

Long-term Outcome of Patients With Elevated Parathyroid Hormone Levels After Successful Parathyroidectomy for Sporadic Primary Hyperparathyroidism

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Hypothesis: Untreated long-term elevated parathyroid hormone (PTH) levels after successful parathyroidectomy may predict recurrent hyperparathyroidism (HPT). Although elevated PTH levels have been reported in eucalcemic patients after parathyroidectomy for sporadic primary HPT, the long-term clinical significance of this finding remains unclear.

Design: Retrospective case series.

Setting: Tertiary referral center.

Patients: Five hundred seventy-six consecutive patients with HPT.

Intervention: Parathyroidectomy guided by intraoperative monitoring of PTH levels.

Main Outcome Measures: Overall incidence of elevated PTH levels (measurements of ≥ 70 pg/mL at any time during follow-up) and recurrent HPT (hypercalcemia

and elevated PTH levels more than 6 months after parathyroidectomy).

Results: Of the 505 patients who underwent successful parathyroidectomy in this series and were followed up for more than 6 months, 337 (66.7%) consistently had PTH levels within the reference range, and 168 (33.3%) had elevated PTH levels. Of the 168 patients with elevated PTH levels, only 8 (4.8%) developed recurrent disease. The earliest recurrence occurred 2 years postoperatively. Factors associated with elevated PTH levels included advanced age, higher preoperative PTH levels, and mild postoperative renal insufficiency.

Conclusion: Although one-third of the patients had elevated PTH levels after successful parathyroidectomy, most of these patients with elevated PTH levels (95%) will achieve long-term eucalcemia.

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ELEVATED PARATHYROID HORMONE (PTH) levels in the setting of serum calcium levels within the reference range (hereinafter referred to as normal levels) after successful parathyroidectomy for hyperparathyroidism (HPT) have been reported, with an incidence ranging from 8% to 40%.¹⁻¹⁰ A biochemical finding after parathyroidectomy that fosters understandable concern to referring physicians and treating surgeons alike, the etiology and clinical significance of this phenomenon remain unclear.^{5-8,11-13} Some authors believe that elevated PTH levels are a transient phenomenon,^{3,4,14,15} whereas others assert that this presentation is a dynamic process in which PTH levels normalize 1 year postoperatively or fluctuate with the occasional development of recurrent disease.¹⁶ Advanced age, sex, disease severity, osteoporosis, adenoma size, multigland disease, decreased peripheral sensitivity to PTH, renal failure, and vitamin D

deficiency have also been described as possible underlying causes in the development of postoperative elevated PTH levels in eucalcemic patients.^{5-8,11-13}

Among these salient issues, the long-term clinical significance of elevated PTH levels after successful surgical treatment is not clearly understood, with the possibility that this biochemical finding may lead to recurrent HPT. The purpose of this study was to determine the long-term outcome and incidence of recurrent HPT in a large group of eucalcemic patients with elevated PTH levels after successful parathyroidectomy.

METHODS

Of 659 consecutive patients who underwent focused parathyroidectomy with intraoperative monitoring of PTH levels for HPT from January 1, 1992, through December 31, 2006, 576 were followed up for at least 6 months to determine operative success and disease recurrence. Success-

Table 1. Long-term Outcome of Parathyroidectomy According to Postoperative PTH Levels^a

	Patient Groups			P Value ^b
	Total (N = 505)	Elevated PTH Levels (n = 168)	Normal PTH Levels (n = 337)	
Calcium, level, mg/dL ^c	9.51 (0.45)	9.47 (0.54)	9.52 (0.46)	.32
PTH level, pg/mL ^d	54 (51)	85 (72)	36 (14)	<.001
Creatinine level, mg/dL ^e	1.00 (0.45)	1.14 (0.67)	0.94 (0.26)	.001
25-Hydroxyvitamin D level, ng/mL ^f	28.4 (14.0)	28.3 (15.0)	28.5 (14.0)	.96
Patients with recurrent HPT, No. (%)	8 (1.6)	8 (4.8)	0	<.001
Follow-up, mo ^g	41 (33)	45 (34)	38 (32)	.03

Abbreviations: HPT, hyperparathyroidism; PTH, parathyroid hormone.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; creatinine to micromoles per liter, multiply by 88.4; PTH to nanograms per liter, multiply by 0.1053; 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.

