Гипокальциемия после проведения тиреоидэктомии и факторы риска ее развития

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Актуальность. Тотальная тиреоидэктомия – одно из самых распространенных хирургических вмешательств в эндокринологии, которое в послеоперационном периоде часто сопровождается развитием гипокальциемии и гиперпаратиреоза. Настоящее исследование было предпринято с целью определения частоты развития гипокальциемии после тиреоидэктомии и факторов риска развития этого осложнения.

Методы. Эта серия случаев включала 166 взрослых пациентов, которым была проведена тотальная, частичная или гемитиреоидэктомия по поводу токсического, простого или злокачественного зоба. Всем пациентам выполняли ультразвуковое исследование (УЗИ) шеи и сканирование щитовидной железы при необходимости, а кроме того, определяли уровень гормонов функции щитовидной железы (ТТГ, свободный Т₃, свободный Т₄). Послеоперационная оценка (день 1-й и 7-й) включала определение гипокальциемии по клиническим признакам, а также мониторинг уровней кальция, фосфора и паратгормона.

Результаты. В исследовании участвовали 122 (73,5%) женщины и 44 (26,5%) мужчины, медиана возраста составила 39 (18–67) лет. В период наблюдения у 48 (28,9%) пациентов развилась гипокальциемия; у 4 (2,4%) из них она была стойкой. Развитие гипокальциемии не зависело от возраста, пола пациента или опыта хирурга. Основными факторами развития этого осложнения являлись вид хирургического вмешательства и диагноз. 3 из 4 пациентов со стойкой гипокальциемией (75%) были старше 40 лет.

Закключение. Гипокальциемия осложнила течение послеоперационного периода у 29% пациентов, перенесших тиреоидэктомию, но только у 2,4% пациентов развилась стойкая гипокальциемия. Основными факторами риска развития этого осложнения являлись вид хирургического вмешательства и диагноз, развитие гипокальциемии не зависело от возраста, пола пациента или опыта хирурга.

Финансирование. Исследование не имело спонсорской поддержки.

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Post-thyroidectomy hypocalcemia and its associated risk factors

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Aim. Total thyroidectomy is one of the most common endocrine surgeries. Hypocalcemia and hyperparathyroidism are frequent complications of thyroidectomy. This study aimed to determine the frequency of post-thyroidectomy hypocalcemia and its risk factors.

Methods. This case series included 166 adult patients who had total, subtotal, or hemithyroidectomy due to toxic, simple, or malignant goiter. All patients were subjected to thyroid function tests (TSH, free T_3 , and free T_4) in addition to neck ultrasound and thyroid scan if needed. The postoperative assessment included the detection of hypocalcemia by clinical signs and monitoring of serum calcium, phosphorus, and parathormone (PTH) on postoperative days 1 and 7.

Results. The study included 122 females (73.5%) and 44 males (26.5%), with a median age of 39 (18–67 years). During the follow-up period, 48 patients (28.9%) developed hypocalcemia; 4 of them (2.4%) had permanent hypocalcemia. The development of hypocalcemia was not affected by age, sex, or surgeon experience. The type of surgical procedure and final diagnosis were the main factors affecting the development of hypocalcemia. Three of the four patients with permanent hypocalcemia (75%) were 40 years or older.

Conclusion. Post-thyroidectomy hypocalcemia complicates about 29% of the patients, but it was permanent in only 2.4% of cases. The type of surgical procedure and final diagnosis were the main factors affecting the development of hypocalcemia, while it was not affected by age, sex, or surgeon experience.

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Thyroid disorders and their surgical management are common in surgical practice worldwide. Thyroidectomy is frequently recommended for patients with thyroid nodules, especially when thyroid cancer is suspected [1, 2]. Among various types of thyroidectomy, total thyroidectomy is one of the most common endocrine surgeries [3].

Postoperative complications after thyroid surgery are numerous and reported more frequently with learning surgeons [4, 5]. Hypocalcemia and hypoparathyroidism are frequent complications of thyroidectomy. Transient hypocalcemia is reported to complicate 9.2 to 25% of cases, while the incidence of permanent hypocalcemia ranges from 0.5 to 2% [6].

