ORIGINAL RESEARCH PAPER

General Surgery

HUNGRY BONE SYNDROME AS A CAUSE OF POSTOPERATIVE HYPOCALCEMIA FOLLOWING TOTAL THYROIDECTOMY AMONG THYROTOXIC PATIENTS

KEY WORDS:

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ABSTRACT

BACKGROUND Postoperative hypocalcemia, a well known complication of total thyroidectomy has a higher incidence in thyrotoxic patients than euthyroids. Though hypoparathyroidism is considered to be the important cause, other potential causes such as hungry bone syndrome (HBS) is not well established. Therefore we designed this prospective case control study to test the causal of hypothesis of hungry bone syndrome as a cause of postoperative hypocalcemia after total thyroidectomy among thyrotoxic patients. **MATERIALS AND METHODS** Frty clinically active hyperthyroid patients and 31 age and sex matched euthyoid patients were included in the study and ontrol group respectively. Bone mineral density (BMD) at femur, lumbar vertebrae and forearm were measured initially at the time of diagnosis and after total thyroidectomy in both groups. Baseline serum corrected calcium, phosphorus, magnesium, alkaline phosphatase and 25-OH VitaminD and serially thereafter in the postoperative period were measured in either group. The results were analysed with SPSS ver. 20 and p value <0.05 was considered significant. **RESULTS** The incidence of postoperative hypocalcemia was higher among hyperthyroid cases at 82.5% as compared to 22.5% amongst euthyroid controls . The incidence of HBS was 32.5% among thyrotoxic cases (Male: Female= 7:6) and constituted 39.5% of the cause for hypocalcemia. There was significant negative correlation between baseline femoral and lumbar BMD and serum alkaline phosphatase. Post treatment BMD revealed significant percent increment of 8.27% and 7.58% at femur and lumbar spine respectively.

INTRODUCTION

Postoperative hypocalcaemia is a common complication following thyroidectomy with reported incidence varying from 1.6 to as high as 83%1-7. Damage, devascularization or inadvertent removal of the parathyroid glands is the most important determinant, but other potential causes include "hungry bone syndrome" (HBS) due to postoperative reversal of thyrotoxic osteodystrophy , reactive hypoparathyroidism due to relative hypercalcaemia in thyrotoxic patients and release of calcitonin during operative manipulation. Hungry bone syndrome usually occurs as a complication after parathyroidectomy for hyperparathyroidism. But hungry bone syndrome occurring after thyroidectomy for thyrotoxicosis has not been established as the cause of hypocalcemia in prospective studies. Therefore, we designed this prospective case control study to determine the contribution of hungry bone syndrome as a cause of postthyroidectomy hypocalcemia among thyrotoxic patients. We evaluated the longitudinal changes in bone mineral density and factors related to bone mineral ion homeostasis among thyrotoxic patients. We compared the same with age and sex matched euthyroid controls.

AIM OF THE STUDY

1.To prospectively evaluate the incidence of hungry bone syndrome as a cause of post-thyroidectomy hypocalcemia among thyrotoxic patients.

2. To evaluate the changes in the bone mineral density at all three sites, namely, femur, lumbar vertebrae and forearm before and after definitive surgical treatment.

3. To serially study the factors related to bone mineral ion homeostasis namely Serum calcium, phosphorus, magnesium, 25- hydroxy Vitamin D, intact Parathormone & Alkaline phosphatase and predict at risk patients likely to develop post operative hypocalcemia.

REVIEW OF LITERATURE

Thyroidectomy is the most common endocrine surgery performedworldwide. Theodor Kocher was awarded noble prize in 1909 for hispioneering work in thyroid surgery.

Postoperative hypocalcemia and vocal cord paralysis due to injury to the recurrent laryngeal nerve are the most common complications of total thyroidectomy.