^aUnless otherwise indicated, data are expressed as mean (SD).

^bBased on comparison of patients with elevated vs normal PTH levels.

^cRange was 7.3 to 11.0 mg/dL.

^dRange was 65 to 3089 pg/mL.

^eRange was 0.4 to 4.8 mg/dL.

^fRange was 7.5 to 80.0 ng/mL, based on the limited data available (50 total patients: 12 with elevated and 38 with normal PTH levels).

^gRange was 6 to 165 months.

ful parathyroidectomy was defined as eucalcemia lasting 6 months or longer. Recurrent HPT was defined as elevated calcium and PTH levels more than 6 months after successful parathyroidectomy. When possible, serum calcium and PTH levels were collected within 7 postoperative days, at 2 and 6 postoperative months, and yearly thereafter. Because PTH levels were unavailable in 56 patients, the final group studied consisted of 505 patients. This study was limited to only those patients with available PTH levels at the last follow-up. The mean follow-up was 41 (range, 6-165) months.

Indications for parathyroidectomy followed the National Institutes of Health guidelines or previously published reports from this institution.^{17,18} Focused parathyroidectomy with intraoperative monitoring of PTH levels was performed in all patients. A frozen section was only obtained to confirm the presence of parathyroid tissue in equivocal cases and did not guide any resections. The criterion of intraoperative monitoring of PTH levels for operative success was defined as a more than 50% drop in PTH level from the highest preincision or the pre-excision level 10 minutes after gland excision.¹⁹

Main outcomes measured were overall incidence of elevated PTH levels and recurrent HPT. Patients who underwent successful parathyroidectomy (n=505) were divided into the following 2 groups: (1) those with elevated PTH levels, consisting of patients with normal calcium and elevated PTH levels (≥ 70 [range 17-65] pg/mL [to convert to nanograms per liter, multiply by 0.1053]; 70 pg/mL was used as the cutoff value because it represents the typical upper limit of normal [65 pg/mL] plus a coefficient of variance of 10%) (n=168) and (2) those with normal PTH levels, consisting of patients with normal calcium and persistently normal PTH levels (n=337). The patients in the group with elevated PTH levels were further subdivided into those with elevated PTH levels that normalized at the last follow-up (n=60) and those with levels that did not (n=108).

Clinical and laboratory data points were collected prospectively and compared between groups. Age, sex, preoperative and postoperative calcium and PTH levels, bone mineral density T scores, and the number of true-positive sestamibi scan results were reviewed. Vitamin D levels were not routinely collected but were included in the database when available. Furthermore, patients with low vitamin D levels did not routinely receive supplements. Intraoperative information such as gland size (volume of ellipsoid, $\frac{4}{3} \pi r_1 \times r_2 \times r_3$, where r indicates the radii in 3 different directions), the number of explorations confined to 1 side of the neck, the presence of multiglandular disease, operative time, and same-day discharge was also studied.

Data were analyzed using the statistical software package SPSS (version 15.0; SPSS Inc, Chicago, Illinois). Statistical significance was considered to be $P < .05$. This study was approved by the institutional review board at the University of Miami Miller School of Medicine. Unless otherwise indicated, data are expressed as mean (SD).

RESULTS

Parathyroidectomy was successful in 561 of 576 patients (97.4%), with final PTH level measurements available for 505. The mean age of all patients was 59 years (range, 15-96 years). There were 385 female patients (76.2%) and 120 male patients (23.8%). The mean preoperative serum calcium and PTH levels were 11.9 mg/dL (range, 10.2-20.0 mg/dL) (to convert to millimoles per liter, multiply by 0.25) and 190 pg/mL (range, 65-3089 pg/mL), respectively. One patient with a PTH level of 3089 pg/mL presented with hypercalcemic crisis. There were 168 patients (33.3%) with elevated PTH levels and 337 (66.7%) with persistently normal PTH levels. Most of the patients with elevated PTH levels had variability of their levels for an extended period of time. Parathyroid hormone levels normalized in some patients, whereas the levels fluctuated in others. Patients with elevated PTH levels were older (mean age, 62 [13] vs 57 [14] years; $P < .001$) and had significantly higher preoperative PTH levels than patients with normal PTH levels (mean levels, 227 [259] vs 172 [103] pg/mL; $P = .004$). Sex, preoperative calcium and creatinine levels, the incidence of osteoporosis, and true-positive localization on sestamibi scans were not significantly different between groups.

