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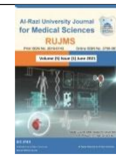

Incidence and Associated Factors of Post-Thyroidectomy Hypocalcaemia (Single-Center Study).

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Abstract:

Background: Thyroid surgery represents a widely used intervention since thyroid nodules detection is increasing. Hypocalcemia following total thyroidectomy is a common complication that is sometimes difficult to correct. Apparently there were no studies conducted in Yemen on hypocalcemia after thyroidectomy and their associated factors. **Objective**: The aim of our study was to estimate incidence of hypocalcemia following thyroidectomy and determine its associated factors. **Patients and Methods**: From January 2021 to march 2022, a cross-sectional study was conducted at Al Thawra Modern General Hospital, Sana’a city, Yemen. We included all patients who underwent total or completion thyroidectomy with normal range perioperative calcium level, including those who underwent concomitant neck dissection. All patients who underwent lobectomy, resection of lobe thyroid gland, and diagnosed pathology of parathyroid glands were excluded from the analysis. Data were collected directly from patients during pre and postoperative periods using a pre-prepared questionnaire. The primary outcome measures were the rate of biochemical hypocalcaemia. **Results**: A total of 50 patients enrolled in this study. Females outnumbered males (74% versus 26% respectively) with female to male ratio 3:1. The mean age of the patients at surgery was 38.46 ± 11.5 years with a range of 15-70 years. The majority (76%) of the patients underwent a total thyroidectomy without neck dissection, whereas total thyroidectomy with neck dissection was performed in 8% patients. Completion thyroidectomy without neck dissection and with neck dissection were done in 12% and 4% patients, respectively. Incidence of biochemical hypocalcaemia within 48 hours of surgery was 54% observed in 27 patients (mean =8.5 ± 0.65 mg/dl). There were no statistically differences between males and females in age, postoperative calcium, type of thyroid disease and type of surgery. Decreased pre-operative calcium, malignancy, and underwent total thyroidectomy were significantly related to the development of hypocalcemia. **Conclusion**: Compared with other countries, incidence of hypocalcemia following thyroidectomy was high in our patients. Decreased pre-operative calcium, malignancy, and underwent total thyroidectomy were associated factors of hypocalcemia following thyroidectomy at Al Thawra Modern General Hospital, Sana’a city, Yemen.

Keywords: Post-Thyroidectomy, Hypocalcaemia, Sana’a, Yemen.

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Introduction

Thyroid diseases are considered amongst one of the common endocrine gland disorders worldwide. In the United States alone, an estimated 20 million Americans have some form of thyroid disease [(1)]. In 2017, 45,379 new cases of thyroid cancer were reported and 1,892 died of thyroid cancer in the United States [(2)]. Among patients with thyroid swelling, it had been found in one series of Yemeni patients that approximately 30% of them had thyroid malignancy [(3)]. The management of thyroid diseases can include medical and/or surgical treatment [(4)]. Thyroid surgery is the definitive management option for thyroid malignancies, and also for benign diseases such as multinodular goiter with compression symptoms [(5)]. Thyoidectomy could be either total thyroidectomy or subtotal thyroidectomy [(4, 6, 7)].

Thyoidectomy represents a widely used intervention since thyroid nodules detection is increasing; actually 50-70% of adult population might have a thyroid incidentaloma [(8-10)].

With newer medical developments and increased surgical experience, thyroidectomy has become a safe procedure with low postoperative morbidity and mortality rates for experienced surgeons with higher annual thyroidectomy volume [(11)]. However, subsequent major complications such as incidental parathyroidectomy during thyroid resection, postoperative hemorrhage, hypocalcaemia and recurrent laryngeal nerve injury can threaten the postoperative quality of life of patients [(12, 13)].

Hypocalcemia following total thyroidectomy is a relatively frequent complication, which is sometimes difficult to correct [(14)], with an overall prevalence of 7–51% [(15, 16)]. The prevalence of hypocalcaemia 6 months after surgery is 3.6% and the prevalence of permanent hypocalcaemia is 1.5–4% [(17, 18)].