Injury or devascularization of the parathyroid glands is mostly recognized as the most common cause for post-thyroidectomy hypocalcemia [7]. Postoperative hypoparathyroidism is a clinical challenge for thyroid surgeons due to the relatively high frequency and limited preoperative predictors [8]. Many patient-related, disease-related, biochemical, and surgical factors may influence the risk of post-thyroidectomy hypocalcemia [9].

This study aimed to determine the overall frequency of post-thyroidectomy hypocalcemia, whether symptomatic or asymptomatic, transient or permanent, and risk factors associated with the development of hypocalcemia.

Patients and methods

this case series was conducted in the Department of General Surgery at Cairo University hospital and Assiut police hospital from November 2016 to May 2018. The study included 166 patients who had total, subtotal, or hemithyroidectomy due to toxic, simple, or malignant goiter. All participants of the study provided informed consent, and the study was approved by the Ethical Committee of the Faculty of Medicine, Cairo University.

Included are euthyroid patients aged >18 years. Exclusion criteria were current or previous parathyroid diseases, or laryngeal or vocal cord lesions, abnormal serum creatinine, renal disease, osteopenia, osteoporosis, metabolic bone diseases, other malignancies, previous neck surgery, or drugs like calcium, vitamin D, menopausal hormone replacement therapy, thiazide diuretics, and antiepileptic agents.

All patients were subjected to preoperative full clinical assessment and laboratory investigations, including serum ionized calcium and thyroid function tests (TSH, free T_3 , and free T_4) in addition to neck ultrasound and thyroid scan if needed. The intraoperative policy was to identify and preserve all parathyroid glands after the identification of their vascular pedicles. If one of the glands was accidentally compromised, it was fragmented and auto-transplanted on the contralateral sternomastoid muscle immediately.

Postoperative assessment

The assessment included the occurrence of post-thyroidectomy hypocalcemia by detecting any clinical signs for hypocalcemia as paresthesia, Chvostek's sign, and Trousseau's sign and by close monitoring of serum calcium, phosphorus, and parathormone (PTH) on postoperative days 1 and 7.

The normal level of serum calcium was defined to be between 6.8 and 10.4 mg/dL. Critical value of serum calcium is <6.0 mg/dL, and the critical value of serum ionized calcium is <3.2 mg/dL. Patients with low serum calcium (<6.8 mg/dL) were treated with oral or parenteral calcium according to the level of hypocalcemia and severity of symptoms.

Management protocol

Serum ionized calcium was checked 8 hours and 24 hours postoperatively. If two consecutive calcium values were within the normal range or increasing, the check was discontinued, and the patient was discharged and re-evaluated one week later. If calcium level was decreasing, oral calcium was started with a dose of 3 gm elemental/day. If calcium level was stabilized with this dose, gradual tapering of oral calcium was started. The magnesium level was checked and corrected if needed. The calcium level was re-checked one week later.

If serum calcium continued to decrease, or the patient became symptomatic, 0.5 µg of 1,25-dihydroxy vitamin D was added per day. If serum calcium level continued to decrease or the patient developed symptoms, the dose was increased to 0.5 µg twice daily. If the patient required vitamin D, the patient was sent home on the dose of oral calcium and vitamin D that stabilized the ionized calcium. The calcium level was checked one week after discharge. If the level of calcium was within the normal range, gradual Tapering of oral calcium and vitamin D was started.

For patients severely symptomatic with ionized calcium <3.2, IV calcium was administered. One amp of calcium gluconate (10 ml calcium gluconate 10% containing 1 gm calcium gluconate) in 500 ml sodium chloride was given IV over 5 hours. The calcium level was re-checked after administration. If the infusion did not stop the symptoms, this was repeated. The magnesium level was checked and corrected if needed. Oral 1,25-dihydroxy vitamin D and oral elemental calcium were maximized in consultation with the Endocrinology department. The patient was checked one week after discharge. If serum ionized calcium was within the normal range, oral calcium and vitamin D were tapered gradually.

