Elevated Serum Parathyroid Hormone Concentration in Eucalcemic Patients After Parathyroidectomy for Primary Hyperparathyroidism and Its Relationship to Vitamin D Profile

Kimvir S. Dhillon, Pejman Cohan, Christine Darwin, Andre Van Herle, and Inder J. Chopra

Elevation of serum parathyroid hormone (PTH) level in eucalcemic patients after parathyroidectomy for primary hyperparathyroidism has been described in up to 40% of patients, but little is known about its etiology or clinical significance. To better understand the cause of this phenomenon, we studied 49 patients without renal dysfunction or osteomalacia who underwent parathyroidectomy for primary hyperparathyroidism. Patients were categorized into 2 groups based on their serum PTH and calcium levels after parathyroidectomy: (1) elevated PTH with eucalcemia (n = 21), (2) normal PTH with eucalcemia (n = 28). Elevation of serum PTH with eucalcemia after parathyroidectomy occurred in 43% of patients. Patients in group 1 had significantly higher preoperative and postoperative mean serum PTH levels and significantly lower postoperative serum levels of $1,25(OH)_2D_3$, $1,25(OH)_2D_3/25(OH)D_3$ ratio, and $1,25(OH)_2D_3$/PTH ratio compared with patients in group 2. Serum PTH in group 1 patients normalized as early as 3 months, but remained elevated in some patients for more than 4 years, and was not associated with development of recurrent hypercalcemia. Normalization of serum PTH in group 1 patients was associated with significant increase in $1,25(OH)_2D_3$ and $1,25(OH)_2D_3$/PTH ratio. Our data suggest that elevation of serum PTH in eucalcemic patients after parathyroidectomy is a frequently reversible state of resistance of the kidneys to PTH-mediated 1-α hydroxylation of $25(OH)D_3$ and does not signify subsequent recurrence of hyperparathyroidism.

PRIMARY HYPERPARATHYROIDISM occurs with an incidence of about 42 per 100,000 persons. It may be caused by parathyroid adenoma (80%), hyperplasia (15%), or carcinoma (<5%).[1] Parathyroidectomy is the mainstay of treatment with cure, defined as normalization of serum calcium and parathyroid hormone (PTH) levels, occurring in about 95% of patients.[2] However, we and others have observed a subset of these patients who demonstrate a prolonged elevation of PTH accompanied by normal serum calcium levels after parathyroidectomy. This phenomenon has been reported to occur in 16% to 40% of patients having undergone parathyroidectomy for primary hyperparathyroidism.[3-12] The basis for this elevation of serum PTH is not known, but has been theorized by others to occur in response to diminished calcium reserve from excessive bone demineralization, renal impairment, or osteomalacia.[5,8,10] Recently, a study by Nordenstrom et al[13] has asserted that elevation in serum PTH in eucalcemic patients postparathyroidectomy is due to decreased peripheral sensitivity to PTH. Renal impairment and osteomalacia are causes of secondary hyperparathyroidism known to be associated with elevation of serum PTH.[11] Many previous studies did not exclude patients with renal impairment or osteomalacia in examining elevation of serum PTH after parathyroidectomy, thus making it difficult to evaluate the basis for serum PTH elevation. In this report, we describe our experience of PTH elevation postparathyroidectomy in normocalcemic patients who had no evidence of renal impairment or osteomalacia. Our data suggest that diminished 1-α hydroxylation of 25-hydroxy vitamin D_3 [$25(OH)D_3$] is an important factor contributing to the occurrence of this phenomenon.

MATERIALS AND METHODS

We conducted a retrospective chart analysis of 164 patients of the endocrine service who underwent parathyroidectomy between October 1997 to October 2002 at the UCLA Medical Center. Patients were excluded from the study if they had renal impairment (n = 45), osteomalacia (n = 1), persistent hypocalcemia (n = 5), persistent hypercalcemia (n = 4), or lack of serum PTH measurement after parathyroidectomy (n = 57). We also excluded patients with parathyroid cancer (n = 1) or multiple endocrine neoplasia syndrome (MEN, n = 2) because of the concern about recurrence of hyperparathyroidism. After these various exclusions, there remained a total of 49 patients for detailed analysis. Patients were categorized into 2 groups: persistent elevation of serum PTH with normal serum calcium levels postparathyroidectomy (group 1, n = 21), and normal serum PTH and serum calcium levels postparathyroidectomy (group 2, n = 28).