Recent studies have identified various risk factors for postoperative hypocalcaemia, including perioperative parathyroid hormone levels, incidental parathyroidectomy during thyroid resection, postoperative vitamin D, magnesium levels [(19-21)], female sex, reoperation [(22)], as well as the patient, and the disease [(23)]. Actually the underling parathyroid condition is usually a transitory hypoparathyroidism but permanent damage is registered in less than 3% of subjects [(8-10)]. The initial thyroid condition seems less important in relationship to the risk of developing hypocalcemia: malign conditions display a higher risk while Basedow-Graves's disease is potentially more frequently involved than multinodular goitre regarding benign diseases [(9, 10)]. However the surgical skills and the surgeon's approach is an important contributor to post-operative hypocalcemia [(24)].

Hypocalcaemia can be asymptomatic; however, clinical manifestations such as paraesthesia and muscle spasms can be distressing for the patient, while persistent untreated hypocalcaemia can be life threatening [(25)]. Post-thyroidectomy hypocalcaemia has potential wide-ranging implications for patient experience and healthcare costs [(18)], as well as is important in deciding the patient's discharge after thyroidectomy and also in influencing the others hospitalizations for low calcium levels associated with severe symptoms [(26)]. However, what matters most to the patients is not only quality of life, but also prolonged hospital stays and an unfavourable prognosis [(27)].

To the best of our knowledge and on reviewing the current medical literature, there are no studies conducted in Yemen, about the associated factors of post-thyroidectomy hypocalcaemia. Accordingly, we aimed to estimate incidence of hypocalcemia following thyroidectomy and determine its associated factors at Al Thawra Modern General Hospital, Sana'a city, Yemen.

Patients and Methods

From January 2021 to march 2022, single center cross-sectional study was conducted at Al Thawra Modern General Hospital, Sana'a city, Yemen. In Al Thawra Modern General Hospital all operations were performed by high-volume thyroid surgeons. We included all patients who underwent total or completion thyroidectomy with normal range perioperative calcium level, including those who underwent concomitant neck dissection. All patients who underwent lobectomy, resection lobe of thyroid gland, and diagnosed pathology of parathyroid glands were excluded from the analysis.

Data Collection

Data were collected directly from patients during pre and postoperative periods using a pre-prepared questionnaire. The following data were collected:

- Demographics (age, gender)

- Preoperative clinical data including functional states of thyroid gland (euthyroid, hyperthyroid, hypothyroid), and preoperative Ca level in mg/dl.
- Type of thyroid surgery (completion, total, with or without neck dissection)
- Histological diagnosis (malignant, benign)
- The duration of hospital stay
- Symptoms of hypocalcaemia and their types and management (Ca and/or vitamin D supplementations).

Outcome measures

The primary outcome measures were the rate of biochemical hypocalcaemia (less than 8.5 mg/dl) at 2 days and ≤ 3 days, and the rate of clinical hypocalcaemia at any point following thyroidectomy. Secondary outcome measures assessed the impact of other factors on the rate of biochemical hypocalcaemia. These included sex, age, histological diagnosis, type of surgery and oral calcium and/or Vitamin D supplementations.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY). Continuous variables were tested for normality by the Kolmogorov–Smirnov test. Normally distributed data were presented as means ± standard deviation (SD), while the median with data range (minimum to maximum) was used for non-normally distributed data. The rates and proportions of discrete variables were determined using the chi-squared test, whenever any of the expected values were less than 5, Fisher's exact test was used instead. Independent T test was used for normally distributed data, while Mann–Whitney U test was used for nonparametric groups. Wilcoxon Signed rank test was used to compare differences in Ca level between pre and post thyroidectomy. Analysis of receiver operator characteristics (ROC) curves and risk analysis models using logistic regression was used to make risk predictions of preoperative Ca parameter against post-operative hypocalcemia. The two-sided P-value of < 0.05 was considered statistically significant.

Results

A total of 50 patients enrolled in this study. All patients presented to surgery with normal calcium level with median 9.15 (8.50-10.20) mg/dl.

