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Postoperative Tetany in Graves Disease

Important Role of Vitamin D Metabolites

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Objective
To test the authors' hypothesis of the causal mechanism(s) of postoperative tetany in patients with Graves disease.

Summary Background Data
Previous studies by the authors suggested that postoperative tetany in patients with Graves disease occurs during the period of bone restoration and resulted from continuation of a calcium flux into bone concomitant with transient hypoparathyroidism induced by surgery.

Patients and Methods
A prospective study was carried out to investigate sequential changes in serum levels of intact parathyroid hormone (iPTH), calcium and other electrolytes, 25-hydroxyvitamin D (25OHD), 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), and bone metabolic markers in 109 consecutive patients with Graves disease who underwent subtotal thyroidectomy.

Results
Preoperative serum iPTH levels negatively correlated with ionized calcium levels and positively correlated with 1,25$(OH)_2$D or 1,25$(OH)_2$D/25OHD. After the operation, there was a significant decline in levels of ionized calcium, magnesium, and iPTH. Serum iPTH was not detected in 15 patients after surgery. Four of these 15 patients, and 1 patient whose iPTH level was below normal, developed tetany. Preoperative serum ionized calcium levels were significantly lower, and iPTH levels were higher, in the 5 patients with tetany than in the 11 patients who did not develop tetany despite undetectable iPTH levels. The tetany group had significantly lower serum 25OHD levels and higher 1,25$(OH)_2$D levels, and had increased 1,25$(OH)_2$D/25OHD as an index of the renal 25OHD-1-hydroxylase activity than those in the nontetany group. These results suggest that patients with a high serum level of iPTH as a result of low serum calcium levels (secondary hyperparathyroidism) are susceptible to tetany under conditions of hypoparathyroid function after surgery.

Conclusions
Postoperative tetany occurs in patients with secondary hyperparathyroidism caused by a relative deficiency in calcium and vitamin D because of their increased demand for bone restoration after preoperative medical therapy concomitant with transient hypoparathyroidism after surgery. Calcium and vitamin D supplements may be recommended before and/or after surgery for patients in whom postoperative tetany is expected to develop.

The mechanisms of postoperative hypocalcemia and tetany are disputed and have yet to be clarified: these conditions have been suggested to result from surgical interference with the parathyroid,[1–3] abnormal release of calcitonin by manipulating the thyroid gland at operation,[4] and the sudden reversal of thyrotoxic osteodystrophy present before thyroidectomy, which leads to a rapid skeletal uptake of calcium referred to as "hungry bone syndrome."[5–7] We have recently reported the predictive risk factors for postoperative tetany in patients with Graves disease after subtotal thyroidectomy.[8] These factors are preoperative lower serum calcium level, younger age, higher serum alkaline phosphatase concentration, larger size of goiter, and higher value of thyroid-stimulating hormone (TSH)-binding inhibitory immunoglobulin, in order of decreasing probability of significance. The lower serum calcium level, which is the most significant risk factor for postoperative tetany, could be interpreted as being caused by a considerable amount of calcium flux into bone during antithyroid drug therapy. It is

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well known that hypercalcemia, although mild, occurs in a significant proportion of patients with thyrotoxicosis, and tends to return to normal after antithyroid drug therapy.[9,10] From these results, combined with previous observations,[11] we hypothesized that postoperative tetany occurs during the period of bone restoration and may result from a continuation of calcium flux into bone concomitant with transient hypoparathyroidism induced by surgery. Formation of bone requires calcium and phosphorus as substrates and is regulated by complex interactions of PTH, 1,25-dihydroxyvitamin D($1,25(OH)_2D$), the gonadal steroids, and thyroid hormones.

To test our hypothesis and to elucidate the causal mechanism(s) of postoperative tetany, we designed a prospective study to investigate sequential changes in serum levels of PTH, calcium and other electrolytes, 25-hydroxyvitamin D (25OHD), $1,25(OH)_2D$, and bone metabolic markers in 109 consecutive patients with Graves disease who underwent subtotal thyroidectomy.

PATIENTS AND METHODS

Patients

We studied 109 consecutive patients with Graves disease who underwent subtotal thyroidectomy between June 1996 and August 1996. Patients gave written informed consent. There were 20 men and 89 women; the mean age was 32 years (range 12 to 64 years). Among the 109 patients who underwent surgery, 32 patients had received antithyroid medication for long periods, 21 patients developed adverse effects due to antithyroid drugs, 13 patients exhibited large goiter, 6 patients demonstrated concomitant neoplasms in the thyroid, and 37 patients selected their own preferred surgical treatment. The relatively wide indications for surgery were explained by the special conditions of our clinic: the majority of patients came from remote areas and were referred to us mainly for surgical treatment rather than radioiodine therapy. The diagnosis of Graves disease was made based on clinical grounds and on the basis of elevated serum levels of free triiodothyronine (FT3) and free thyroxine (FT4) with undetectable TSH concentrations, positive anti-TSH receptor antibody, and higher uptake rate of ^{131}I. None of the patients had severely impaired hepatic or renal function. The patients received antithyroid drugs (methimazole, in most cases) to achieve and maintain a euthyroid state. Potassium iodide was administered to patients who developed adverse effects from antithyroid drugs. Lugol's solution was given for 7 to 10 days before surgery to all patients except those given potassium iodide.

