Estimation of free calcium levels after thyroidectomy

Hitoshi Miki, Hiroyuki Inoue, Masayo Kitaichi, Eitaro Masuda, Kansei Komaki, and Yasumasa Monden

Second Department of Surgery, The University of Tokushima School of Medicine, Tokushima, Japan

Abstract : Total calcium is routinely measured after thyroidectomy in a clinical setting, while the measurement or calculation of the free calcium level is not generally performed. We reviewed total and free calcium levels in patients who underwent lobectomy (n=15), subtotal thyroidectomy (n=15) and total thyroidectomy (n=15). Postoperative total calcium levels decreased significantly in comparison to preoperative levels in all thyroidectomies ($p<0.01$), and this fall was significantly related to the extent of surgery ($p<0.01$). In contrast, there was no significant difference between preoperative and postoperative free calcium levels in patients undergoing lobectomy, although we found a decrease in free calcium levels after both subtotal and total thyroidectomy. Total protein levels decreased regardless of the type of operation. Serum total calcium levels were thought to be altered by serum protein levels through the change of protein-bound calcium levels. When examined for free calcium levels, some patients were administered unnecessary calcium supplementation because hypocalcemia had been judged from the total calcium level. Since the wrong diagnosis may be given with regard to hypoparathyroidism by measurement of total calcium levels alone, we propose that free calcium levels should be routinely measured or calculated after thyroidectomy. J. Med. Invest. 44 : 83-87, 1997

Key Words : *free calcium, thyroidectomy, hypocalcemia*

INTRODUCTION

Postoperative hypocalcemia is one of complication of thyroidectomy ; its incidence is more common after total thyroidectomy than after other more conservative thyroidectomies. The reported incidence of transient hypocalcemia ranges from 1.6% to 9.3% after subtotal thyroidectomy and from 6.9% to 42% after total thyroidectomy (1-3). In contrast, permanent hypocalcemia has been reported in 0.2% to 3% of patients after subtotal thyroidectomy and in 0.4% to 29% of patients after total thyroidectomy (2,4,5). The pathogenesis of hypocalcemia after thyroidectomy is not completely understood.

To determine the incidence of hypocalcemia after thyroidectomy in our institution, we reviewed serum calcium levels and total protein levels in patients who underwent thyroidectomy. We also studied the cause of hypocalcemia after thyroidectomy and the validity of calcium supplementation as a treatment for hypocalcemia.

PATIENTS AND METHODS

We reviewed three groups of consecutive patients who underwent thyroidectomy at Tokushima University Hospital : Fifteen patients underwent unilateral lobectomy for a benign nodule of the thyroid gland ; fifteen patients underwent subtotal thyroidectomy for papillary carcinoma, in which the upper portion of the contralateral lobe was retained, with unilateral modified neck dissection that included paratracheal, superficial and deep cervical lymph nodes of the thyroid gland ; and fifteen patients underwent total thyroidectomy with bilateral modified neck dissection for papillary carcinoma. Resection of the trachea was associated with total thyroidectomy in three patients because of the invasion of the thyroid carcinoma. The mean age±SD of patients with lobectomy, subtotal thyroidectomy and total thyroidectomy were 50.8±15.3, 53.1±10.4, and 57.1±15.5 years, respectively, and there was no significant difference in age among the three groups.

Serum total calcium and total protein levels were serially measured. Normal values of total calcium and protein in our laboratory ranged from 8.0 to 9.6 mg/dL, and from 6.5 to 8.2 g/dL, respectively. For each patient the free calcium level was retrospectively calculated according to the following formula(6) :

Ca^{++}(mmol/L)=[59.88×total calcium (mg/dL)-3.33×total proteins (g/dL)]/[4×{10×total proteins (mg/dL)+60}]

The individual nadirs of total calcium, total protein and free calcium levels calculated after thyroidectomy were determined in every patient, and the influence of the three types of operations—lobectomy, subtotal thyroidectomy and total thyroidectomy—on calcium levels was evaluated

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[1] Address correspondence and reprint requests to Hitoshi Miki, M.D., Ph.D., Second Department of Surgery, The University of Tokushima School of Medicine, 3-18-15, Kuramoto-cho, Tokushima, Japan.

by these postoperative nadirs. Statistical analysis consisted of paired Student's t-test, chi-square test, and single factor analysis of variance.

