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Calcium and vitamin D supplementation after total thyroidectomy in thyrotoxic patients

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Objective
Evaluation of the efficacy of routine postoperative oral calcium and vitamin D supplementation in preventing symptomatic hypocalcemia after total thyroidectomy in cases of hyperthyroidism.

Background
Thyroidectomy is the most common surgical procedure performed in the neck by surgeons. Hypocalcemia is the most frequent complication after total thyroidectomy, and it is the main cause of prolonged hospital stay.

Patients and methods
Thirty patients who underwent total thyroidectomy for toxic goiters were randomly assigned to routinely receive or not receive oral calcium (3 g/day) and vitamin D (1 μg/day) for 4 weeks. Hypocalcemic symptoms and signs, and total serum calcium and parathormone levels were monitored and compared between the two groups.

Results
The incidence of symptomatic and laboratory hypocalcemia was lower in the treatment group receiving the supplement than in the control group not receiving the supplement: one of 15 patients (6.7%) versus five of 15 (33.3%). The hypocalcemic symptoms were minimal in the treatment group, but more severe in the control group not receiving the supplement. Serum calcium levels decreased in both groups after surgery, but were less in the treatment group.

Conclusion
Routine administration of oral calcium and vitamin D supplementation may be effective in reducing the incidence and severity of hypocalcemia after total thyroidectomy.

Keywords:
calcium, hypocalcaemia, thyroid, total thyroidectomy, vitamin D

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Introduction

Thyroidectomy is the most common surgical procedure performed in the neck by surgeons. Hypocalcemia is the most frequent complication after total thyroidectomy, and it is the main cause of prolonged hospital stay [1]. A common complication of thyroid surgery is transient postoperative (PO) hypocalcemia, which occurs in up to 30–35% of patients. The rate of permanent hypocalcemia is thought to be less than 2% in the hands of experienced surgeons. The actual number of events has been estimated to be much higher in the population at large. The actual prevalence of important hypocalcemia is unknown, since there is no accepted level of calcium that defines hypocalcemia [2]. In most patients, hypocalcaemia after thyroid surgery is self-limiting, but in some it may be potentially dangerous [3]. There are various causes for PO hypocalcemia, which have been suggested to include hemodilution or increased urinary calcium excretion secondary to surgical stress, calcitonin release secondary to thyroid gland manipulation, hungry bone syndrome (reversal of toxic thyroid osteodystrophy), and interference with the function of the parathyroid glands either through direct injury, removal, or devascularization [4]. The prevention of significant symptomatic hypocalcemia will allow early discharge of post-thyroidectomy patients from the hospital [5]. A phenomenon in which the serum intact parathormone hormone (iPTH) levels rise to values above the normal range during the PO period has been reported in Graves' disease patients [6]. A combined measurement of iPTH and serum calcium levels is recommended to identify patients at risk for developing hypocalcemia. Severe, progressive hypocalcemia is unlikely to occur with normal iPTH level, and thus iPTH can be used cautiously to facilitate early discharge for many patients [7]. Routine oral calcium and vitamin D supplements have been proposed to prevent the development of symptomatic hypocalcemia and to increase the likelihood of early hospital discharge after bilateral surgical treatment of the thyroid gland or exploration of the parathyroid glands [8,9].

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This study aims to evaluate the role of oral calcium and vitamin D supplementation in the prevention of hypocalcaemia after total thyroidectomy for patients with toxic goiter.

Patients and methods

The study sample was an exhaustive sample that included all patients being hospitalized in the Surgical Department of Menoufia Main University Hospital after being assured of toxic goiter, fulfilling the study criteria in the period from April 2016 to October 2017.

A prospective randomized controlled study of 30 patients undergoing total thyroidectomy was performed. All patients underwent total thyroidectomy for toxic goiter, either primary or secondary, using the same surgical technique by the same surgeons unaware of the study group allocation. Informed consent was obtained from all patients before inclusion in the study and it was approved by the Ethics Committee at El-Menoufia University.