Gland volume was greater in patients with elevated compared with normal PTH levels (2.17 vs 1.43 cm³; $P = .08$), but this difference was not statistically significant. Unilateral neck exploration, operations during which multiple glands were removed, and the length of operative time were not significantly different between patient groups.

As expected, patients with elevated PTH levels had significantly higher postoperative PTH levels than those with normal PTH levels (85 [72] vs 36 [14] pg/mL; $P < .001$) (**Table 1**). Postoperative creatinine levels were also sig-

Table 2. Preoperative and Postoperative Laboratory Findings in Patients With Elevated PTH Levels That Did or Did Not Normalize

	Patient Groups ^a		P Value ^b
	PTH Levels Normalized (n = 60)	PTH Levels Did Not Normalize (n = 108)	
Calcium level, mg/dL			
Preoperative	11.7 (0.78)	12.1 (1.55)	.02
Postoperative	9.6 (0.46)	9.6 (0.65)	.87
PTH level, pg/mL			
Preoperative	178 (78)	254 (315)	.02
Postoperative	44 (14)	110 (80)	<.001
Creatinine level, mg/dL			
Preoperative	0.94 (0.24)	1.1 (0.43)	.01
Postoperative	1.04 (0.42)	1.19 (0.76)	.26
No. of patients with recurrent HPT	0	8	<.001
Follow-up, mo (range)	51 (32) (11-165)	43 (35) (6-151)	.13

Abbreviations: HPT, hyperparathyroidism; PTH, parathyroid hormone. SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; creatinine to micromoles per liter, multiply by 88.4; PTH to nanograms per liter, multiply by 0.1053.

^aUnless otherwise indicated, data are expressed as mean (SD).

^bBased on comparison of the patients with elevated PTH levels that were or were not normalized at last follow-up.

nificantly higher in patients with elevated PTH levels compared with those with normal PTH levels (1.14 [0.67] vs 0.94 [0.26] mg/dL; $P = .001$). Among the patients in the group with elevated PTH levels, 4.0% had creatinine levels of greater than 2.0 mg/dL (to convert to micromoles per liter, multiply by 88.4) compared with 0.3% of the patients in the group with normal PTH levels ($P = .003$). Follow-up was significantly longer for patients with elevated PTH levels (45 vs 38 months; $P = .03$).

Patients with elevated PTH levels were subdivided into those with PTH level normalization ($n = 60$ [35.7%]) and those with persistently elevated PTH levels ($n = 108$ [64.3%]) at the last follow-up (**Table 2**). Patients with PTH level normalization at the last follow-up had significantly lower preoperative calcium, PTH, and creatinine levels when compared with patients in whom PTH levels did not normalize. Postoperative calcium and creatinine levels did not differ significantly between these 2 subgroups. The patients who developed recurrent HPT had persistently elevated PTH levels that never fell below 70 pg/mL during the postoperative period.

The overall recurrence rate for the entire series of patients was 1.6% (8 of 505). The mean follow-up of the 8 patients with elevated PTH levels and disease recurrence was 67 months. The earliest and latest recurrences occurred at 24 and 120 months, respectively. The estimated 5-year recurrence-free survival in the patients with elevated PTH levels was 95% (**Figure**). Because the earliest recurrence occurred 24 months after parathyroidectomy, patients followed up for more than 2 years ($n = 314$) were studied from that time point; the recurrence rate of this population was 2.5% (8 of 314). When the group of patients with elevated PTH levels were stud-