All the operations were carried out using standardized procedures[12] by three chief surgeons who had practiced thyroid surgery for >15 years in our thyroid clinic. Postoperative tetany was defined as the occurrence of a positive Trousseau's test with overt hypocalcemia (serum calcium level < 1.96 mmol/l).

Laboratory Tests

Blood and urine samples were collected after an overnight fast on the day before surgery and on the first and seventh postoperative days. Serum levels of alkaline phosphatase (normal range, 36 to 92 U/l), total calcium (2.20 to 2.54 mmol/l), albumin (35 to 48 g/l), and inorganic phosphate (81 to 1.45 mmol/l) were measured by routine automated procedures. Ionized calcium (1.08 to 1.28 mmol/l) and magnesium (0.74 to 0.95 mmol/l) concentrations were determined using an electrolyte analyzer (NOVA Biochemical, Waltham, MA). The corrected calcium (mmol/l) level was calculated by the formula (calcium concentration [mg/dl] + 4-albumin [g/dl]) × 0.250. Levels of FT4 (9 to 21.9 pmol/l), FT3 (3.4 to 6.3 pmol/l), and TSH (0.30 to 3.50 mU/l) were determined by a chemiluminescent immunoassay using assay kits (Ciba Corning Diagnostics Corp., Medfield, MA). The TSH-binding inhibitory immunoglobulin concentration (−15% to 8%) was measured with TRAb assay kits (INCSTAR Corp., Stillwater, MN). Serum bone-specific alkaline phosphatase levels (10 to 35 U/l) were measured by enzyme immunoassay. Serum osteocalcin levels (3.1 to 12.7 ng/ml) were measured by radioimmunoassay. Serum iPTH levels (1.8 to 5.7 pmol/l) were measured by a two-site immunochemiluminometric assay. Serum 25(OH)D (25 to 137 nmol/l) levels were measured by a competitive protein-binding assay using high-performance liquid chromatography purification with intra- and interassay coefficients of variation of 5.8% and 12.6%, respectively.[13] Serum $1,25(OH)_2D$ levels (48 to 144 pmol/l) were measured by a receptor-binding assay using bovine mammary gland receptor with intra- and interassay coefficients of variation of 8.1% and 8.3%, respectively.[14] To assess bone resorption, we measured urinary excretions of deoxypyridinoline and pyridinoline (Pyrilink) by enzyme-linked immonosorbent assay, and the results were corrected using urinary creatinine concentration, assessed using a standard calorimetric method. The protocol used was approved by the staff meeting at the Noguchi Thyroid Clinic.

Statistics

Data are expressed as the mean ± standard deviation. Comparisons of continuous variables were made using one-way analysis of variance. Biochemical changes before and after surgery were analyzed using the paired t test. Cross-tabulated data were analyzed using Fisher's exact probability test. Correlations were tested by calculating Spearman's rank-order correlation coefficient. These statistical analyses were done using SAS-JMP version 3.1R software programs for Macintosh (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 shows the preoperative clinical and biochemical data on 109 patients. There was a significant negative cor-

Table 1. PREOPERATIVE CLINICAL AND BIOCHEMICAL DATA OF PATIENTS

Parameter	Value (range)	Reference range
Number	109	
Sex (women/men)	89/20	
Age (years)	32 ± 12 (12 ~ 64)	
FT3 (pmol/l)	5.0 ± 2.2 (2.5 ~ 12.7)	3.4 ~ 6.3
FT4 (nmol/l)	14.3 ± 7.5 (3.9 ~ 45.0)	9.0 ~ 21.9
TSH (μU/ml)	2.5 ± 6.9 (0 ~ 41)	0.3 ~ 3.5
TBII (%)	32 ± 28 (−10 ~ 92)	−15 ~ 8
Osteocalcin (ng/ml)	19 ± 13 (3 ~ 72)	3.1 ~ 12.7
Alkaline phosphatase (U/l)	153 ± 80 (44 ~ 399)	36 ~ 92
Alkaline phosphatase (bone-specific) (U/l)	85 ± 59 (7 ~ 296)	10 ~ 35
Pyridinoline/creatinine (nmol/mmol Cr)	95 ± 99 (6 ~ 693)	
Deoxypyridinoline/creatinine (nmol/mmol Cr)	22 ± 26 (2 ~ 183)	
Cholesterol (mmol/l)	4.2 ± 0.9 (1.9 ~ 6.9)	3.4 ~ 5.7
Operation time (min)	64 ± 17 (37 ~ 155)	
Blood loss (g)	118 ± 64 (40 ~ 450)	
Excised amount of thyroid (g)	48 ± 45 (11 ~ 350)	
Estimated remnant thyroid (g)	4.6 ± 3.3 (1.5 ~ 10.0)	