All patients included in this study were diagnosed of having toxic goiter, either primary (Graves disease) or secondary, and they received antithyroid drugs (carbimazole) preoperatively to become controlled in the euthyroid state. In addition to this, all patients had normal serum calcium and PTH level preoperatively.

Patients' demographic and clinical data including age and sex are recorded. A total of 23 patients are presented with goiter and thyrotoxic manifestations, but the other seven patients are presented only with goiter. Nine patients have chronic diseases as diabetes mellitus, hypertension, and bronchial asthma. Positive family history of thyroid disease was found in six patients, history of previous surgeries such as tonsillectomy, appendecectomy, hernioplasty, and cholecystectomy were irrelevant.

During surgery, meticulous dissection and preservation of parathyroid glands were done. We exclude from the study patients with chronic renal failure, with parathyroid gland diseases, using calcium supplementation for any chronic disease before the operation, and patients with thyroid enlargement other than toxic goiter.

Patients were hospitalized for a minimum of 2 days after surgery to observe the signs and symptoms of hypocalcemia and to measure serum calcium and PTH level 48 h after surgery, then the patients were discharged and follow-up was conducted 1 week, 1 month, and 3 months thereafter.

After total thyroidectomy, patients were randomized and divided into two groups:

(1) Group A: a total of 15 patients received routine oral calcium (3 g/day) and vitamin D supplementations (alphacalcidol, 1 μg/day) starting from the first PO day and continued for 4 weeks
(2) Group B members: a total of 15 patients served as the control group. These patients did not receive any supplementation of calcium or vitamin D.

Blood samples were taken PO from every patient for total serum calcium and PTH levels 48 h, 1 month, and 3 months, respectively. Serum calcium level was estimated by CPC reagent method manufactured in Biolabo S.A.S. (Les Hautes Rives, Maizes, France). However, PTH level was estimated by using Immulite 2000 Intact PTH reagent (Siemens healthcare Diagnostics Products Ltd. Glyn Rhonwy, Llanberis, Gwynedd, LL55 4EL UK).

The presence and the type of symptoms of hypocalcemia was registered together with the evaluation of Chovostek's sign that was done for every patient twice daily and Trousseau sign that was done daily from the day of the operation (PO_0) till the second PO day (PO_2).

Hypocalcemic patients received the supplementation therapy even if asymptomatic; supplementation therapy included oral calcium and/or vitamin D. Intravenous calcium gluconate was administered if symptoms persist, despite of oral therapy. Supplementation therapy was tapered subsequently on the basis of serum calcium measurements that were measured daily till normalization.

Statistical analysis was done using the SPSS software package version 17.0 (SPSS Inc., Chicago, Illinois, USA). Statistical analysis was done to obtain the mean, the SD, the SE of each mean, and for comparison between the different groups involved in this study one-way test was used for comparison between independent samples.

Arithmetic mean ($\bar{X}$) was calculated as follows:

$$\bar{X} = \frac{\sum X}{n}$$

where $\bar{X}$, the arithmetic mean; ΣX, the sum of observations; n, the number of observations.

SD was calculated as follows:

$$\mathrm{SD} = \sqrt{\frac{\sum \left(X - \bar{X}\right)}{n-1}}$$

where n, the number of cases; X, individual values; $\bar{X}$, the arithmetic mean of the group.

Student '*t*' test was performed to test the significance of difference between the two groups. It was calculated according to the formula:

$$T_2 = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{S^2P}{n_1} + \frac{S^2P}{n_2}}}$$

Pooled variance (SP^2):

$$\left(SP^2\right) = \frac{{S_1}^2\left(n_1 - 1\right) + {S_2}^2\left(n_2 - 1\right)}{n_1 + n_2 - 2}$$

where n_1, number of observations of the first group; n_2, number of observations of the second group; X_1, mean of first group; X_2, mean of second group; ${S_1}^2$, SD of the first group; ${S_2}^2$, SD of the second group.