Postoperative hypocalcemia is of particular concern because it manifests late usually in the 3rd or 4th postoperative day. This in turn requires prolonged patient hospitalization or readmission. Hypocalcaemia may be transient or permanent (persistent for more than 6 months after surgery). The reported incidence of transient hypocalcemia varies from 1.6 to 53.5%. Permanent hypoparathyroidism after total thyroidectomy is found in 1.5 to 4% of the patients.The causes of hypocalcemia after Total thyroidectomy are multifactorial.

Damage, devascularization or inadvertent removal of the parathyroid glands are the major determinants of hypoparathyroidism. The presence of retrosternal extension, concomitant neck dissections,hyperthyroidism, thyroiditis, thyroid carcinoma, experience of the surgeon, prolonged operative time, and number of parathyroid glands left insitu also contribute to hypocalcemia.

Number of parathyroids preserved - All the four parathyroids should be identified and preserved. Atleast three parathyroids should be preserved to maintain calcium homeostasis. When the vascularity of the parathyroid is compromised or inadvertently removed, it is harvested and cut into fragments of less than 1 cu.mm and autotransplanted into ipsilateral sternomastoid. This practice decreases the risk of permanent hypoparathyroidism to less than 1%

OTHER CAUSES OF POSTOPERATIVE HYPOCALCEMIA

1.HYPOMAGNESEMIA
2.POSTOPERATIVE HEMODILUTION
3.BLOODTRANFUSION
4.THYROTOXICOSIS
5.HYPERPHOSPHATEMIA
6.PREOPERATIVE INGESTIONS OF DRUGS LIKE Anti-convulsants, chlorpromazine, diazepam, oral contraceptives, steroids and mithramycin
7.HYPERPHOSPHATEMIA

HUNGRY BONE SYNDROME (HBS)

HBS is characterized by rapid, profound and prolonged

hypocalcemia associated with hypophosphatemia and hypomagnesemia,due to an excessive bone remineralization. HBS is caused by the shift of calcium ion along with phosphorous and magnesium in to the hungry bones due to the sudden removal of stimulus for high bone turnover. The sudden removal of high circulating level of PTH following parathyroidectomy in hyperparathyroidism (and thyroidectomy in thyrotoxicosis) leads to sudden arrest of osteoclastic bone resorption in the phase of active bone turnover.This leads to enhanced bone remineralisation.

CLINICAL MANIFESTATION OF HBS

Hypocalcaemia causes neuromuscular irritability and manifests as acral and perioral parasthesia, positive Chvostek sign and Trousseau sign,carpopedal spam, laryngospasm, stridor, cardiac arrhythmia and
congestive heart failure. In severe cases seizures, coma and death.

PREDISPOSING FACTORS FOR HBS

a) Advanced age 47
b) High preoperative serum calcium
c) Two-fold elevation of serum alkaline phosphatase47
d) Preoperative low magnesium and albumin47, 48
e) Skeletal involvement(thyrotoxic osteodystrophy) 48-51
f) Vitamin D depletion48-51
g) number of functional parathyroid left behind

BIOCHEMICAL CHANGES IN HBS

* Serum corrected serum calcium decreases to 8 mg/dl within 48-72
hours but further fall occurs after the fourth post-operative day in
patients with HBS 47
* Fall of Serum phosphate levels postoperatively
* Hypomagnesaemia
* 2- fold elevation of serum alkaline phosphatase
Sudden fall in intact parathormone to less than 1.7+/-0.4 pmol/l in
PHPT. In contrast to PHPT, hypocalcemia of HBS in thyrotoxicosis is
characterized by appropriate increases in parathormone.

MANAGEMENT OF HBS

Aim of the treatment is to
Short-term - replenish the circulating calcium deficit.
Long-term normalizing the bone turnover and remineralising skeleton.

MATERIALS & METHODS

STUDY DESIGN : Prospective case control study
PERIOD OF STUDY : November 2019 to February 2022

SUBJECTS:

A total of 71 patients admitted in our department for surgery of benign thyroid diseases were included in the study and categorized selectively into two groups namely, study and control group. Institutional ethical committee's clearance and informed consent was obtained.