Parameters evaluated in each group of patients included age, sex, race, weight of parathyroid tissue removed, bone mineral density (BMD), and serum levels of preoperative and postoperative PTH, alkaline phosphatase, ionized calcium, magnesium, phosphorus, creatinine, 25-hydroxy vitamin D_3 [$25(OH)D_3$], 1,25-dihydroxy vitamin D_3 [$1,25(OH)_2D_3$], and chloride/phosphate ratio. $25(OH)D_3$ levels were available for 8 patients preoperatively and 10 patients postoperatively in group 1 and for 11 patients preoperatively and 7 patients postoperatively in group 2. $1,25(OH)_2D_3$ was measured in 7 patients preoperatively and 12 patients postoperatively in group 1 and in 12 patients preoperatively and 9 patients postoperatively in group 2. Meaningful determination of the duration of hypercalcemia could not be measured due to lack of sufficient data to determine the onset of hypercalcemia for a number of patients prior to their evaluation at UCLA Medical Center. Ratios of $1,25(OH)_2D_3$/PTH and $1,25(OH)_2D_3/25(OH)D_3$ were calculated in both groups of patients to determine and compare the relative efficacy of PTH in promoting the formation of the active vitamin D metabolite $1,25(OH)_2D_3$ from its precursor $25(OH)D_3$.

Serum intact PTH assay was performed at the UCLA clinical laboratories using the Nichol's Advantage Chemiluminescence System (Quest Diagnostics, San Diego, CA) (normal range, 10 to 55 pg/mL). Vitamin D levels were measured using the Quest Diagnostics radioim-

From the Division of Endocrinology, Diabetes, and Hypertension, Department of Medicine and Gonda Diabetes Center, University of California Los Angeles School of Medicine, Los Angeles, CA.

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Address reprint requests to Inder J. Chopra, MD, UCLA School of Medicine, Department of Medicine-Endocrinology, 24-130 Warren Hall, 900 Veteran Ave, Los Angeles, CA 90095.

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Table 1. Comparison of Various Study Parameters in Patients in Group 1 (elevated serum PTH and eucalcemia postparathyroidectomy) and Group 2 (normal serum PTH and normocalcemia postparathyroidectomy)

	Group 1 (preop) (n)	Group 2 (preop) (n)	*P* Value*	Group 1 (postop) (n)	Group 2 (postop) (n)	*P* Value†
Age (yr)	52 ± 18 (21)	56 ± 11 (28)	NS	NA	NA	NA
Sex (female/male)	15/21	24/28	NS	NA	NA	NS
Tumor weight	NA	NA		1959 ± 1016 (21)	630 ± 73 (28)	NS
BMD (g/cm^2) (lumbar)	0.88 ± 0.08 (7)	0.85 ± 0.08 (16)	NS	0.79 ± 0.10 (7)	0.94 ± 0.14 (5)	NS
BMD (g/cm^2) (femoral neck)	0.80 ± 0.08 (7)	0.89 ± 0.04 (16)	NS	0.83 ± 0.08 (7)	0.88 ± 0.08 (5)	NS
PTH (10–55 pg/mL)	173 ± 24 (21)	114 ± 10 (28)	<.05	78 ± 6 (21)‡	34 ± 2 (28)‡	<.01
Ionized calcium (1.09–1.29 mmol/L)	1.37 ± 0.03 (21)	1.33 ± 0.02 (28)	NS	1.15 ± 0.01 (21)‡	1.18 ± 0.02 (28)‡	<.01
Magnesium (1.5–2.1 mEq/L)	1.8 ± 0.04 (21)	1.7 ± 0.06 (28)	NS	1.7 ± 0.03 (21)	1.7 ± 0.07 (28)	NS
Alkaline phosphatase (35–110 U/L)	100 ± 9.8 (18)	96 ± 8.1 (26)	NS	77 ± 6.9 (21)‡	69 ± 6.9 (26)‡	NS
Serum phosphorus (2.4–5.1 mg/dL)	2.8 ± 0.14 (14)	3.0 ± 0.10 (19)	NS	3.7 ± 0.13 (19)‡	3.8 ± 0.35 (12)‡	NS
Chloride/phosphate	38 ± 1.7 (14)	38 ± 1.3 (19)	NS	28 ± 0.9 (19)‡	29 ± 1.6 (12)‡	NS
25-OH vitamin D (10–72 ng/mL)	25 ± 2.0 (8)	21 ± 3.3 (11)	NS	24 ± 2.3 (10)	21 ± 1.0 (7)	NS
1,25-DIOH vitamin D (24–65 pg/mL)	54 ± 9.5 (7)	66 ± 6.8 (12)	NS	25 ± 5.0 (12)‡	56 ± 6.8 (9)	<.01
Vitamin D 1,25-DiOH/25-OH	2.6 ± 0.70 (7)	4.5 ± 0.80 (11)	NS	1.1 ± 0.40 (10)‡	2.7 ± 0.25 (7)	<.01
Vitamin D 1,25-DIOH/PTH	0.71 ± 0.20 (7)	0.79 ± 0.10 (12)	NS	0.31 ± 0.05 (12)‡	1.76 ± 0.35 (9)‡	<.01
Serum creatinine (0.7–1.2 mg/dL)	0.8 ± 0.04 (21)	0.8 ± 0.03 (28)	NS	1.0 ± 0.03 (21)	0.9 ± 0.03 (28)	NS