Values are given as mean ± SD.
TBII = thyroid-binding inhibitory immunoglobulin; TSH = thyroid-stimulating hormone.

relation between preoperative serum iPTH and ionized calcium levels (Fig. 1). Figure 2 demonstrates a significant correlation between ionized calcium and FT3 or FT4 levels. There was no correlation between ionized calcium and phosphorus or magnesium levels.

All the patients underwent bilateral subtotal thyroidectomies. There were no intraoperative complications. Postoperative transient recurrent laryngeal nerve paralysis was diagnosed in eight patients (7.3%); all patients recovered within 2 months after surgery. Postoperative bleeding occurred in two patients (1.8%).

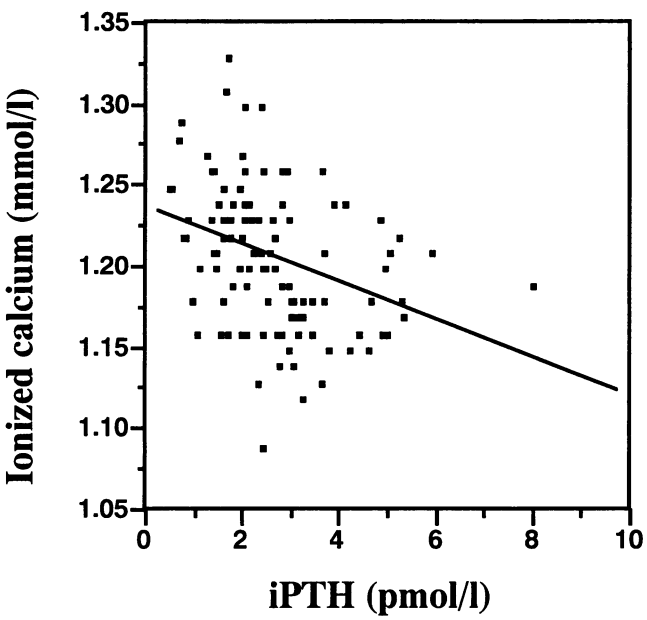

Figure 1. Negative correlation between preoperative serum values of intact parathyroid hormone and ionized calcium (r = −0.35, p = 0.0003).

Of the 109 patients, postoperative tetany occurred in 5 (4.6%); all were women. Tetany occurred in all five patients on the first postoperative day. Of the five patients, one (0.9% of the total patients) required small amounts of vitamin D supplements for >6 months after surgery.

After the operation, there was a significant decline in the serum levels of calcium, ionized calcium, magnesium, and iPTH (Table 2). Serum iPTH was not detected in 15 patients after surgery (the detection limit was 0.54 pmol/l in our assay). A value of 0.54 pmol/l was assigned to the undetectable values of iPTH. Tetany developed in 4 of these 15 patients and in 1 patient whose iPTH level was below normal on the first postoperative day. The following analysis is focused on these 16 patients.

Table 3 shows the clinical and laboratory data on the tetany group (n = 5) and the nontetany group (the patients in whom tetany did not develop despite severely decreased PTH levels; n = 11). The tetany group had lower levels of FT3 and FT4 and higher levels of TSH and cholesterol, but these did not produce a significant difference. Marked differences were observed in serum levels of ionized calcium and iPTH between the two groups (Table 4), suggesting that patients with hyperparathyroidism due to low serum calcium levels are susceptible to tetany under the condition of hypoparathyroid function after surgery. Figure 3 shows the serum levels of ionized calcium according to the periods of euthyroidism. The levels in the short periods of euthyroidism fluctuated from low to high, and four of five patients with postoperative tetany underwent surgery after a short euthyroid period.