All patients with hypocalcemia were followed up till normalization of serum calcium. If oral calcium or vitamin D were still required after six months, the patient was defined to have permanent hypocalcemia

and hypoparathyroidism. Patients with serum calcium levels of more than 9 mg/dL on the first postoperative day and did not have any other complications were discharged on the same day and re-evaluated after seven days.

Statistical analysis

Statistical analysis was done using IBM® SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as median and range as appropriate. Qualitative data were expressed as frequency and percentage. The Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. A two-tailed $p < 0.05$ was considered statistically significant.

Results

The study included 166 patients; 122 (73.5%) females and 44 (26.5%) males, with a median age of 39 years (range 18–67 years). Table 1 shows the disease characteristics and types of management procedures.

During the follow-up period, 48 (28.9%) patients developed hypocalcemia. Of these 48 patients, 44 recovered from hypocalcemia within 6 months, i.e., transient hypocalcemia (26.5%), and four patients need oral calcium or vitamin D after six months post-operatively, i.e., permanent hypocalcemia (2.4%). 37 (77.1%) patients with hypocalcemia developed manifestations of hypocalcemia within the first 48 hours. 5 (10.4%) patients did not develop signs or symptoms of hypocalcemia.

Table 1. Clinical and histological characteristics of thyroid disease and its management procedures

	Number	Percentage
<i>Preoperative clinical diagnosis</i>		
Simple goiter	114	68.7
Toxic goiter	35	21.1
Malignant goiter	17	10.2
<i>Type of procedure</i>		
Total thyroidectomy	86	51.8
Hemi-thyroidectomy	32	19.3
Subtotal thyroidectomy	30	18.1
Completion thyroidectomy	7	4.2
Total thyroidectomy with neck dissection	11	6.6
<i>Final histopathological diagnosis</i>		
Thyroid malignancy	11	6.6
Thyroid adenoma	32	19.3
Toxic nodular goiter	21	12.7
Grave's disease	14	8.4
Nodular (colloid goiter)	60	36.1
Hashimoto's thyroiditis	24	14.5
Lymphocytic thyroiditis	4	2.4

Table 2. Relation between the development of hypocalcemia and demographic and clinical characteristics of the studied group

	n	No hypocalcemia n=118	Hypocalcemia n=48	p-value
<i>Age</i>				
<40 years	105	77 (73.3%)	28 (26.7%)	0.402
≥40 years	61	41 (67.2%)	20 (32.8%)	
<i>Sex</i>				
Male	44	31 (70.5%)	13 (29.5%)	0.914
Female	122	87 (71.3%)	35 (28.7%)	
<i>Clinical diagnosis</i>				
Simple goiter	114	95 (83.3%)	19 (16.7%)	<0.001
Toxic goiter	35	19 (54.3%)	16 (45.7%)	
Malignant goiter	17	4 (23.5%)	13 (76.5%)	
<i>Type of Surgery</i>				
Total thyroidectomy	86	63 (73.3%)	23 (26.7%)	
Hemi thyroidectomy	32	30 (93.8%)	2 (6.3%)	
Subtotal thyroidectomy	30	22 (73.3%)	8 (26.7%)	<0.001
Completion thyroidectomy	7	1 (14.3%)	6 (85.7%)	
Total thyroidectomy with neck dissection	11	2 (18.2%)	9 (81.8%)	
<i>Surgeon</i>				
Consultant	84	58 (69.0%)	26 (31.0%)	0.558
Non consultant	82	60 (73.2%)	22 (26.8%)	
<i>Histological Diagnosis</i>				
Thyroid malignancy	11	0 (0.0%)	11 (100.0%)	<0.001
Thyroid adenoma	32	29 (90.6%)	3 (9.4%)	
Toxic nodular goiter	21	13 (61.9%)	8 (38.1%)	
Grave's disease	14	5 (35.7%)	9 (64.3%)	
Nodular (colloid goiter)	60	48 (80.0%)	12 (20.0%)	
Hashimoto's thyroiditis	24	19 (79.2%)	5 (20.8%)	
Lymphocytic thyroiditis	4	4 (100.0%)	0 (0.0%)	

Table 2 shows a comparison between patients developed hypocalcemia and those who did not, concerning demographic and clinical characteristics.