RESULTS

Serum Total Calcium Levels

There was no significant difference in the preoperative mean levels of total calcium among the three groups (Table 1), whereas nadirs after thyroidectomies which were significantly lower than preoperative levels in all groups ($p<0.01$, Fig.1), was influenced by the extent of the surgical procedure ($p<0.05$). The mean nadirs after lobectomy, subtotal thyroidectomy and total thyroidectomy were 8.1±0.4 mg/dL (mean±SD), 7.6± 0.4 mg/dL, and 6.8±0.8 mg/dL, respectively. Serum total calcium nadirs even after lobectomy were below normal in 6 of 15 patients, and those after total thyroidectomy were below normal in all patients except one.

Serum Total Protein Levels

It has been known that the total protein level can affect the total calcium level through the change of the level of protein-bound calcium, which comprises about half the total calcium (2). The preoperative total protein levels showed no significant difference among the three groups (Table 1). Serum total protein levels significantly decreased after every procedure in comparison to preoperative levels ($p<0.01$,Fig.2). However, a correlation between postoperative nadirs and the extent of surgical procedures was not found.

Serum Free Calcium Levels

Serum free calcium levels were calculated from the serum levels of total calcium and total protein in every patient as aforementioned. A normal range of free calcium was considered to be the mean level±2 SD of the preoperative levels of all patients, which in this study was between 0.85 mmol/L and 1.04 mmol/L. The mean preoperative levels of the three groups were almost the same (Table 1). There was no significant difference in the free calcium levels between those before and after lobectomy (Fig.3), although a decrease in serum total calcium levels was observed in most patients who underwent lobectomy. After subtotal thyroidectomy, free calcium levels significantly decreased in comparison with preoperative levels ($p<0.01$), but the free calcium level after subtotal thyroidectomy remained within normal limits in all patients except one. The mean postoperative nadir, 0.89 mmol/L was within normal range. A fall in serum free calcium levels was also found after total thyroidectomy ($p<0.01$)

Table 1. Mean (SD) levels of total calcium, total protein and free calcium before and after thyroidectomies

	Lobectomy (*n*=15)		Subtotal Thyroidectomy (*n*=15)		Total Thyroidectomy (*n*=15)	
	Before	After (Nadir)	Before	After (Nadir)	Befor	After (Nadir)
Total Calcium (mg/dL)	8.7 (0.4)	8.1 (0.4)	8.6 (0.4)	7.6 (0.4)**	8.8 (0.3)	6.8 (0.8)***
Total Protein (g/dL)	7.0 (0.4)	6.4 (0.4)	7.1 (0.4)	6.2 (0.5)	7.2 (0.5)	6.0 (0.7)
Free Calcium* (mmol/L)	0.96 (0.04)	0.94 (0.04)	0.93 (0.04)	0.89 (0.04)**	0.95(0.05)	0.85 (0.09)**

*Free calcium levels were calculated values (see text).
**p<0.05 : versus lobectomy.
***p<0.01 : versus subtotal thyroidectomy.