INCLUSION CRITERIA FOR STUDY/TEST GROUP:

40 consecutive newly diagnosed clinically active hyperthyroid patients were recruited into the study/ test group Confirmed biochemically with elevated free triiodothyronine Ft3, free tetraiodothyronine FT4 and suppressed Thyroid stimulating hormone TSH Confirmed by Technitium99m thyroid scintigraphy with increased radiotracer uptake and non- visualization of salivary glands Etiology of hyperthyroidism- 18 cases of Graves' disease and 22 cases of toxic multinodular goiter Patients likely to have surgery as the definitive modality of Treatment.

EXCLUSION CRITERIA FOR STUDY GROUP:

Patients with other causes of reduced BMD(CLD,CKD,Steroid therapy,immunosuppressive,DM) Parathyroid diseases Patients on Oral calcium and Vitamin D supplements,Thiazide diuretics

INCLUSION CRITERIA FOR CONTROL GROUP

36 cases of Age and sex matched euthyroid patients with benign multinodular goiter were included in the controls. Age variation up to 2years was allowed. Patients were recruited at the same time as the test patients to avoid seasonal variation in 25 OH vitamin D levels. However, four male patients and 1 female patient were lost in the follow up and excluded from the study.

EXCLUSION CRITERIA

Reoperative surgery
Neck dissection
Malignancy of thyroid
Retrosternal extension

On admission, all subjects were subjected to thorough history taking and physical examination along with routine investigations. Specific investigations such as thyroid profile, thyroid autoantibodies, high frequency ultrasound neck, FNAC thyroid, 99mTc thyroid scintigraphy for confirming diagnosis.

Baseline BMD was evaluated at all three sites namely, femur,lumbar vertebrae and forearm using DEXA at the time of diagnosis of hyperthyroidism in the test group as well as euthyroid controls and 6months after total thyroidectomy. They were also analysed serially at the baseline, second and third post operative day and 6 months after surgery for the following
biochemical indices,

1.Serum Corrected Calcium
2.Serum Phosphorus
3.Serum Magnesium
4.Serum 25-Hydroxy Vitamin D
5.Serum Parathormone
6.Serum Alkaline phosphatase (SAP)

STATISTICAL ANALYSIS-

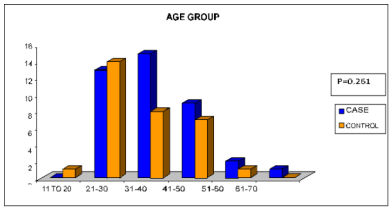
Data were expressed as mean+/- standard deviation. Statistical analysis was performed with IBM SPSS statistics version 20.0. by two tailed paired student t- test, two tailed unpaired student t- test, Chi –square test and analysis of variance ANOVA where appropriate. P value<0.05 was considered significant.

RESULTS

A total of 71 patients were included in the series. Study group consisted of 40 clinically active hyperthyroid cases and control group consisted of 31 euthyroid patients. Initially 36 patients were recruited in the control group but 34 men and I woman were lost in the follow up and excluded from the study.

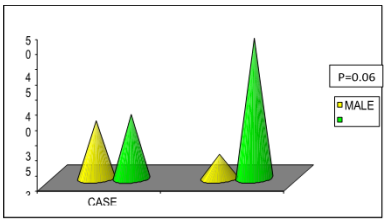
AGE DISTRIBUTION:

Most of the patients in either group were in the third and fourth decade of life with mean age of 36.48+/-9.84 and 33.9+/-9.012 in the study and control group respectively.

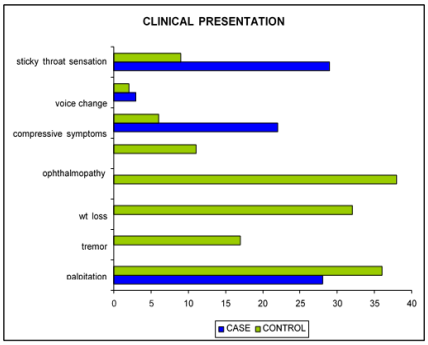


GENDER DISTRIBUTION:

Of the 40 hyperthyroid patients, there were 19 men and 21 women and among euthyroid controls, there were 8 men and 23 women. P=0.063.