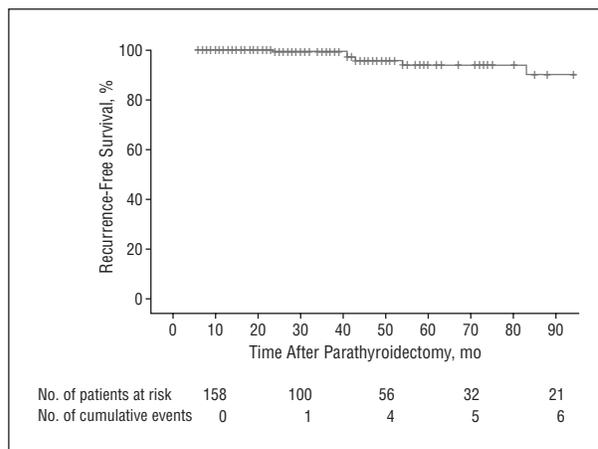


Figure. Kaplan-Meier curve showing recurrence-free survival in patients with persistently elevated parathyroid hormone (PTH) levels after successful parathyroidectomy.

ied within the same 2-year time, the incidence of recurrence was 6.8% (8 of 117).

COMMENT

Elevated PTH levels after successful parathyroidectomy constitute a clinical finding that may represent persistent or recurrent HPT, which is of much concern to referring physicians and treating surgeons alike. In this larger series of patients, the frequency of elevated PTH levels in the postoperative period was 33.3%. Patients with elevated PTH levels had an estimated 5-year recurrence rate of 4.7%. Conversely, the actual recurrence rate for patients with elevated PTH levels who were followed up for at least 2 years was 6.8%.

Elevated PTH levels after parathyroidectomy may reflect a "less complete" parathyroidectomy.²⁰ In one study, patients with elevated PTH levels tended to have fewer bilateral neck explorations and were less likely to have multiple glands removed. These results suggest that patients with elevated PTH levels may have undergone a less complete parathyroidectomy with remaining persistent mild HPT. In this study, patients with or without elevated PTH levels had the same number of bilateral neck explorations and the same incidence of multiglandular disease. Previous studies demonstrated that the incidence of elevated PTH levels after parathyroidectomy does not appear to depend on surgical approach.⁹ Recurrent disease may more likely be due to 1 or more normal glands at the time of the first intervention that later become hyperfunctioning. The etiology of this phenomenon is likely multifactorial and not well understood.

As this study shows, elevated PTH after successful parathyroidectomy heralds recurrent disease in only a few patients, as first suggested by Nordenström and colleagues¹⁶ in a series of 99 patients who were followed up for 5 years. Of interest, and similar to the present study, the presence of elevated PTH levels after successful parathyroidectomy seems to be a dynamic phenomenon, not a transient one. Levels of PTH fluctuated from normal to elevated over time, with some patients showing signs of renal impairment and disease recurrence.¹⁶

Factors that contribute to elevated PTH levels after successful parathyroidectomy remain unclear. In this report, patients with elevated PTH levels had higher postoperative creatinine levels and slightly lower calcium levels. In addition, patients with elevated PTH levels were older, had higher preoperative PTH levels, and had slightly larger glands. When patients with elevated PTH levels were subdivided according to normalization vs nonnormalization of PTH levels at the last follow-up, patients in whom the levels did not normalize were more likely to have higher preoperative calcium and creatinine levels, perhaps signifying more severe HPT before parathyroidectomy.

Similar to the present study, previous authors have reported that patients with elevated PTH levels are more likely to have elevated creatinine levels,^{1,8} whereas others have found no difference.^{14,21} In addition, elevated PTH levels are more likely to occur in older patients with more severe or advanced HPT.^{3,4,8,10} Patients with elevated PTH levels also have higher gland weights, higher preoperative PTH and creatinine levels, more bone disease, abnormal PTH regulation, and lower vitamin D levels. Some authors suggest that primary HPT may coexist with secondary HPT that is unmasked after surgical cure of serious and neglected HPT that should have been treated sooner.⁶

Elevated PTH levels after parathyroidectomy have been described as a transient phenomenon owing in part to a compensatory response to relative hypocalcemia and bone remineralization,^{3,4,14} and also to lower calcium absorption.²¹ Patients who take calcium and vitamin supplements immediately after surgery may be less likely to have postoperative elevation of PTH levels.⁵ What has been described as compensatory normocalcemic elevation may arise from dietary deficiency. A recent report also found that patients who routinely received calcitriol supplementation after parathyroidectomy were less likely to have elevated PTH levels in the postoperative period.²² Others have suggested that elevated PTH levels may be due to renal resistance to PTH exacerbated by vitamin D deficiency or renal insufficiency.^{7,12} A major limitation of the present study is the lack of vitamin D data and of calcium supplementation records after parathyroidectomy. Starting in 2003, patients with vitamin D deficiency at this institution received inconsistent supplementation. Some of these patients with elevated PTH levels and vitamin D deficiency may have normalized PTH levels once they are treated with vitamin D and calcium supplements.

