Persistent Parathyroid Hormone Elevation Following Curative Parathyroidectomy for Primary Hyperparathyroidism

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Background: Persistent elevation of parathyroid hormone (PTH) levels following parathyroidectomy may indicate residual abnormal parathyroid tissue.

Objective: To determine the clinical significance and risk factors for persistent PTH elevation following curative parathyroidectomy.

Methods: A prospective study of consecutive patients with primary hyperparathyroidism who had resolution of hypercalcemia following parathyroidectomy. Patients with low or normal serum calcium and increased PTH levels postoperatively were identified, and serial calcium and PTH levels and clinical course were monitored. A multivariate analysis was performed to identify features associated with an elevated postoperative PTH level.

Results: Of 85 patients with resolution of hypercalcemia following parathyroidectomy, postoperative PTH levels were elevated in 23 (27%) (mean, 99 pg/mL; range, 70-194 pg/mL) and normal in 62 (mean, 30 pg/mL; range, 3-65 pg/mL) (P<.001). No significant differences in preoperative or postoperative calcium or preoperative PTH levels were found between groups. Among patients with persistent PTH elevation, 18 had adenoma and 5 had multiglandular disease, compared with 52 with adenoma and 10 with multiglandular disease in patients with normal postoperative PTH levels (P>.05). Multivariate analysis demonstrated that black race and musculoskeletal symptoms were associated with an elevated postoperative PTH level (P=.01). After an average 16-month follow-up, PTH levels normalized in 13 patients, decreased in 5, and were unchanged in 2. Three patients were lost to follow-up.

Conclusions: Persistent PTH elevation occurs in 27% of patients following curative parathyroidectomy and is usually a transient phenomenon more common in patients with musculoskeletal symptoms and of the black race. It is not a manifestation of persistent disease but is most likely a secondary response to bone remineralization.


PERSISTENTLY elevated parathyroid hormone (PTH) levels with normocalcemia have previously been documented following parathyroidectomy for primary hyperparathyroidism.1-7 It has been referred to as postoperative secondary hyperparathyroidism, implying that it occurs as a result of a compensatory response to an abnormality in calcium homeostasis.6 However, the pathogenesis of this phenomenon has not been clearly elucidated. The purpose of our study was to review our experience with the surgical treatment of primary sporadic hyperparathyroidism and to determine the frequency of occurrence, clinical significance, and risk factors for development of persistent postoperative PTH level elevation following apparently curative parathyroidectomy.

From January 1991 until March 2001, 85 patients (74 women and 11 men; average age, 56 years; range, 28-76 years) with primary hyperparathyroidism underwent curative parathyroidectomies. Their presenting manifestations are listed in Table 1. Only 13 patients (15%) were asymptomatic. A bilateral neck exploration was performed in all patients. Patients with a single or double adenoma were treated by adenoma excision alone. Patients with parathyroid hyperplasia were treated with subtotal parathyroidectomy and transcervical thymectomy. Manifestations included adenoma in 70 patients (82%), double adenoma in 8 (9%), and 4-gland hyperplasia in 7 (8%). The average weight of the resected parathyroid tissue was 1588 mg (range, 70-13470 mg). All patients had low

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PATIENTS AND METHODS

All patients undergoing parathyroidectomy for primary hyperparathyroidism between January 1991 and March 2001 were evaluated prospectively. Sex, race, age, and the presence of symptoms associated with hyperparathyroidism were determined. Preoperative laboratory evaluations included measurement of serum PTH, calcium, alkaline phosphatase, phosphorus, serum urea nitrogen, and creatinine. Serum intact PTH levels were measured using a 2-site immunoradiometric assay (Cleveland Clinic Foundation Laboratory, Cleveland, Ohio).

Assessed perioperative data included the weight and pathologic characteristics of the resected parathyroid tissue, postoperative calcium levels, and the presence of symptoms of hypocalcemia. A serum calcium level was routinely obtained the morning after surgery. Calcium levels were checked again and PTH levels measured at the initial postoperative visit, which usually occurred 10 to 14 days after surgery. For patients with elevated postoperative PTH levels (defined as a PTH level ≥70 pg/mL), serial calcium and PTH levels were monitored. All patients were evaluated for symptoms associated with hyperparathyroidism.

Clinical and laboratory data in patients with elevated postoperative PTH levels were compared with those of patients with normal postoperative PTH levels to assess what factors might affect PTH levels postoperatively. Pearson correlations were calculated where indicated. Stepwise logistic regression analysis with a variable entrance criteria of 0.10 was conducted to identify demographic factors, laboratory values, symptoms, and pathologic findings associated with an elevated postoperative PTH level (model \( \chi^2 = 10.7; P = .01 \)). Analyzed variables included age; sex; presence of symptoms associated with hyperparathyroidism; preoperative levels of calcium, PTH, alkaline phosphatase, serum urea nitrogen, and creatinine; and the weight of the resected parathyroid tissue. A P value lower than .05 was considered statistically significant. Statistical analysis was performed using SPSS statistical analysis software (SPSS Inc, Chicago, Ill).