CLINICAL PRESENTATION



Clinical and biochemical indices analysed between the two groups are given in the following Table.

S.No	PARAMETERS	CASE	CONTROL	P value
1.	Age in years	36.48+/-9.84	33.9+/-9.01	0.261
2.	Male: Female	19:21	8:23	0.063
3.	Weight in kg	47.2+/-8.6	52.4+/-5.2	<0.05
4.	Duration of disease in months	7.5+/-5.9	7.26+/-3.19	0.837
5.	Duration of antithyroid drugs in months	3.25+/-1.15	-	
6.	FT3 pg/ml	16.66+/-7.23	2.14+/-0.98	0.001
7.	FT4ng/dl	5.22+/-2.38	1.12+/-0.78	0.022
8.	TSHmIU/ml	0.011+/-0.018	2.84+/-1.15	0.043
9.	Anti Thyroperoxidase antibody	607.46+/-365.015	4.25+/-2.225	0.001
10.	Anti Thyroglobulin	266.5+/-400.4	3.54+/-11.25	0.013

Thus, in the study group, free hormones were elevated and TSH suppressed. In addition the thyroid autoantibodies, namely Antithyroglobulin antibody and Anti-Thyroperoxidase antibody were elevated.

HISTOPATHOLOGY	CASE	CONTROL		
	Hyperplastic goitre	14	Nodular colloid goiter	14
	Toxic nodular goitre	18	colloid cystic goiter	4
	Hashimoto'st hyroiditis	8	Follicular adenoma	6
			Adenomatous goiter	2
			Lymphocytic thyroiditis	5
TOTAL		40		31

MAJOR COMPLICATION	CASE	CONTROL
Transient hypocalcemia	32	7
Permanent Hypocalcemia	1	-
Temporary recurrent laryngeal nerve palsy	3	1
Permanent recurrent laryngeal nerve palsy	1	-

The biochemical indices related to bone mineral ion homeostasis

PARAMETERS	CASE	CONTROL	P VALUE	
PRETREATMENT				
S.CORRECTED CALCIUM mg/dl	9.13+/-0.66	9.45+/-0.73	0.055	NS
S.PHOSPHOROUS mg/dl	4.12+/-0.76	3.99+/-0.85	0.054	NS
S.MAGNESIUM mg/dl	1.78+/-0.67	2.18+/-0.45	0.004	S
S. INTACT PARATHORMONE pg/ml	50.56+/-35.61	42.66+/-16.73	0.218	NS
S.ALKALINE PHOSPHATASE IU/L	143.18+/-72.0	71.97+/-23.07	<0.001	S
S.25OH VITAMIND ng/ml	24.27+/-10.61	26.12+/-14.63	0.555	NS

From the above table, we observed that serum magnesium was significantly in the low normal range among hyperthyroid patients compared to euthyroid controls in the pretreatment phase. Serum alkaline phosphatase was two-fold higher than euthyroid controls.Also observed that the 25-OH vitamin D were in the insufficient range in both groups and preoperative parathormone was high normal. The prevalence of hypovitaminosis D in our population leading to secondary hyperparathyroidism could be the probable reason.

PARAMETERS	CASE	CONTROL	P VALUE	
POSTOPERATIVE PHASE				
S.CORRECTED CALCIUM mg/dl	7.715+/-0.81	8.961+/-0.771	<0.001	S
S.PHOSPHOROUS mg/dl	4.16+/-1.20	4.23+/-0.76	0.792	NS
S.MAGNESIUM mg/dl	1.95+/-0.79	1.95+/-0.46	0.974	NS
S. INTACT PARATHORMONE pg/ml	29.67+/-21.97	18.89+/-12.73	0.012	S
S.ALKALINE PHOSPHATASE IU/L	120+/-51.99	65.68+/-20.34	<0.001	S

POSTOPERATIVE PHASE

Marked hypocalcemia was observed in the study group with a mean of 7.715 +/- 0.81 mg/dl in the postoperative phase. The magnitude of severity of hypocalcemia was also high as compared to the controls. However, intact parathormone was in the normal range among hyperthyroid cases. But it was significantly reduced in the control group.Serum alkaline phosphatase showed two fold rise in the postoperative period in the study group.

