathyroid gland injury was the only independent risk factor identified. Because this injury is observed and

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recorded by the surgeon at the time of operation, it offers a practical, immediately available trigger for intensified post-operative calcium surveillance. Prospective studies incorporating perioperative parathyroid hormone measurement and long-term follow-up are needed to determine how much of this early hypocalcaemia progresses to permanent hypoparathyroidism.

Declarations

Ethics approval and consent to participate. Approved by the institutional research ethics committee of Tobruk Medical Center **(3588)**. The requirement for individual informed consent was waived owing to the retrospective design and the use of anonymised records.

Consent for publication. Not applicable.

Availability of data and materials. The anonymised dataset analysed during the current study is available from the corresponding author on reasonable request.

Competing interests. The author declares that he has no competing interests.

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