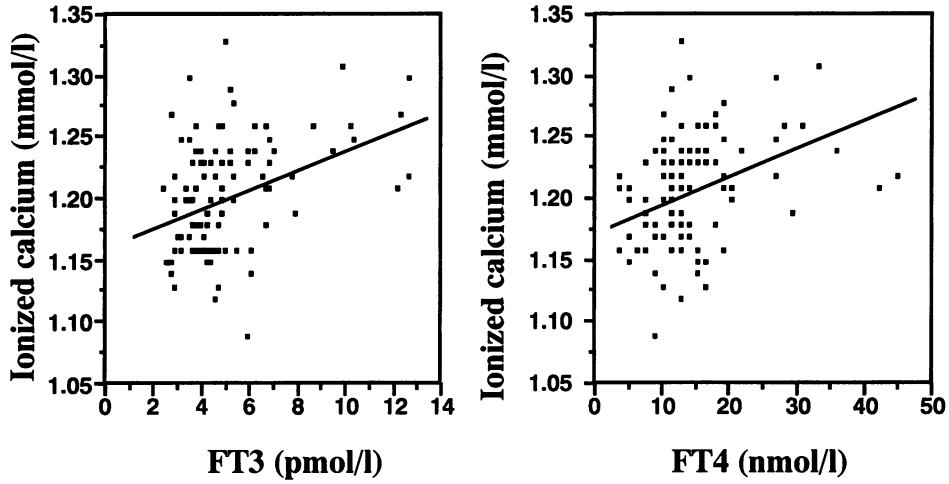

Figure 2. Correlation between preoperative serum levels of ionized calcium and free triiodothyronine (FT3) or free thyroxine (FT4) ($r = 0.39$, $p = 0.0001$ and $r = 0.38$, $p = 0.0001$, respectively).

We measured 25OHD and $1,25(OH)_2D$ levels in serum obtained the day before surgery and on the first postoperative day in these 16 patients. There were significant positive correlations between serum iPTH and $1,25(OH)_2D$ levels or $1,25(OH)_2D/25OHD \times 10^3$ (Fig. 4). Figure 5 shows significant negative correlations between $1,25(OH)_2D$ and FT3 or FT4 levels. Table 4 shows significant differences in serum concentrations of 25OHD and $1,25(OH)_2D$, and also a significant difference in $1,25(OH)_2D/25OHD \times 10^3$ as an index of the renal 25OHD-1-hydroxylase activity, between the tetany and nontetany groups. Another significant finding was that the tetany group had a lower serum level of 25OHD (mean value 27 nmol/l); three of five patients had values below normal (25 to 137 nmol/l). Changes in all of these parameters after thyroidectomy were significant between the two groups (Table 5).

DISCUSSION

Bilateral subtotal thyroidectomy in patients with Graves disease is associated with a higher incidence of postoperative hypocalcemia or tetany compared with the same procedure performed in patients with nodular thyroid disease.[15,16] This can be explained by the differences in calcium and bone metabolism induced by thyroid hormones, which have an important influence on bone development and bone turnover.[9,10]

Several causative mechanisms of postoperative tetany in patients with Graves patients have been proposed, but they cannot fully explain the clinical findings. If it is caused merely by parathyroid insufficiency related to injury, devascularization, or inadvertent excision of the parathyroid glands, how could we explain the above-mentioned difference and the gender difference in the incidence of tetany in Graves patients?[8,17] Wilkin et al[4] suggested the possible role of calcitonin release in early postthyroidectomy hypocalcemia. Suzuki et al[18] observed that manipulation of the thyroid at operation produced a transient fall in serum calcium, but Michie et al[5] and McHenry et al[16] could not confirm this finding. The clinical importance of calcitonin in postoperative tetany is somewhat doubtful, because calcito-

Table 2. CHANGES IN BIOCHEMICAL DATA OF PATIENTS (N = 109) AFTER THYROIDECTOMY

Parameter	Preoperative Value	1st Postoperative Value	p Value*
Albumin (g/l)	3.6 ± 0.2	3.6 ± 0.2	0.4924
Serum calcium (mmol/l)	2.53 ± 0.08	2.38 ± 0.16	0.000*
Ionized calcium (mmol/l)	1.21 ± 0.04	1.13 ± 0.08	0.000*
Serum phosphate (mmol/l)	1.45 ± 0.17	1.46 ± 0.17	0.7557
Magnesium (mmol/l)	0.85 ± 0.06	0.82 ± 0.07	0.000*
iPTH (pmol/l)	2.65 ± 1.29	2.24 ± 1.39	0.0003*

Values are given as mean ± SD.
* Significant changes evaluated by paired t-test.
iPTH = intact parathyroid hormone.