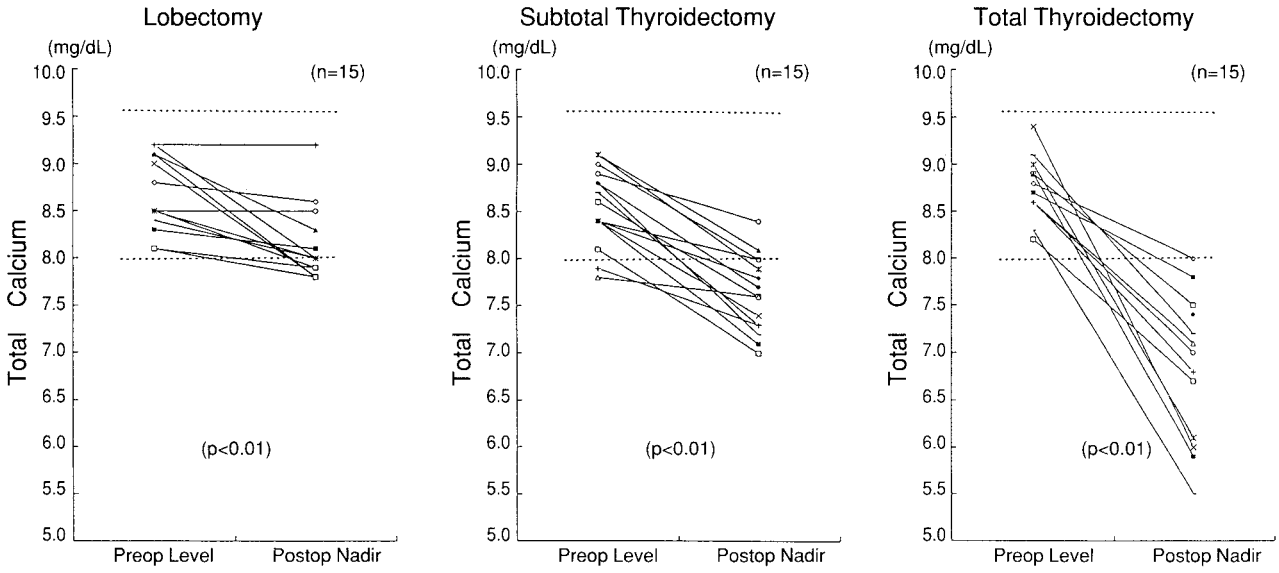

Fig.1. Total calcium levels before and after thyroidectomies.
Postoperative levels were represented by nadirs after thyroidectomies. Dotted lines indicate the normal range. There were significant differences between preoperative levels and postoperative nadirs in all thyroidectomies.

and the mean nadir after total thyroidectomy was 0.85 mmol/L. Postoperative nadirs after total thyroidectomy remained within normal limits in 8 of 15 patients.

Postoperative Paresthesia and Tetany

There were no cases of paresthesia or tetany after lobectomy. One of 15 patients with subtotal thyroidectomy developed transient tingling of the hands, whereas 5 of 15 patients who underwent total thyroidectomy developed this symptom. Tetany appeared in only one patient who underwent total thyroidectomy. The appearance rate of postoperative symptoms increased in relationship to the extent of thyroid resection ($p<0.01$). However, of 15 patients who underwent total thyroidectomy, neither the mean nadirs of serum total calcium levels, nor the free calcium levels in six patients with symptoms, were significantly different from those in nine patients without symptoms. Moreover, the differences in free calcium levels between preoperative and postoperative levels in six patients with symptoms were almost the same as those in patients without symptoms.

Calcium Supplementation

Initiation of calcium supplementation was decided after consideration of both serum total calcium levels and symptoms. No patients required supplementation after lobectomy (Fig.4). In contrast, 2 of 15 patients were administered calcium gluconate intravenously for only a short period (2 days and 9 days) after subtotal thyroidectomy because of low serum levels of total calcium

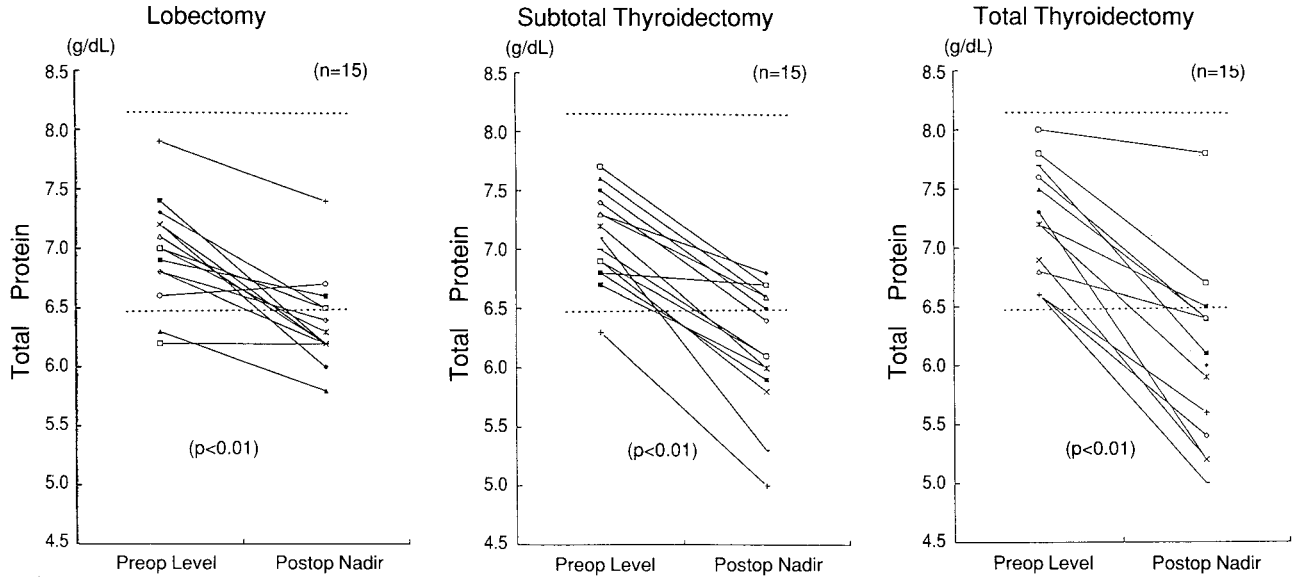

Fig. 2. Total protein levels before and after thyroidectomies.
Postoperative levels were represented by nadirs after thyroidectomies. Dotted lines indicate the normal range. There were significant differences between preoperative levels and postoperative nadirs in all thyroidectomies.