The present study does not elucidate the underlying causes of eucalcemic PTH elevation after successful parathyroidectomy. Future investigations may focus on examining patients with mild or advanced HPT who are treated with parathyroidectomy to determine whether the incidences of elevated PTH levels and disease recurrence are different. Rigorous control of the secondary causes of elevated PTH levels should be an essential component of these future studies.

In conclusion, elevated PTH levels can occur in up to one-third of patients after successful parathyroidectomy. The overwhelming majority of these patients will achieve long-term eucalcemia. Elevated PTH levels do not

indicate operative failure but rather may herald recurrent disease in rare instances. Although several associated factors have been attributed to this phenomenon, no specific cause has been clearly identified. Until further studies determine the underlying etiology and clinical significance of elevated PTH levels after successful parathyroidectomy, these patients should be monitored closely for recurrent HPT.

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DISCUSSION

Peter Angelos, MD, Chicago, Illinois: Dr Solorzano and colleagues have shared with us an examination of a vexing problem for anyone who does parathyroid surgery. Why are there some patients who seem to have a successful operation with long-term eucalcemia and yet their PTH levels are subsequently found to be elevated? Perhaps even more importantly, what should we do about this when we find it? The authors have sought in this large single-institution series to give us data regarding these 2 related and important questions.

The authors report an elevated PTH level in the presence of normal calcium levels at any time during follow-up occurred in 33% of their patients who had a successful parathyroidectomy. Yet, only 5% of these who had elevated PTH

levels went on to develop recurrent HPT. Interestingly enough, the choice of operation, whether that was bilateral exploration or focused exploration, did not correlate with elevated PTH levels. So I have 3 questions.

First of all, since most of us agree that there is an entity known as normocalcemic HPT—in other words, the calcium is within normal range, but the patient really does have HPT—I want to know, how do you distinguish that group of patients—in other words, those patients with normocalcemic HPT—from those patients who simply have an elevated PTH level postoperatively, but the PTH will normalize in time?

Second, since many patients will have a transient rise in PTH after surgery and this finding will inevitably result in more blood draws and perhaps more follow-up visits, at what point do you recommend checking PTH levels postoperatively when the serum calcium level is normal? And this has significant implications for how long patients will be followed because, from your data, if you have an elevated PTH level, you seem to follow the patients longer.

And finally, based on your results, how do you now counsel patients or referring physicians? Do you counsel them any differently about what to expect after parathyroid surgery?

Dr Mendez: Regarding your first question, our group does not operate on patients with normocalcemic PTH elevation. We usually perform further workup in these patients. If the serum calcium is normal, we obtain an ionized calcium. We also look for vitamin D insufficiency and, if this is the situation, we treat it prior to recommending an operation. Another important test is a 24-hour urine for calcium. If it is normal to high, we may be dealing with a urinary leak. In these cases, we treat these patients with a calcium-sparing diuretic. If the ionized calcium is high or the serum calcium increases after the diuretic or after vitamin D supplementation, then we definitely have primary hyperparathyroidism and we recommend parathyroidectomy.

In answer to your second question, we routinely draw calcium and PTH levels at 1 week, 2 and 6 months, and yearly thereafter, because our definition for recurrence would be elevated calcium and elevated PTH 6 months or more after parathyroidectomy. If the PTH is elevated and the calcium is normal (beyond 6 months), we pay more attention to those patients. Again, we try to find any underlying cause such as vitamin D insufficiency. But definitely, the calcium level is what will tell if you have recurrence, and you can follow them every 6 months with just calcium levels.

In answer to your third question, yes, we counsel physicians, particularly endocrinologists, that elevated PTH in the postoperative period is not uncommon but it does not mean operative failure or imminent recurrence of disease. We also counsel our patients that PTH may be elevated in the postoperative period but that this doesn't mean noncure.

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