Table 3. DIFFERENCES IN CLINICAL AND BIOCHEMICAL DATA BETWEEN THE TWO GROUPS

Parameter	Tetany Group (n = 5)	Nontetany Group (n = 11)	p Value
Age (years)	33 ± 16	26 ± 14	0.430
Sex (women/men)	5/0	7/4	0.245
FT3 (pmol/l)	3.6 ± 0.9	6.5 ± 0.6	0.112
FT4 (nmol/l)	10.6 ± 5.3	17.0 ± 11.0	0.241
TSH (μU/ml)	1.1 ± 2.4	0.4 ± 0.9	0.401
TBII (%)	41 ± 34	47 ± 23	0.703
Osteocalcin (ng/ml)	26 ± 18	20 ± 11	0.426
Alkaline phosphatase (bone-specific) (U/l)	142 ± 30	77 ± 20	0.095
Pyridinoline/creatinine (nmol/mmol Cr)	111 ± 129	182 ± 199	0.479
Deoxypyridinoline/ creatinine (nmol/mmol Cr)	23 ± 24	41 ± 44	0.412
Cholesterol (mmol/l)	4.69 ± 0.35	3.86 ± 0.23	0.069
Operation time (min)	75 ± 40	62 ± 18	0.307
Blood loss (g)	96 ± 26	99 ± 65	0.932
Excised amount of thyroid (g)	50 ± 46	48 ± 48	0.933
Estimated remnant thyroid (g)	4.0 ± 0.8	4.2 ± 1.7	0.766

Values are given as mean ± SD.
* Significant.
TBII = thyroid-binding inhibitory immunoglobulin; TSH = thyroid-stimulating hormone.

nin in physiologic concentrations has no effect on calcium homeostasis in humans.[19] Further, McHenry et al[16] recently reported that serum calcitonin levels were essentially unchanged after thyroid surgery. We also confirmed no significant change after subtotal thyroidectomy in the other set of patients with Graves disease.

Table 4. DIFFERENCES IN THE BIOCHEMICAL DATA BETWEEN THE TWO GROUPS

Parameter	Tetany Group (n = 5)	Nontetany Group (n = 11)	p Value
Serum calcium (mmol/l)	2.49 ± 0.05	2.58 ± 0.10	0.069
Ionized calcium (mmol/l)	1.17 ± 0.05	1.23 ± 0.04	0.015*
Serum phosphate (mmol/l)	1.40 ± 0.18	1.52 ± 0.24	0.339
Magnesium (mmol/l)	0.87 ± 0.03	0.80 ± 0.02	0.061
iPTH (pmol/l)	3.11 ± 0.33	1.17 ± 0.23	0.000*
25OHD (nmol/l)	27 ± 7	49 ± 5	0.001*
$1,25(OH)_2D$ (pmol/l)	102 ± 11	48 ± 8	0.027*
$1,25(OH)_2D/25OHD \times 10^3$	4.95 ± 0.71	1.28 ± 0.71	0.001*

Values are given as mean ± SD.
* Significant
iPTH = intact parathyroid hormone.

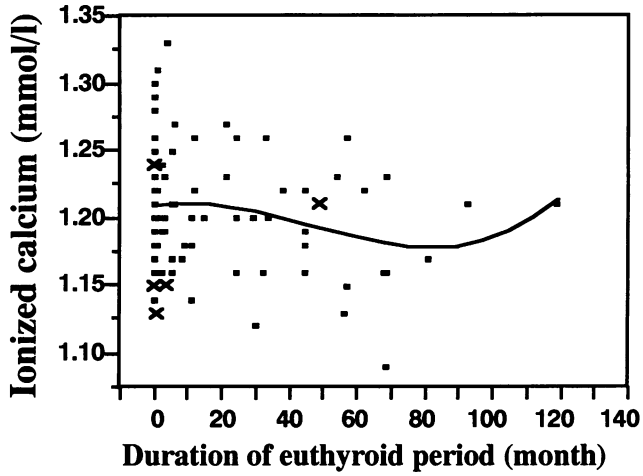

Figure 3. Relation between the duration of a euthyroid period and the preoperative serum ionized calcium level. Values for patients with tetany (X) and those for the others (■).

Michie et al[5] showed that an important role for hypocalcemia after thyroidectomy for thyrotoxicosis was a rapid reversal of an osteodystrophy that existed before surgery, and this theory has been supported by other investigators.[6,7] Recalcification tetany, referred to as "hungry bone syndrome," is well recognized after surgery in primary hyperparathyroidism, whereas there are marked differences in the metabolism of calcium and other minerals between patients with primary hyperparathyroidism and those with Graves disease. In patients with primary hyperparathyroidism, a negative calcium balance usually continues until the resection of the pathologic parathyroid gland(s), whereas antithyroid drugs led to some restoration of the lost bone in patients with Graves disease, in whom accelerated bone metabolism with a negative calcium balance has been frequently found in the hyperthyroid state.[10,20] Krolner et al[10] reported that patients treated for thyrotoxicosis with antithyroid drugs have a significant recovery of bone mineral density.