FOLLOW UP				
PARAMETER	CASE	CONTROL	P VALUE	
S.CORRECTED CALCIUM mg/dl	8.88+/-0.69	8.58+/-1.72	0.927	NS
S.PHOSPHOROUS mg/dl	3.80+/-0.67	3.94+/-0.73	0.44	NS
S.MAGNESIUM mg/dl	2.21+/-0.34	2.26+/-0.32	0.533	NS
S.INTACT PARATHORMONE pg/ml	60.17+/-38.44	40.28+/-16.07	0.006	S

S.ALKALINE PHOSPHATASE IU/L	102.52+/-8.26	67.78+/-13.68	<0.001	S

Serum calcium returned to normocalcemic range 6 months after surgery in the hyperthyroid group. Intact parathormone climbed up to high normal range among throtoxic cases. Though there was a fall in serum alkaline phosphatase in the follow up, it still remained higher than euthyroid controls.

COMPARISON WITHIN THE GROUP WITHIN THE STUDY GROUP

We observed a very significant fall in the level of serum calcium in the postoperative period. Though there was a drop in the parathormone postoperatively it was still in the normal range. Serum alkaline phosphatase remained two – fold higher than normal range.

ST UDY GROUP PREOPERATIVEVS POSTOPERATIVE

PARAMETER	PREOPERATIVE	POSTOPERATIVE	P VALUE
S.CORRECTED CALCIUM mg/dl	9.13+/-0.66	7.715+/-0.81	<0.001
S.PHOSPHOROUS mg/dl	4.12+/-0.76	4.16+/-1.20	0.829
S.MAGNESIUM mg/dl	1.78+/-0.67	1.935+/-0.79	0.319
S. INTACT PARATHORMONE pg/ml	50.56+/-35.61	29.67+/-21.97	0.005
S.ALKALINE PHOSPHATASE IU/L	143.18+/-72.0	120+/-51.99	0.011

STUDY GROUP- POSTOPERATIVEVS FOLLOW UP

PARAMETER	POSTOPERATIVE	FOLLOW UP	P VALUE
S.CORRECTED CALCIUM mg/dl	7.715+/-0.81	8.88+/-0.69	<0.001
S.PHOSPHOROUS mg/dl	4.16+/-1.20	3.80+/-0.67	0.035
S.MAGNESIUM mg/dl	1.935+/-0.79	2.21+/-0.31	0.020
S. INTACT PARATHORMONE pg/ml	29.67+/-21.97	60.17+/-38.44	<0.001
S.ALKALINE PHOSPHATASE IU/L	120+/-51.99	102.52+/-8.26	0.041

Serum calcium restored to normocalcemic range with concomitant increase in serum parathormone. Serum magnesium and phosphorus also returned to normal range. Though serum alkaline phosphatase showed a significant drop, it still remained elevated especially in those with osteoporosis or osteopenia. One case of permanent hypoparathyroidism occurred in the study group.

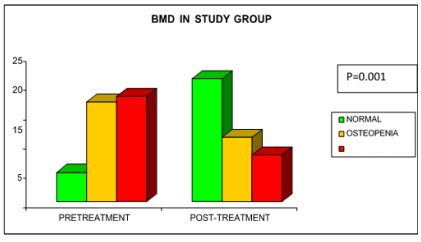
COMPARISON WITHIN THE CONTROL GROUP

We documented a significant fall in the level of corrected serum calcium and magnesium along with a rise in the level of phosphorus postoperatively in the euthyoid controls. Intact parathormone showed a significant drop to low normal values.