The probability '*P*' value was obtained from the special table for probability (*P*) value, where degree of freedom ($n_1 + n_{2-2}$) was used.

where n_1, number of observations of the first group (the control group); n_2, number of observations of the second group (the patient group).

A '*P*' value of less than 0.05 was considered statistically significant.

Results

A total of 30 patients underwent total thyroidectomy, they were divided PO into two groups A and B. Group A (15 patients) was given oral supplementations [for a month starting from (PO_1)] of 3 g/day of calcium and 1 μg/day of vitamin D1. Group B (15 patients) was not given any supplementation.

By PO histopathological examination of the specimens, we found parathyroid gland in two patients who were excluded from the study.

In each group, there were three male and 12 female patients. In group A, the age ranged from 18 to 57 years, with mean of 39.3 and SD of 10.69, whereas in group B, the age ranged from 32 to 56 years, with mean of 9.7 and SD of 7.03. Clinically, patients were divided into five patients that had primary toxic goiter (two in group A and three in group B) and 25 patients that had secondary toxic goiter.

Six (20%) out of 30 patients experienced hypocalcemia, two of them experienced symptomatic hypocalcemia, and the other four patients experienced chemical asymptomatic hypocalcemia; in all hypocalcemic patients (six patients), only one is from the supplement group (group A) and five are from the nonsupplement group (group B), significant value indicates the reliability of oral calcium and vitamin D to prevent PO hypocalcemia.

In group A (supplement), the preoperative calcium level was normal, ranging from 9.11 to 10.4. After 48 h, we found that only one patient had laboratory hypocalcemia without the manifest hypocalceaemia, with serum calcium level of 7.3. The serum calcium level in this group after 48 h was ranging from 7.3 to 9.9 and, in the same group, after 1 month, there was no manifestation of hypocalcaemia, with serum calcium level ranging from 9.2 to10.2. After 3 months, there was no manifestation of hypocalcaemia, with serum calcium level ranging from 9.6 to10.8.

In group B (nonsupplement), the preoperative calcium level was normal and after 48 h, five patients developed laboratory hypocalcaemia and four of them with manifest hypocalcaemia that needed urgent treatment with intravenous Ca gluconate infusion, and after 1 month, from those five patients, two patients continued to have laboratory hypocalcemia, with no patient having manifest hypocalcaemia and *P* value less than 0.001. Hence, there was significant decrease in the serum calcium level in the nonsupplement group. After 3 months, there were no cases with manifest or even laboratory hypocalcemia.

In comparison of group A and group B as regard to calcium levels after 48 h, the *P* value of 0.007* with significant difference between group A and B after 1 month in comparison between the same two groups we found that the *P* value of 0.001* with significance (Table 1 and Fig. 1).

Although, the PTH blood levels were within normal range in all cases PO, those patients who showed a

Table 1 Comparison between the studied groups according to S-Ca level

S-Ca level	Group A (*n*=15)	Group B (*n*=15)	*t*	*P*
Preoperative				
Minimum-maximum	9.11-10.40	9.11-10.36	0.536	0.603
Mean±SD	9.72±0.36	9.65±0.40		
Median	9.76	9.56		
48 h				
Minimum-maximum	7.30-9.90	6.50-9.30	2.973*	0.007*
Mean±SD	9.41±0.62	8.45±1.07		
Median	9.50	9.10		
1 month				
Minimum-maximum	9.20-10.20	8.70-6.80	4.462*	<0.001*
Mean±SD	9.79±0.26	9.31±0.33		
Median	9.80	9.40		
3 months				
Minimum-maximum	9.60-10.80	9.40-10.60	2.544*	0.017*
Mean±SD	10.19±0.33	9.87±0.37		
Median	10.20	9.80		

t, *P*: *t* and *P* values for Student's *t*-test for comparing the two groups. *$P \leq 0.05$, statistically significant.

decrease in PTH blood levels greater than 50% were the same six patients who suffered from hypocalcaemia, whereas in the other 24 normocalcemic patients, this decrease was less than or equal to 50% of the preoperative value (Table 2 and Fig. 2).