Considering these findings, a more important factor for postoperative hypocalcemia and tetany is the extent of bone restoration and calcium homeostasis, rather than the rapid reversal of an osteodystrophy after surgery.

Our previous study of the predictive risk factor analysis for postoperative tetany in patients with Graves disease suggested that parathyroid damage may not be the sole cause.[8] This is evidenced by the fact that postoperative tetany developed in only 4 of 15 patients with severe hypoparathyroidism (defined as an undetectable serum iPTH level after surgery). Searching for the differences between the patients with and without postoperative tetany despite the decreased hypoparathyroid function is important for clarifying the mechanism(s) of postoperative tetany. There-

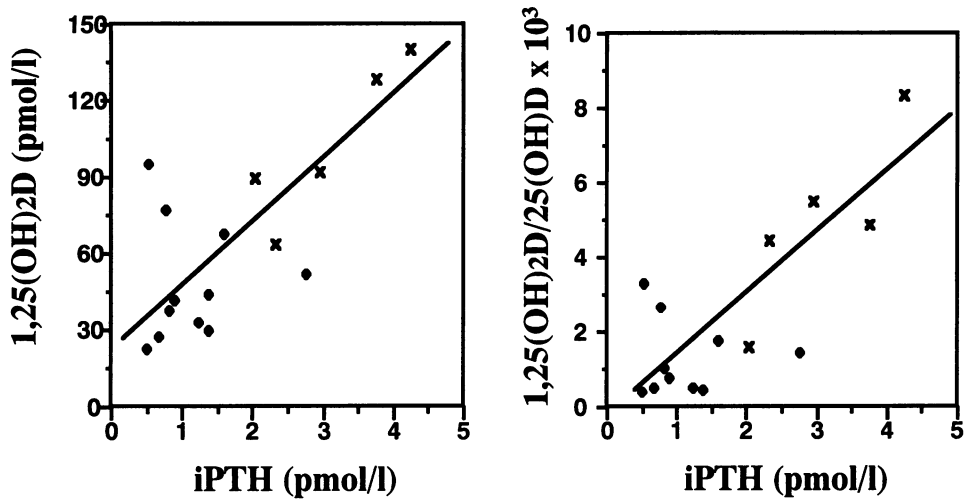

Figure 4. Correlations between preoperative serum values of intact parathyroid hormone and $1,25(OH)_2D$ or $1,25(OH)_2D/25OHD \times 10^3$ ($r = 0.74$, $p = 0.0011$ and $r = 0.88$, p,=,0.0005, respectively). Values for patients with tetany (**X**) and those without tetany (solid diamond).

fore, we focused on these patients, plus the one patient with a below-normal iPTH level in whom tetany developed.

The most significant difference between patients with and without tetany was the $1,25(OH)_2D/25OHD$ ratio, which indicates renal 25OHD-1-hydroxylase activity. PTH is essential for regulating renal conversion of 25OHD to $1,25(OH)_2D$ in response to increasing calcium and phosphorus requirements of the body.[21,22] Several studies have shown increased circulating levels of PTH and $1,25(OH)_2D$ in calcium-deficient animals.[22,23] A marked increase in the serum level of $1,25(OH)_2D$ has been recognized as a biochemical hallmark of lactation in the rat.[24,25] This elevation seemed to occur in response to the additional calcium demand for milk production during this period. During hyperthyroidism, the chronic net loss of calcium is expected as a result of reduced intestinal calcium absorption in addition to bone resorption. Therefore, calcium intake should be increased during bone restoration in patients with Graves disease after antithyroid drug therapy. The lower serum calcium level could be interpreted as being caused by a considerable amount of calcium flux into bone during the treatment. McHenry et al[16] reported low serum levels of calcium with elevated PTH concentrations in patients with medically controlled hyperthyroidism. Conversely, in hyperthyroidism, calcium release from bone leads to an increase in the serum calcium level, resulting in suppression of PTH and $1,25(OH)_2D$.

Taken together, the results of animal studies and the present study indicate that patients with high levels of serum PTH and $1,25(OH)_2D$, by increased activity of 25OHD-1-