PARAMETER	PREOPERATIVE	POSTOPERATIVE	P VALUE
S.CORRECTED CALCIUM mg/dl	9.45+/-0.73	8.961+/-0.771	0.005
S.PHOSPHOROUS mg/dl	3.99+/-0.85	4.23+/-0.76	0.08
S.MAGNESIUM mg/dl	2.18+/-0.45	1.95+/-0.46	0.039
S. INTACT PARATHORMONE pg/ml	42.66+/-16.73	18.89+/-12.73	<0.001
S.ALKALINE PHOSPHATASE IU/L	71.97+/-23.07	65.68+/-20.34	0.021

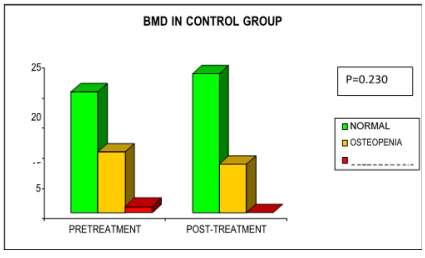
In the follow up surveillance, we documented a significant increase in the intact parathormone with normalization of calcium and phosphorus. Serum magnesium also improved significantly.

EVALUATION OF BONE MINERAL DENSITY IN STUDY VS CONTROL



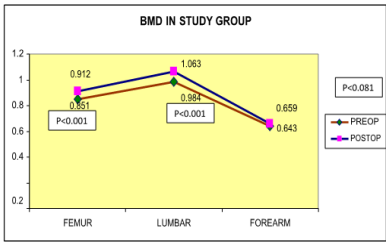
BMD IN STUDY GROUP				
DEXA SCAN	PRETREATMENT		POST-TREATMENT	
NORMAL	5	12.5%	21	52.5%
OSTEOPENIA	17	42.5%	11	27.5%
OSTEOPOROSIS	18	45%	8	20%
TOTAL	40	100%	40	100%

Pretreatment DEXA revealed bone involvement in 87.5% of the hyperthyroid cases initially at the time of diagnosis Post-treatment DEXA scan taken 6 months after surgery showed significant improvement in the BMD ($p<0.001$) and normalized in 52.5% of the cases.

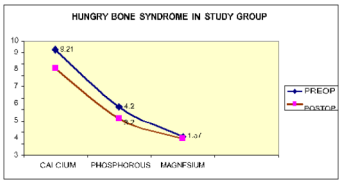


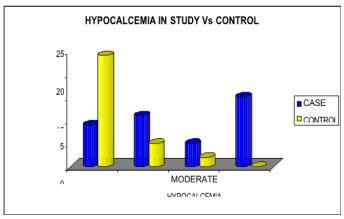
BMD IN CONTROL GROUP				
DEXA	PRETREATMENT		POST-TREATMENT	
NORMAL	20	64.51%	23	74.19%
OSTEOPENIA	10	32.25%	8	25.80%
OSTEOPOROSIS	1	3.22%	0	0
TOTAL	31	100%	31	100%

On the other hand, pretreatment DEXA was normal in majority of the euthyroid controls and not much change after surgery.



There was not significant change in the BMD of the controls before and after treatment.





	HBS	HYPOCALCEMIA	
	cases	cases	Control
Normal PTH	7	21	2(28.57%)
Low PTH	3	6	5(71.4%)
High PTH	3	4	-
Total	13	33	7

Among euthyroid controls, transient hypoparathyroidism occurred in 5 of 7 patients with hypocalcemia (71.4%) and was the major determinant of postoperative hypocalcemia. 2 patients had severe hypocalcemia requiring i.v calcium gluconate and oral supplementation. Hypocalcemia and hypomagnesemia were observed in 3 of these patients requiring oral calcium and magnesium supplementation. In another three patients, in the absence of biochemical hypocalcemia, symptoms of neuromuscular irritability occurred and were found to have hypomagnesemia. Mean preoperative & postoperative S.Magnesium were 2.17+/-0.454 and 1.95+/-0.46 mg/dl respectively among controls. Thus, there was significant fall in serum magnesium level in the postoperative period (p0.039) among controls in our series.