No significant differences were shown in iPTH levels between group A and B after 48 h, 1 month, and 3 months.

During the follow-up, three patients from the group receiving calcium supplements complained of constipation, anorexia, and polyuria, which was considered to occur because of this supplement.

Discussion

Hypocalcemia is a well-known complication and occurs after thyroid surgery. Although in most cases it is only temporary, post-thyroidectomy, hypocalcemia can lead to an increased cost by prolonging the length of stay and increasing the need for expensive medications, frequent biochemical tests, and multiple outpatient visits [10]. Severe hypocalcemia remains the limiting factor for such a short in-hospital stay policy as tetany may affect a relevant number of patients after early discharge. Identification of preoperative and perioperative risk factors associated with high risk of PO tetany is an important step for patient selection. Intraoperative and PO monitoring of the iPTH has been embraced with enthusiasm by many surgeons because this helps to detect patients at highest risk of severe hypocalcemia [11]. Prevention of significant symptomatic hypocalcemia will allow early discharge of post-thyroidectomy patients from the hospital [12].

In a prospective controlled study done Salvatore *et al.*, they included 79 patients who underwent total thyroidectomy for different causes: multinodular goiter, toxic goiter, suspicious nodule, and thyroid cancer. Patients were randomly allotted to one of three groups: group A (20 patients with multinodular goiter, three patients with toxic goiter, three patients with suspicious nodules, and two patients with cancer) and they received no treatment, group B (17 patients with multinodular goiter, two patients with toxic goiter, five patients with suspicious nodules, and one patient with cancer) who received 3 g/day or oral calcium supplement, and group C (17 patients with multinodular goiter, three patients with toxic goiter, five patients with suspicious nodules, and one patient with cancer thyroid) who received oral calcium 3 g of oral calcium and 1 mg/day of oral vitamin D supplements. Treatment was started on PO day 1 in groups B and C [13].

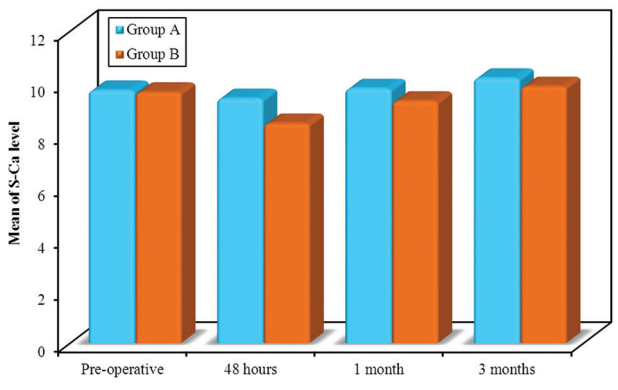
The results were that few patients in groups B and C experienced symptoms when compared with group A (P = 0.005). Patients in groups B and C had only minor symptoms, whereas two patients in

Table 2 Comparison between the studied groups according to S-parathormone hormone level

S-PTH level	Group A (n=15)	Group B (n=15)	t	P
Preoperative				
Minimum-maximum	34.89-68.46	35.03-67.70	0.927	0.362
Mean±SD	47.36±8.96	50.77±11.08		
Median	47.12	50.34		
48 h				
Minimum-maximum	31.25-57.02	28.42-57.90	0.114	0.910
Mean±SD	43.20±7.41	43.57±10.0		
Median	42.69	46.13		
1 month				
Minimum-maximum	28.92-37.90	26.83-36.40	1.076	0.291
Mean±SD	34.08±2.74	32.98±2.84		
Median	34.71	33.52		
3 months				
Minimum-maximum	31.41-59.12	27.15-54.68	0.356	0.724
Mean±SD	45.54±7.04	44.50±8.89		
Median	45.18	48.13		