Development of hypocalcemia was not affected by age, sex, or surgeon experience. Meanwhile, preoperative clinical suspicion of malignancy was associated with a significantly higher proportion of postoperative hypocalcemia compared to toxic or simple goiter. The type of surgical procedure and final diagnosis were the main factors affecting the development of hypocalcemia. All of the 11 patients with thyroid malignancy eventually developed hypocalcemia. Among 14 patients with Grave's disease, 9 (64.3%) developed postoperative hypocalcemia. Patients with lymphocytic thyroiditis and those with thyroid adenoma were the least affected by hypocalcemia. Completion thyroidectomy and total thyroidectomy with neck dissection were associated with a significantly higher proportion of patients with postoperative hypocalcemia. Hemi-thyroidectomy was the safest surgery; only 6.3% of the patients developed hypocalcemia.

Characteristics of the four patients who developed permanent hypocalcemia

3 of the 4 patients (75%) were 40 years or older. They were 2 males and 2 females. 2 patients had

completion thyroidectomy, and 2 had total thyroidectomy; one of them had neck dissection in addition. 2 patients had malignant thyroid disease, one had Grave's disease, and the last one had Hashimoto's thyroiditis.

Discussion

Hypocalcemia is the most frequent complication after thyroid surgery [9]. However, different studies reported a wide variation in the incidence of post-thyroidectomy hypocalcemia. In the current study, 26.5% developed transient hypocalcemia, while 2.4% developed permanent hypocalcemia. Ozogul et al. reported an incidence of 24% in 196 patients (24%) with total thyroidectomy [10]. Edafe et al. reported an incidence of 29.0% [11]. Nevertheless, these authors found that the incidence of post-thyroidectomy hypocalcemia was underestimated by 6% when only measurements during postoperative day one were considered. Another study reported a much lower incidence of hypocalcemia in 5846 patients subjected to bilateral thyroid surgery for benign and malignant thyroid disease. The authors reported an overall incidence of transient and permanent hypoparathyroidism was 7.3 and 1.5%, respectively [12].

A retrospective study evaluated the incidence of complications in 1020 patients submitted to thyroidectomy in a cancer hospital. The authors reported that transient hypocalcemia was the main postoperative complication affecting 13.1% of patients. Permanent hypocalcemia affected only 1.4% of the patients [13]. Generally, the frequency of transient hypocalcemia after thyroid surgery is between 6.9 and 49% [9].

The mechanism of post-thyroidectomy hypocalcemia is not precisely revealed. Probably, it is accepted to be multifactorial, including patient-related, disease-related, and surgical technique-related factors. In the current study, age and sex were not associated with the development of hypocalcemia. These results are in agreement with previous studies [9, 14, 15]. However, the literature is separated as to whether age is a risk factor for hypocalcemia after thyroidectomy. Some studies found a significant association of hypocalcemia with advanced age [14–17]. Other studies reported an association with younger age [18–20]. Noureldine et al. found a positive association between young age and development of hypocalcemia on univariate analysis, but on multivariate analysis, age was no more an independent predictor of hypocalcemia [21]. A recent meta-analysis of 115 studies, including 2576 patients, found no significant difference in mean age between patients with hypocalcemia and those without [7]. Similarly, the literature contains conflicting reports regarding the association with sex. Some studies did not find an impact of sex on postoperative hypocalcemia [22, 23]. Conversely, several studies found that females were significantly more prone to hypocalcemia compared with males [7, 21, 24–26].

The development of hypocalcemia in the current study was not affected by surgeon experience. However, this was controversial to most studies that emphasize the significance of expertise and experience. It is believed that professional expertise significantly affects the success of surgery. Then, the surgical skill develops from appropriate training and continuous practice within a specialty. Many studies confirmed the relationship between surgeon volume and outcomes in thyroid surgeries [27–30]. It was reported that surgeons who have performed 100 or more thyroidectomies showed the lowest rate of complications, but the hospital volume is not statistically associated with the outcomes [29, 30]. However, some studies demonstrated that the operations are frequently accomplished by surgeons whose experience is not mainly focused on endocrine surgery [31, 32].