As shown in table 1, females outnumbered males (74% versus 26% respectively) with female to male ratio 3:1. The mean age of the patients at surgery was 38.46 ± 11.5 years with a range of 15-70 years. Regarding the functional state of thyroid gland, euthyroid patients outnumbered hypothyroid patients (94% versus 6%), while no hyperthyroid cases were seen. In 36 (72%) patients, the diagnosis was benign. In respect to type of surgery, the majority (76%) of the patients underwent a total thyroidectomy without neck dissection, whereas total thyroidectomy with neck dissection was performed in 8% patients. Completion thyroidectomy without neck dissection and with neck dissection were done in 12% and 4% patients, respectively.

Table 1: Patient' demographics and clinical characteristics

Variable	Value
Age in Years, Mean (SD)	38.46 (11.5)
Gender, n (%)	
Males	13 (26)
Females	37 (74)
Functional state of thyroid gland, n (%)	
Euthyroid	47 (94)
Hypothyroid	3 (6)
Hyperthyroid	0 (0)
Type of thyroid disease, n (%)	
Benign	36 (72)
Malignant	14 (28)
Type of surgery, n (%)	
Total thyroidectomy without neck dissection	38 (76)
Total thyroidectomy with neck dissection	4 (8)
Completion thyroidectomy without neck dissection	6 (12)
Completion thyroidectomy with neck dissection	2 (4)

Post-operative calcium measurements and the duration of hospital stay

Incidence of biochemical hypocalcaemia within 48 hours of surgery was 54% observed in 27 patients, with mean post-operative serum calcium level 8.5 ± 0.65 mg/dl.

Of the 27 patients with hypocalcemia, clinical symptoms were observed in 11 (22%) patients while laboratory hypocalcaemia was observed in 16 (32%) patients.

Carpopedal spasm and numbness of fingers were observed in 8 (16%) and 3 (6%) patients respectively.

Table 2 shows that the majority (46%) of patients didn't received treatments of prescribed oral or intravenous preparations of Ca and vitamin D. The patients who received both Ca and vitamin D treatments were 15 (30%) patients, while 13 (26%) patients received treatments of prescribed oral or intravenous preparations of Ca only. Majority (66%) of our patients were stay in the hospital for 2 days.

Table 2: Calcium measurement after surgery, presentation of hypocalcaemia, and the duration of hospital stay

Variable	Value
Post-operative Ca in mg/dl, Mean (SD)	8.5 (0.65)
Post-operative Ca level, n (%)	
Normocalcemia	23 (46)
Hypocalcaemia	27 (54)
Symptomatic hypocalcaemia	11 (22)
Asymptomatic hypocalcaemia	16 (32)
Presentation of hypocalcaemia, n (%)	
Perioral and finger numbness	8 (16)
Carpopedal spasm	3 (6)
Treatment with Ca and vitamin D after surgery, n (%)	
Non	23 (46)
Oral or intravenous preparations of Ca only	13 (26)
Oral or intravenous preparations of Ca and vitamin D	14 (28)
The duration of hospital stay, n (%)	
2 days	33 (66)
≤ 3 days	17 (34)

Differences between pre and post-operative Ca: As shown in table 3, the average of Ca levels in patients decreased significantly at 48 hours following the surgery (p-value =0.000).

Table 3: Differences between pre and post-operative calcium

Variable	Value	Z	P-value
Pre-operative Ca	Median (Range) = 9.15 (8.50-10.20)	- 6.16	**0.000***
Post-operative Ca	Mean (SD) = 8.5 (0.65)		

Differences between males and females

As shown in table 4, there were no statistically differences between males and females in age, postoperative Ca, type of thyroid disease and type of surgery (p-value > 0.05).