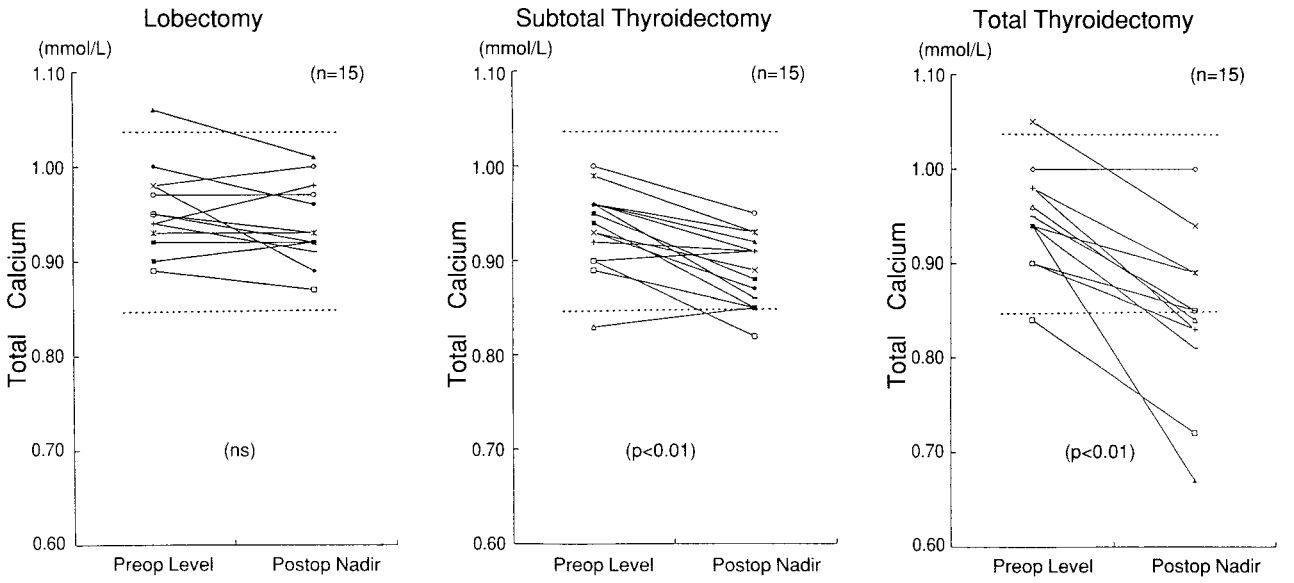

Fig. 3. Free calcium levels before and after thyroidectomies.
Free calcium levels were calculated values, and postoperative levels were represented by nadirs after thyroidectomies. The range between the dotted lines shows the range of mean±2 SD of the preoperative free calcium levels. There were significant differences between the preoperative levels and the postoperative nadirs in all thyroidectomies except lobectomy.

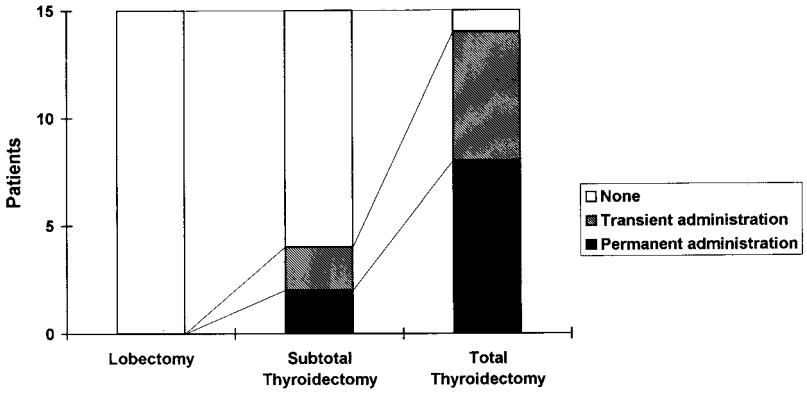

Fig. 4. Calcium supplementation.