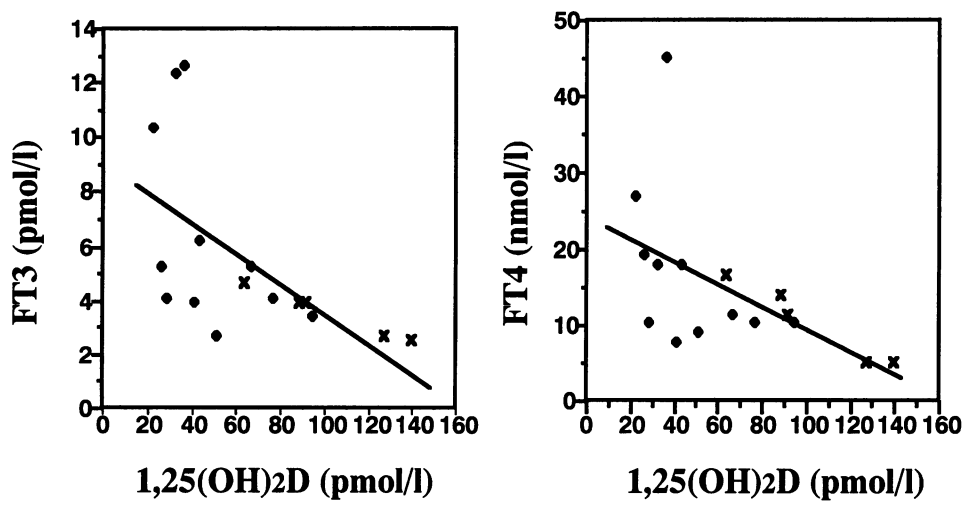

Figure 5. Negative correlations between preoperative serum levels of $1,25(OH)_2D$ and free triiodothyronine (FT3) or free thyroxine (FT4) ($r = -0.60$, $p = 0.0145$ and $r = -0.55$, $p = 0.0271$, respectively). Values for patients with tetany (**X**) and those without tetany (solid diamond).

Table 5. CHANGES IN BIOCHEMICAL INDICES AFTER THYROIDECTOMY FOR THE TWO GROUPS

Parameter	Tetany Group (n = 5)	Nontetany Group (n = 11)	p Value
Serum calcium (mmol/l)	−0.51 ± 0.1	−0.21 ± 0.11	0.000*
Ionized calcium (mmol/l)	−0.26 ± 0.3	−0.13 ± 0.04	0.000*
Serum phosphate (mmol/l)	0.12 ± 0.27	0.09 ± 0.18	0.785
Magnesium (mmol/l)	−0.11 ± 0.02	−0.03 ± 0.02	0.014*
iPTH (pmol/l)	−2.45 ± 0.36	−0.64 ± 0.24	0.000*
25OHD (nmol/l)	4.49 ± 2.13	−3.49 ± 1.50	0.009*
$1,25(OH)_2D$ (pmol/l)	−37.4 ± 5.1	−7.2 ± 3.2	0.000*
$1,25(OH)_2D/25OHD \times 10^3$	−2.24 ± 0.38	−0.12 ± 0.25	0.006*

Calculated by values obtained at the first operative day minus preoperative values; values are given as mean ± SD.
* Significant
iPTH = intact parathyroid hormone.

hydroxylase (secondary hyperparathyroidism) to adapt to relative calcium deficiency, are susceptible to tetany under the condition of hypoparathyroid after surgery. Conversely, in patients with hypercalcemia, frequently observed in the hyperthyroid state, tetany may not develop, even if the parathyroid glands are damaged transiently during surgery. Bouillon et al[26] reported that the $1,25(OH)_2D/25OHD$ ratio, used as an indicator of 25OHD-1-hydroxylase activity, was suppressed in hyperthyroidism and increased in hypothyroidism.

We observed relatively low levels of 25-hydroxyvitamin D in patients with Graves disease, in agreement with the report by Mosekilde et al,[27] whereas in another study the level in patients with hyperthyroidism was not different from control subjects.[28] The discrepancies between the different studies can be explained by differences in dietary vitamin D intake and exposure to sunlight. A low serum 25(OH)D concentration is the most significant diagnostic marker of vitamin D deficiency.[29] The low levels of 25(OH)D may also be explained by an increased metabolic clearance of 25(OH)D. Vieth et al[30] and Clements et al[31] demonstrated that the vitamin D requirement was increased in rats treated with low dietary calcium. Clements et al also showed that the rate of inactivation of vitamin D in the liver is increased by calcium deprivation. The effect was mediated by $1,25(OH)_2D$, produced in response to secondary hyperparathyroidism, which promotes hepatic conversion of vitamin D to polar inactivation products that are excreted in bile. Gascon-Barré et al[32] reported that patients with urolithiasis placed on diets containing low calcium (300 mg/day) had significantly lower levels of 25(OH)D and significantly higher levels of $1,25(OH)_2D$ than those with high dietary calcium (1000 mg/day). From our findings, we cannot attribute the lower values of 25(OH)D in the tetany group to calcium deficiency alone. Because vitamin D deficiency also results in increased activity of the renal 25OHD-1-hydroxylase activity, patients in whom tetany developed in our series may have had vitamin D deficiency as well as calcium deficiency. In Japan, there is no routine fortification