Table 4: Differences between males and females

Variable	Males (N= 13)	Females (N= 37)	P-value
Age in Years, Mean (SD)	34.23 (11.7)	39.9 (11.24)	0.125
Preoperative Ca in mg/dl, Median (Range)	9.50 (8.50-10.20)	9.0 (8.50-10.20)	0.348
Postoperative Ca in mg/dl, Mean (SD)	8.6 (7.60-9.50)	8.5 (7.20-9.80)	0.422
Type of thyroid disease, n (%)			
Benign	7 (14)	6 (12)	0.090
Malignant	29 (58)	8 (16)	

Differences between normocalcemic and hypocalcemic

Table 5 shows that comparison of the patients with hypocalcemia following surgery and the patients without hypocalcemia showed that the following variables were significantly related to the development of hypocalcemia: decreased pre-operative Ca, malignancy, and underwent total thyroidectomy. However, age and gender did not significantly relate to the development of hypocalcemia (p-value > 0.05)

Table 5: Impact of various characteristics on incidence of post-thyroidectomy hypocalcaemia within 48 h

Variable	Incidence of hypocalcaemia		P-value
	Yes (N= 27)	No (N= 23)	
Age in Years, Mean (SD)	40 (13.4)	36.9 (8.9)	0.400
Preoperative Ca in mg/dl, Median (Range)	9.0 (8.50-10.20)	9.50 (8.80-10.20)	**0.008***
Gender, n (%)			
Males	6 (12)	7 (14)	0.509
Females	21 (42)	16 (32)	
Type of thyroid disease, n (%)			
Benign	16 (32)	20 (40)	**0.030***
Malignant	11 (22)	3 (6)	
Type of surgery, n (%)			
Total thyroidectomy without neck dissection	23 (46%)	15 (30)	**0.045***
Total thyroidectomy with neck dissection	3 (6%)	1 (2)	
Completion thyroidectomy without neck dissection	1 (2%)	5 (10)	
Completion thyroidectomy with neck dissection	1 (2%)	1 (2%)	

As shown in both table 6, and figure 1, preoperative Ca level may be used as predictive model of post-operative hypocalcemia, because it has an area under the curve (AUC) > 0.7. Preoperative Ca level has a sensitivity value of 74.1% and specificity of 78.3% with cutoff value of 9.15 mg/dl.

Table 6: Area under the curve (AUC), cutoff value, confidence interval (CI), sensitivity, specificity of preoperative Ca level for post-operative hypocalcemia

Parameter	AUC	95% CI	Cutoff value	Sensitivity	Specificity	P-value
Preoperative Ca	0.748	(0.608- 0.888)	9.15	74.1%	78.3%	**0.003***