Among patients with persistent PTH elevation, 18 had adenoma and 5 had multiglandular disease compared with 52 with adenoma and 10 with multiglandular disease in patients with normal postoperative PTH levels (\( P = .52 \)). There was also no significant difference in the weight of the resected tissue: 1479 mg (range, 70-13470 mg) vs 1851 mg (range, 100-8900 mg) in those with persistent elevation and normalization of their PTH levels, respectively (\( P = .09 \)). We performed a multivariate analysis and determined that black race (\( P = .03 \)) and the presence of musculoskeletal symptoms (\( P = .08 \)) were associated with an elevated postoperative PTH level (\( \chi^2 = 7.76; P = .002 \)). Women were also more likely to have an elevated postoperative PTH level, although the likelihood was not statistically significant (\( P = .13 \)).

After an average follow-up of 16 months, 20 patients with an elevated postoperative PTH level had follow-up data available. All 20 were asymptomatic and had either normal or low calcium levels: 13 experienced normalization of their PTH levels; 5 showed a progressive decrease; and 2 showed no change. Three patients were lost to follow-up. No variable was identified that was predictive of normalization of PTH. Among the 13 patients with normalization of their PTH levels, 8 had more rigorous follow-up and were shown to experience normalization of PTH levels within 1 to 5 months following parathyroidectomy. The remaining 5 patients had interrupted follow-up and were proven to have normalization of PTH levels within 1 to 8½ years following parathyroidectomy.

The postoperative course following successful surgical treatment of primary hyperparathyroidism is known to

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<th>Manifestation</th>
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Table 1. Presenting Manifestations in 85 Consecutive Patients With Primary Hyperparathyroidism


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be characterized by a rapid decline in serum PTH and calcium levels. Most patients experience a profound drop in PTH levels on the evening of surgery. Many patients develop temporary hypoparathyroidism with PTH levels lower than 10 pg/mL, a phenomenon that occurs as a result of “bone hunger” or suppression of the normal parathyroid glands by chronic hypercalcemia.8 Mandal and Udelsman9 demonstrated that 77 (99%) of 78 patients experienced a drop in PTH levels on the evening of surgery, 55 of whom had intact PTH levels lower than 10 pg/mL. Most of these patients had experienced rapid normalization of calcium homeostasis and parathyroid function by the first postoperative visit.

In the present series, 23 (27%) of 85 patients undergoing curative parathyroidectomy for primary hyperparathyroidism had elevated PTH levels postoperatively despite resolution of their hypercalcemia. These findings confirm the results of other series where persistent elevation of postoperative PTH levels occurred in 11% to 40% of patients (Table 3).1-7 The pathogenesis of this phenomenon remains unclear. Possible explanations include persistent or impending recurrent hyperparathyroidism, impaired renal function, and bone remineralization.

**PERSISTENT OR IMPELLING RECURRENT HYPERPARATHYROIDISM**

Previous reports have demonstrated microscopic hyperplasia in the remaining parathyroid glands after excision of a single adenoma, suggesting the possibility of persistent disease as an explanation for the elevated PTH levels.9 No patient in our series with persistent PTH level elevation and a mean 16-month follow-up developed recurrent hypercalcemia. In other series as well, hypercalcemia has not occurred in this subset of patients. McHenry and colleagues10 reported that patients with elevated postoperative PTH levels and low or normal serum calcium levels responded to oral calcium load tests exactly as normal control patients responded, distinguishing postoperative secondary hyperparathyroidism from persistent hyperparathyroidism. Westerdahl and colleagues7 recently reported that patients who had an elevated PTH level 2 weeks after surgery had initially experienced a decline in PTH (as measured within four days after adenoma excision) comparable with patients who had normal PTH levels 2 weeks postoperatively. This finding, combined with the fact that the 2 groups did not vary in relative PTH suppressibility during an oral calcium load test, led the authors to conclude that increased postoperative PTH levels were not likely due to persistent hyperparathyroidism.7

**IMPAIRED RENAL FUNCTION**

Another proposed cause for persistent elevation of PTH is impaired renal function. Duh and colleagues11 reported that their patients with elevated PTH levels postoperatively had significantly higher serum urea nitrogen and serum creatinine levels than patients with normal PTH levels. Bergenfelz et al12 reported that 6 of 13 patients with normal calcium levels and increased PTH levels 1 year following parathyroidectomy for primary hyperparathyroidism had mildly to moderately decreased renal function. It has also been shown that serum levels of intact PTH correlate with serum creatinine levels.2 No patient in our series had impaired renal function, and no differences were observed in serum urea nitrogen and serum creatinine levels between patients with elevated PTH levels and those with normal PTH levels following curative parathyroidectomy (Table 2). A recent study by Westerdahl and colleagues7 showed no difference in renal function, estimated by glomerular filtration rate and
serum creatinine levels, for patients with or without elevated PTH levels 8 weeks after surgery, suggesting that the PTH levels cannot be explained by impaired renal function.