A large retrospective multicenter study was done to analyze the impact on patient outcomes of total thyroidectomy performed by resident surgeons un-

der close supervision and the assistance of attending surgeons. The study involved 8908 patients. The overall postoperative morbidity was 22.3%. There was no difference in recurrent laryngeal nerve palsy and hypoparathyroidism between procedures performed by residents or attending surgeons. Therefore, the authors concluded that total thyroidectomy could be safely performed by appropriately supervised residents [33].

The nature of thyroid disease has been shown as a predictive factor of postoperative hypocalcemia. In the current study, the clinical diagnosis of malignancy was a significant predictor of postoperative hypocalcemia. After surgery and histological examination, all patients with thyroid malignancies developed hypocalcemia. Also, 64.3% of patients with Grave's disease developed hypocalcemia.

Literature reported that several thyroid conditions carry a higher risk of developing transient and permanent hypoparathyroidism postoperatively. These diseases include Graves' disease, recurrent goiter, and thyroid carcinoma [12].

In agreement with the current study, previous diseases reported and an increased risk of hypocalcemia one day after total thyroidectomy for Graves' disease [34, 35]. It was recommended that patients with Graves' disease patients should be informed of the increased risk of hypocalcemia associated with total thyroidectomy. Another study found that transient but not permanent hypocalcemia was more common in patients with Graves' disease than in patients with nodular goiter [36]. A large retrospective analysis included 215,068 patients who underwent total thyroidectomy; 5.2% of them had Graves' disease, and 43.6% had thyroid malignancy. This study concluded that Graves' disease patients are at increased risk of many postoperative complications, including hypocalcemia [37].

A systematic review of 35 studies found that malignancy, central neck dissection, total thyroidectomy, and reoperation were significant risk factors of Incidental parathyroidectomy during thyroid surgery [38]. However, many studies do not found thyroid malignancy to be an independent risk factor for developing hypocalcemia [39–41]. In fact, it is the extent of surgery, rather than the thyroid disease, that increased the risk of hypocalcemia. Neck dissection appears to be the most frequent cause of hypocalcemia following thyroid surgery [42, 43]. In the current study, total thyroidectomy with neck dissection was associated with a significantly higher proportion (82%) of patients with postoperative hypocalcemia, while only 6.3% of the patients subjected to hemithyroidectomy developed hypocalcemia.

A large study of 119,567 patients who underwent thyroidectomy found that total thyroidectomy

was associated with a significantly higher incidence (9.0%) of hypocalcemia compared to unilateral thyroid lobectomy (1.9%) [44]. In agreement with the current study, these authors reported that thyroidectomy with bilateral neck dissection was the most influential independent risk factor of postoperative hypocalcemia (odds ratio, 9.42) [44]. Total thyroidectomy was emphasized as an independent predictor of postoperative hypocalcemia in many studies [45]. During total thyroidectomies, the risk of injury to the parathyroid glands is clearly higher when dissecting both lobes. Damaging the parathyroid glands can be avoided by careful detection of the inferior thyroid artery branches entering the thyroid capsule with the identification of the end-arteries supplying the four glands [43]. It was found that the higher number of parathyroid glands identified during the surgery, the lower risk of hypocalcemia. Identifying

more than two glands is associated with a four-fold increase in the risk of permanent but not transient hypocalcemia [12].

Conclusion

This study demonstrated that 28.9% developed post-thyroidectomy hypocalcemia mostly of transient nature. Only 2.4% of the patients developed permanent hypocalcemia. The type of surgical procedure and final diagnosis were the main factors affecting the development of hypocalcemia. Total thyroidectomy with neck dissection was associated with a significantly higher proportion (82%) of patients with postoperative hypocalcemia. Thyroid malignancy and Grave's disease were significant predictors of postoperative hypocalcemia. The development of hypocalcemia was not affected by age, sex, or surgeon experience.

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