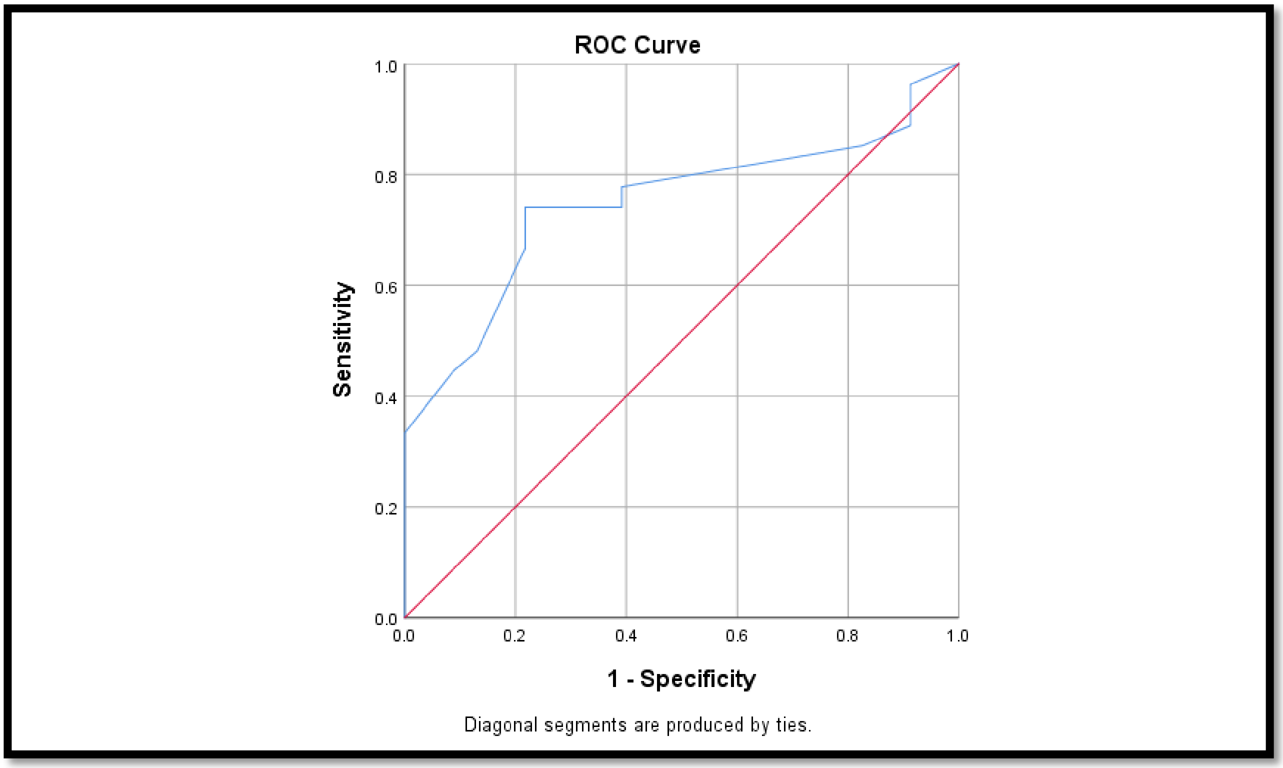

Figure 1: ROC analysis of preoperative Ca level as a predictive marker for post-operative hypocalcemia

Discussion

Our data showed high number of female patients presenting to surgery with thyroid disorders, which was similar to what was reported by ***Alqahtani*** in Saudi Arabia [28]. Our patients present 19 years younger than their western counterparts [14]. Result of a significant lower age in our patients needs more investigated by prospectively longitudinal studies, but bad nutrition, and iodine deficiency might be the culprits. Malignancy was observed in 28% of our patients. This result is lower than that estimated in Saudi Arabia (28% vs. 42.3%) [28].

Not surprisingly, the average Ca levels in our patients decreased significantly at 48 hours after the surgery, as this result was reported by several other studies [14, 28, 29].

According to the literature, post- operative hypocalcemia occurs in 50–68% of patients [30, 31]. In our study, post-operative hypocalcemia developed in 54% of the patients. Hypocalcemia is known as one of the most common and serious complications of total thyroidectomy. In the literature, the majority of patients exhibit asymptomatic hypocalcemia and need no treatment, or only oral administration of Ca and vitamin D preparations [32]. In our study, 32% of all the patients had asymptomatic hypocalcemia (59.2% of the patients with post-operative hypocalcemia). Indeed, in most cases of hypocalcemia, they resolve spontaneously. However, it may become permanent, requiring lifelong treatment and follow-up. Intravenous therapy may be required, especially in severe cases, and thus prolongs the duration of hospital stay and, substantially, increases the overall cost [33].

Overall, 22% of all the patients who participated in our study, or 40.7% of the patients with post-operative hypocalcemia) had one, or two clinical symptoms of hypocalcemia. In a multicenter study with 14,934 patients, ***Rosato et al.*** found that 10% of patients had symptomatic hypocalcemia [30]. However, that study included patients who had total thyroidectomy (64.3%) and smaller-scale surgeries on the thyroid (35.7%) [30].

Consistent with our study, several studies have found that temporary post-operative hypocalcemia develops more often in patients who have a markedly decreased level of Ca before surgery [14, 34-38]. However, a meta-analysis of five studies with 2493 patients did not reveal a statistically reliable association between pre-operative Ca and the frequency of temporary hypocalcemia [39-43]. A sharp decrease in Ca after total thyroidectomy is associated with temporary hypocalcemia [34, 44, 45].