**BONE REMINERALIZATION**

Risk factors for developing postoperative PTH level elevation are also unclear. Other authors have suggested that it is more likely to occur in elderly patients with more severe or advanced hyperparathyroidism. For this reason, we performed a multivariate analysis looking at age, sex, race, symptomatology, biochemical markers, and gland weight to identify variables that might be predictive of persistent postoperative PTH level elevation. In performing this analysis, we found that 85% of our patients had symptoms that could be attributed to hyperparathyroidism, including 47% with musculoskeletal symptoms. In our series, we had 8 patients with osteoporosis, 4 patients with pathologic fractures, and 4 with radiographic evidence of osteopenia. Although severe musculoskeletal disease is uncommon, multiple studies have shown that the bone mineral content in patients with primary hyperparathyroidism is consistently lower than the average for age-, sex-, and race-matched controls. Although we do not routinely determine bone mineral content, 5 of our patients had been referred to us for surgical evaluation because of low bone mineral content.

When we completed our multivariate analysis, we found that the presence of musculoskeletal symptoms and black race were the only factors associated with a persistently elevated postoperative PTH level. Other variables accepted as markers for severity of hyperparathyroidism, such as preoperative calcium and PTH levels and weight of the resected parathyroid tissue, although higher in patients with elevated postoperative PTH levels, were not significantly different from patients with normal postoperative PTH levels (Table 2). We believe that patients with musculoskeletal symptoms are likely to have significant bone turnover with cortical bone remineralization in the postoperative period. This results in a compensatory increase in their PTH secretion to maintain a normal extracellular concentration of ionized calcium. Westerdahl and colleagues documented decreased bone mineral content and higher serum alkaline phosphatase levels preoperatively and higher serum levels of osteocalcin and propeptide of type I collagen in patients with elevated postoperative PTH levels and normal calcium levels. This finding, along with a significant increase in bone mineral content postoperatively, suggests that increased bone turnover with cortical bone remineralization is the cause of this phenomenon.

The explanation for the higher frequency of postoperative PTH elevation in blacks is unknown. Of interest is the fact that black subjects are generally thought to have a higher bone mineral content than age- and sex-matched whites. In one study addressing bone density in hyperparathyroidism, the control value for bone density in black subjects was considered to be 110% of the corresponding value for white control subjects. In white patients with hyperparathyroidism, the initial bone density was below percentile 2.5 of the value for control subjects in 32% of patients and below the mean in 80% of control patients. In black subjects, the initial bone density was below percentile 2.5 of the estimated control value in 18% and below the mean for control patients in 82%. The finding that black race is associated with postoperative PTH elevation cannot be readily explained by bone remineralization and warrants further investigation.

The elevation in postoperative PTH levels observed in our patients with normal calcium levels was usually a transient phenomenon. After an average follow-up of 16 months, PTH levels had normalized in 13 patients, decreased in 5, and increased or remained unchanged in 2. In a study by Leppala et al, bone density was shown to have declined during the years immediately preceding surgery for hyperparathyroidism and then risen by 6.4% during the year following surgery, after which it stabilized. Mautalen and colleagues confirmed that the incremental increase in bone density postoperatively is a limited phenomenon. They reported that the average increase in bone mineral content 9 to 26 months after surgery was 9.9%. No gain was observed 2 years after parathyroidectomy except in 1 patient with extremely severe bone loss. Remineralization of bone seemed to reach its near-maximum point within the first 3 months following curative parathyroidectomy in the study by Mautalen et al and then stabilized, with very little increase in bone mineral content after the first year. However, Silverberg et al have documented that increases in bone mineral content can continue for up to 4 years, and compensatory increases in PTH levels postoperatively have been documented to persist even for 15 years.

We suspect that the increase in bone mineral content occurs over a limited time, probably not exceeding 1 to 2 years after surgery. After that point, further cortical bone remineralization is likely to be minimal; therefore, an increased need for extracellular calcium no longer exists, and stimulation of remaining parathyroid glands may decrease, which would correspond to normalization of PTH levels. This process likely occurs at different intervals postoperatively in different patients based on the severity of their preoperative bone disease. However, we were unable to identify any definite factors that would help predict normalization of PTH levels. Theoretically, oral calcium supplementation may help resolve this phenomenon by providing the additional calcium necessary for active bone remineralization.

In conclusion, we have demonstrated that persistently elevated PTH levels occur in 27% of patients following curative parathyroidectomy. This seems to be a compensatory response to remineralization of cortical bone. This phenomenon occurs most commonly in blacks and in patients with associated musculoskeletal symptoms. It is transient in most patients, resolving within 5 months of surgery. The time of resolution of postoperative PTH level elevation corresponds to the period during which the near-maximum increases in bone mineral content occur in patients with bone disease of hyperparathyroidism. The higher incidence of musculoskeletal symptoms observed in these patients also supports the notion that cortical bone remineralization is the cause.
for the increases in PTH levels seen in patients with normal calcium levels following parathyroidectomy.

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