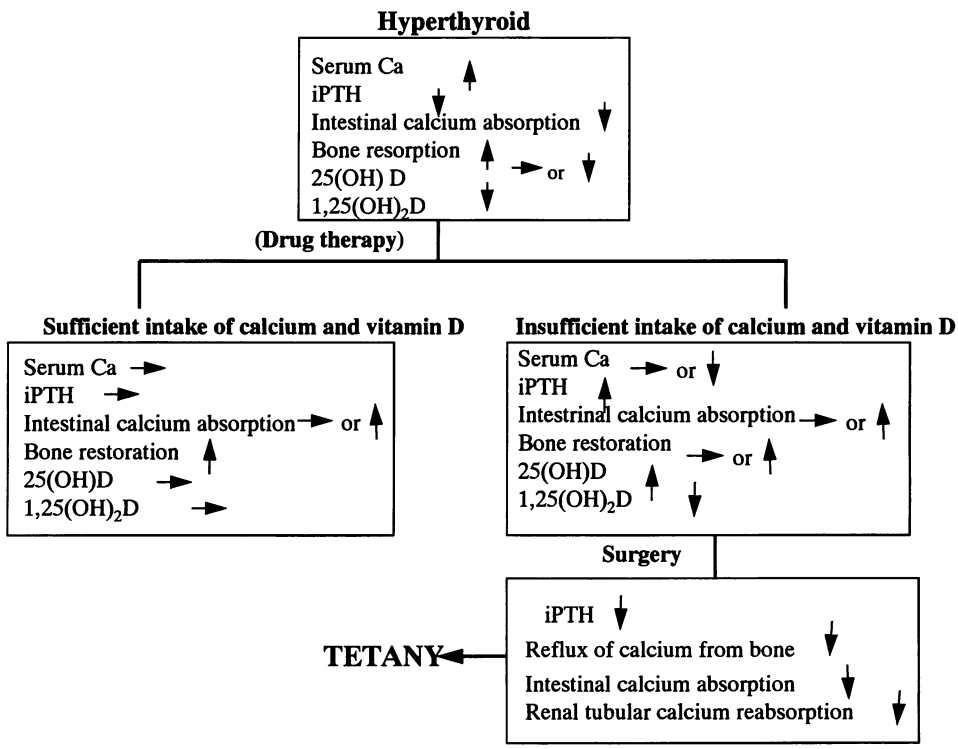

Figure 6. Mechanisms for transient postoperative tetany in patients with Graves disease in relation to serum calcium homeostasis after antithyroid drug therapy.

of foods with vitamin D, and dietary calcium intake is lower than the recommended dose for adults (*i.e.*, 600 mg), although we did not assess the intake of calcium and vitamin D in this study.

From the literature and our own findings, we could illustrate the mechanisms for transient postoperative tetany (Fig. 6). The rising PTH and $1,25(OH)_2D$ levels mobilize calcium to maintain the blood calcium level and increase the efficacy of intestinal absorption to meet the demands of the mineralizing skeleton. Because most of the patients with tetany underwent surgery after a short euthyroid period (see Fig. 3), we speculate that postoperative hypocalcemia or tetany is not necessarily related to the degree of bone restoration, as originally thought, but is related to calcium and vitamin D deficiency during antithyroid drug therapy.

The present data point out another interesting observation regarding the management of patients with postoperative hypocalcemia. In recent years the synthetic analog of vitamin D, $1\alpha OH$, has been the mainstay of treatment for hypocalcemia instead of vitamin D. $1\alpha OH$ is rapidly converted to $1,25(OH)_2D$ in the liver. The majority of patients with Graves disease with postoperative hypocalcemia can be readily treated by administration of this analog for a short period; however, there are some patients with prolonged hypocalcemia despite the recovery of parathyroid function and normal range of serum $1,25(OH)_2D$. Considering the etiology of postoperative tetany set forth in this study, vitamin D and calcium administration may be considered in such patients with prolonged hypocalcemia who have lower 25(OH)D levels because of vitamin deficiency and the reduced 25-hydroxylase activity of vitamin D. Heaney et al[33] recently reported that vitamin D and 25(OH)D cause dose-dependent increases in calcium absorption efficiency without a detectable rise in circulating total $1,25(OH)_2D$. Bell et al[34] demonstrated that 25(OH)D and $1,25(OH)_2D$ act together to maintain serum calcium levels by enhancing intestinal absorption of calcium and release of calcium from bone.

Our results suggest that postoperative tetany occurs in patients with Graves disease with secondary hyperparathyroidism because of a relative deficiency of calcium and vitamin D concomitant with hypoparathyroidism caused by surgery. Calcium and vitamin D supplements may be recommended in these patients during the medical treatment for efficient bone restoration, and also in patients who plan to undergo surgery to prevent postoperative tetany.

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