In a multicenter study with 1157 patients, ***Hallgrimsson et al.*** found that the patients who experienced a 2–3% decrease in postoperative Ca in the 24 h following surgery, in comparison with the pre-operative level of Ca, had a 94% chance of developing temporary hypocalcemia [46]. Changes in the levels of Ca in the blood during the first 24 h following surgery allow prediction of temporary hypocalcemia with 19–91% sensitivity [47, 48].

Studies report that females have a higher incidence of hypocalcaemia after thyroidectomy [15, 29, 49-51], which was inconsistent with our finding, where there were no significant differences between males and females. According to ***Tongol and Mirasol,*** being female is a risk factor of hypocalcaemia, which might be due to the influence of sex steroids on parathyroid hormone secretion, genetic variations of cell signalling pathways or anatomical differences between males and females [50]. In addition, accidental parathyroid gland removal can easily occur during surgery owing to the high proportion of female parathyroid glands that are located in the thyroid parenchyma, contributing to a significantly higher incidence of postoperative hypocalcaemia in patients with thyroidectomy [52, 53].

In agreement with our study, three different studies conducted in Lithuania, Saudi Arabia and Iran revealed that the age was not significantly correlated with post-thyroidectomy hypocalcaemia as showcased in [14, 28, 29] respectively. However, other studies have correlated age with post-thyroidectomy hypocalcaemia [18, 37, 54]. The researchers argued that correlation between increasing age and incidence of post-thyroidectomy hypocalcaemia may be a consequence of the younger generation feeling more comfortable in voicing their symptoms and concerns in comparison to their seniors [18]. Theoretically, it would be expected that the physiological changes brought with increasing age would result in higher rates of post-thyroidectomy hypocalcaemia because of the reduced availability of calcium ions [54].

Pathological type is one of the most important risk factors because of the large scope of surgery and the need for neck lymph node removal, which increases the probability of hypocalcaemia and persistent hypoparathyroidism in patients with malignant tumors undergoing thyroid surgery alone [55]. Two previous studies demonstrated that the incidence of postoperative hypocalcaemia was higher in patients with malignant tumors compared with patients with benign tumors [7, 56], which was consistent with our finding. By contrast, two other studies revealed that the higher rates of post-thyroidectomy hypocalcaemia were significantly associated with benign thyroid disease [18, 57]. They postulated that their result might be a reflection of the intraoperative challenges frequently encountered in common benign thyroid diseases such as Graves and multinodular goitre where the vascularity and size of the gland can cause technical difficulties [18].

As was foreseeable, patients who underwent total thyroidectomy had greater incidence of hypocalcemia after the surgery, which was consistent with several previous studies [14, 28, 51].

Our study provides a different view of the role of preoperative Ca level as a predictive marker for post-operative hypocalcemia, not only defining the correlation of preoperative Ca level, but also providing a cutoff value of preoperative Ca level that might be a new valuable value in management of post-operative hypocalcemia.

Limitations

Our study was a single-center study and was limited by the small number of available cases and the cross-sectional nature of the study which cannot confirm causality. Furthermore, inadvertent parathyroid gland removal was not investigated in our study, so there is likely to be a bias that could affect Ca level following thyroidectomy.

Conclusion

Compared with other countries, incidence of hypocalcemia following thyroidectomy was high in our patients. Decreased pre-operative calcium, malignancy, and underwent total thyroidectomy were associated factors of hypocalcemia following thyroidectomy at Al Thawra Modern General Hospital, Sana’a city, Yemen. Pre-operative Ca show potential marker that can be used in predicting occurrence of hypocalcemia following thyroidectomy surgery. Our results shed further light on factors that influence post-thyroidectomy hypocalcaemia, although large scale multicenter and prospective study may be of greater help. We are planning to continue to extend the study prospectively to achieve this endeavor.

Ethical aspect

Permission from the administration of Al Thawra Modern General Hospital was obtained for this study. All patients signed a consent form before surgery. In addition, we carried out this study according to the Declaration of Helsinki.

Acknowledgment

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Disclosure

The authors declare there are no conflicts of interest regarding all elements in this study.

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