	Cases	Control
Mild hypocalcemia	11	5
Moderate hypocalcemia	5	2
Severe Hypocalcemia	15	-
Mild hypomagnesemia	6	-
Severe Hypomagnesemia	13	3
Hypomagnesemic hypocalcemia	9	3

Interestingly, preoperative serum magnesium were found to be lower in patients with Hypomagnesemic hypocalcemia syndrome in both study and control group.Among hyperthyroid patients, the higher the T3 concentration during hyperthyroidism and longer the duration of hyperthyroidism, the greater was the subsequent increase in lumbar and femoral BMD. However, this was not statistically significant. Further, BMD did not have correlation with advancing age nor hypovitaminosis. There was strong correlation between BMD and serum alkaline phosphatase($p<0.05$).Hypovitaminosis D was prevalent in either group. The mean serum 25 OH Vitamin D was 24.27+/-10.61 ng/ml among hyperthyroid vs. 26.12+/-14.63 ng/ml among controls (p= 0.804).

CONCLUSION

The incidence of post-thyroidectomy hypocalcemia was significantly higher in thyrotoxic patients than euthyroid controls.The incidence of hungry bone syndrome was 32.5% and constituted the major determinant of postoperative hypocalcemia among thyrotoxic patients.Reduced BMD in the femur and lumbar vertebrae with elevated alkaline phosphatase and intact parathormone are important predictive risk factors for postoperative hypocalcemia in thyrotoxic patients.Transient hypoparathyroidism is the major determinant of postoperative hypocalcemia in euthyoid controls. Magnesium deficiency, especially in young females are the predictive risk factors for post- thyroidectomy hypocalcemia in euthyroid patients.

BIBLIOGRAPHY

1. Pattou F, Combemale F, Fabre S, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. World J Surg 1998;22:718–724.
2. Demeester-Mirkine N, Hooghe L, Van Geetruyden J, deMaertelaer V. Hypocalcemia after thyroidectomy. Arch Surg 1992;127:854–858.
3. McHenry CR, Speroff T, Wentworth D, Murphy T. Risk factors for post-thyroidectomy hypocalcemia. Surgery 1994;116:641–648.
4. Herranz-Gonzalez J, Garlian J, Martinez-Vidal J, Gavilan C.Complications following thyroid surgery. Arch Otolaryngol Head Neck Surg 1991;117:516–518.
5. Shindo ML, Sinha UK, Rice DH. Safety of thyroidectomy in residency: a review of 186 consecutive cases. Laryngoscope 1995;105:1173–1175.
6. Wilson RB, Erskine C, Crowe PJ. Hypomagnesemia and hypocalcemia after thyroidectomy: prospective study. World J Surg 2000;24:722–726.
7. Yamashita H, Noguchi S, Murakami T, et al. Predictive risk factors for postoperative tetany in female patients with Graves' disease. J Am Coll Surg 2001;192:465–468.
8. Michie W, Duncan T, Hamer-Hodges DW et al. Mechanism of hypocalcaemia after thyroidectomy for thyrotoxicosis. Lancet 1971;i:508-13.
9. Randall, R.E., Rossmeisl, E.C., and Bleifer, K.H.: Magnesium depletion in man. Ann. Intern. Med. 50:257, 1959
10. Hamill-Ruth, R.J., and McGory, R.: Magnesium repletion and its effect on potassium homeostasis in critically ill adults: results of a double-blind, randomised, controlled trial. Crit. Care Med. 24:38, 1996
11. Raisz, L.G., and Niemann, J.: Effect of phosphate, calcium and magnesium on bone resorption and hormonal responses in tissue culture. Endocrinology 85:446, 1969.
12. Demeester-Mirkine, N., Hooghe, L., Van Geertrudyen, J., and De Maertelaer, V.: Hypocalcaemia after thyroidectomy. Arch. Surg. 127:854, 1992