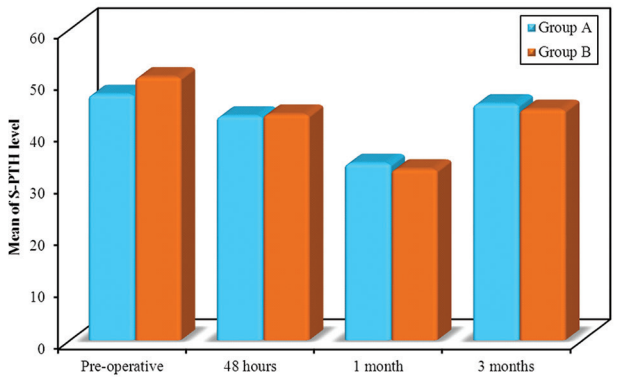
PTH, parathormone hormone; t, P: t and P values for Student's t-test for comparing the two groups.

Figure 1



Comparison between the studied groups according to S-Ca level.

Figure 2



Comparison between the studied groups according to S-parathormone hormone level.

group A experienced major symptoms and six patients required intravenous calcium (P < 0.01). The rate of hypocalcemia was slightly lower in group C (P = not significant) [13].

In our present study, we included only the thyrotoxic patients, five of them had Graves' disease and 25 had secondary toxic goiter, with exclusion of other causes of thyroid enlargement as an indication for total thyroidectomy. All patients underwent total thyroidectomy with preservation of four parathyroid glands. Patients were divided into two groups. Group A consists of 15 patients who received routine oral calcium (3 g/day) and oral vitamin D supplements (alphacalcidol, 1 μg/day) starting from the first PO day and continued for 4 weeks. Group B: consists of 15 patients who served as the control group. These patients did not receive any supplements of calcium or vitamin D. All patients of both the groups (A and B) were hospitalized and observed for any hypocalcemic manifestations such as carpopedal spasm, perioral tingling, and numbness. Both patient groups were informed about the manifestations of hypocalcemia. Serum calcium and serum parathormone level were measured after 48 h, 1 month, and 3 months PO. We found that six (20%) patients, out of the 30 patients, have experienced hypocalcemia and two (6.7%) of them have experienced symptomatic hypocalcemia. The reported hypocalcemic symptoms including numbness (perioral and in both hands) were observed in two patients and one of them was associated with carpopedal spasm. None of the patients have experienced laryngeal spasm or bronchospasm. There were six patients with positive Chovostek's sign; one from group A and five from group B. These are the same cases who have experienced hypocalcaemia, however, four have given positive Trousseau sign; one from group A and three from group B. In all hypocalcaemia patients, only one are from the supplement group and five from the nonsupplement group showed a significant value, indicating reliability of oral calcium and vitamin D to prevent PO hypocalcaemia (P = 0.007*). All symptomatic hypocalcemic patients were from the nonsupplement group (group B). We found that in regard to calcium level after 48 h, group A ranged from 7.3 to 9.9, with mean of 9.41 and group B ranged from 6.5 to 9.3, mean of 8.45, and P value 0.007*, with significant difference between group A and B. After 1 month, the comparison of the same two groups showed a P value of 0.001* with significant difference. No significant differences were observed in iPTH levels between group A and B after 48 h and 1 month, although the PTH blood levels were within the normal range in all patients postoperatively. Those patients who showed a decrease in the PTH blood levels greater than 50% were the same six patients who suffered from hypocalcemia, whereas in the other 24 normocalcemic patients, this decrease was less than or equal to 50% of the preoperative value.

Conclusion

The routine use of calcium and vitamin D after total thyroidectomy for 4 weeks after surgery could prevent or decrease the incidence of clinically relevant post-thyroidectomy hypocalcaemia, and also may be cost effective by reducing the postoperatively hospital stay as it can reduce its incidence that can postpone the patient discharge.

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Conflicts of interest

There are no conflicts of interest.

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