(7.3 mg/dL and 7.2 mg/dL). However, the serum free calcium nadirs in these 2 patients remained within normal limits (0.86 mmol/L and 0.91 mmol/L). Calcitriol was permanently prescribed for 2 patients after subtotal thyroidectomy, and the serum free calcium levels during supplementation in these patients were still close to the lower limit of normal (0.86 mmol/L and 0.87 mmol/L) in spite of supplementation. After total thyroidectomy, vitamin D supplementation was administered transiently in 6 of 15 patients. However, postoperative free calcium levels before the administration of vitamin D remained within the normal range in 4 of these 6 patients with transient supplementation (4 months to 20 months). In the other 2 patients, the free calcium levels before administration of vitamin D were below the normal limit (0.67 mmol/L and 0.84 mmol/L). Vitamin D supplementation for these 2 patients was halted after 18 months and after 36 months, respectively, because of the recovery of function of autotransplanted parathyroid tissue. Vitamin D was administered permanently in 8 of 15 patients with total thyroidectomy. Free calcium levels before vitamin D supplementation were above the lower limit of normal in 2 of these 8 patients. In contrast, the free calcium levels before supplementation in the other 6 patients were below the lower limit.

DISCUSSION

Postoperative hypocalcemia is sometimes encountered after thyroidectomy and is known as a major source of postoperative morbidity in patients who have undergone thyroidectomy(1-3,5,7). In this study, postoperative serum levels of total calcium were significantly lower than preoperative levels in any types of thyroidectomy. However, postoperative levels of free calcium in most patients undergoing lobectomy or subtotal thyroidectomy remained within normal limits. There was an obvious discrepancy between the total calcium level and the free calcium level, and this discrepancy may be explained by the decrease in the serum levels of total protein after surgery. Since total protein levels fell postoperatively regardless of the extent of thyroidectomy, the decrease in total protein levels seemed to be due to the nonspecific release of an antidiuretic hormone in response to the general stress of surgery and consequent water retention by the kidneys and hemodilution, as others have suggested (2,3,5). There are three forms of calcium in the extracellular fluids including blood : (a) free calcium, which has the physiological properties of calcium and composes approximately half of the total calcium ; (b) protein-bound calcium, which also composes roughly half of the total calcium and is altered easily by total protein levels ; and (c) a small amount of calcium complexed with organic acids(2). The fall in the total protein level after lobectomy decreased the level of total calcium through the decrease in the level of protein-bound calcium, despite a stable free calcium level. Therefore, the evaluation of free calcium levels seems to be essential to determine the parathyroid function. It also seems to be important because serum free calcium levels can exert influence on intracellular processes such as muscular contraction and hormonal secretion as well as on the formation and resorption of bone through parathyroid hormone(8).

Free calcium levels dropped significantly after both subtotal and total thyroidectomy, and postoperative free calcium levels were below normal in 7 of 15 patients with total thyroidectomy. These decreases in free calcium levels must have resulted from hypoparathyroidism due to the removal and/or the ischemia of parathyroid tissues.

Tetany and paresthesia such as tingling around the mouth and in the distal extremities are commonly seen with hypocalcemia(9). The appearance of these symptoms is thought to be related to the degree or speed of decrease in calcium levels after thyroidectomy. These symptoms were found postoperatively in 7% of patients with subtotal thyroidectomy and in 40% of patients with total thyroidectomy, but no patients developed them after lobectomy. These symptoms seemed to be related to the extent of the surgical procedure. However, appearance was independent of the serum levels of total and free calcium in our study. The patients with symptoms revealed an equal decrease in free calcium levels after thyroidectomy as patients without symptoms. Tetany and paresthesia might be caused by the simple consequence of anxiety or hysterical reaction as well as by true hypocalcemia(10,11).

Postoperative short-term calcium supplementation was given to two patients after subtotal thyroidectomy because of their low serum levels of total calcium. The postoperative free calcium nadirs before supplementation, however, remained within normal limits in these patients. Supplementation in these patients might be unnecessary. In 8 of 16 patients who received vitamin D supplementation for more than four months, free calcium levels before initiation of supplementation remained within normal limits. For these eight patients, long-term supplementation of vitamin D might be unnecessary. Unnecessary supplementation may cause hypercalcemia and hypercalciuria which would result in renal failure. The evaluation of free calcium levels seems to be very important in treating patients with calcium supplementation. Although

the serum total calcium level is routinely measured in a clinical setting, we propose that the serum free calcium level should be measured or calculated in order to check the parathyroid function after thyroidectomy and to avoid unnecessary calcium supplementation, because the fall in the serum total protein level due to hemodilution associated with the stress of surgery causes a decrease in the serum total calcium level unrelated to the parathyroid function.

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