NOTE. Data shown as mean ± SEM with normal ranges for each parameter shown in parentheses.

Abbreviations: N, number of patients; NA, not available; NS, nonsignificant.

**P* value comparing parameters between groups 1 and 2 preparathyroidectomy.

†*P* value comparing parameters between groups 1 and 2 postparathyroidectomy.

‡$P < .05$ for the specified parameter compared before and after parathyroidectomy within each group.

munoassay with normal range for $25(OH)D_3$ of 10 to 72 ng/mL and that for $1,25(OH)_2D_3$ of 24 to 65 pg/mL. Ionized calcium was measured using an ion-selective electrode on a radiometer blood gas analyzer with normal range of 1.09 to 1.29 mmol/L. Data were expressed as mean ± SEM, and the variables between the groups were compared using Student's *t* test. *P* values were adjusted using the Bonferroni modification for multiple comparisons.[14] The study was approved by the Institutional Review Board (IRB) at UCLA.

RESULTS

All patients underwent bilateral neck exploration. Eighteen patients in group 1 had excision of a single parathyroid adenoma, 1 had removal of 2 parathyroid adenomas, and 2 patients with parathyroid hyperplasia had removal of 3.5 parathyroid glands. Twenty-six patients in group 2 had excision of a single parathyroid adenoma, none had removal of 2 parathyroid adenomas, and 2 patients with parathyroid hyperplasia had removal of 3.5 parathyroid glands.

Patients in group 1 were followed for a mean duration of 9 months after parathyroidectomy with follow-up ranging from 1 month to 4 years. Patients in group 2 were followed for a mean duration of 6 months after parathyroidectomy, with a follow-up ranging from 1 month to 5 years. Serum PTH was first measured from 1 week to 13 months after parathyroidectomy with an average of 6 weeks after surgery in group 1, while serum PTH was first measured from 1 week to 9 months after parathyroidectomy with an average of 4 weeks after surgery in group 2.

At baseline (ie, preoperatively), there was no significant difference between patients in groups 1 and 2 in age, sex, race, BMD (lumbar or femoral neck), serum ionized calcium, alkaline phosphatase, chloride/phosphate ratio, creatinine, $25(OH)D_3$, $1,25(OH)_2D_3$, $1,25(OH)_2D_3/25(OH)D_3$ ratio or $1,25(OH)_2D_3$/PTH ratio. However, preoperative mean serum PTH level was significantly higher in group 1 than that in group 2 (173 *v* 114 pg/mL, $P < .05$) (Table 1).

Similarly, there was no significant difference between patients in groups 1 and 2 postoperatively in weight of parathyroid tissue removed (although there was a trend towards higher parathyroid mass in group 1), pathology of parathyroid glands removed (ie, adenoma *v* hyperplasia), BMD (lumbar or femoral neck), serum levels of alkaline phosphatase, creatinine, $25(OH)D_3$ levels, or serum chloride/phosphate ratio. Patients in group 1 had significantly higher postoperative mean serum PTH level (78 *v* 34 pg/mL, $P < .01$), and their mean serum ionized calcium, while clearly normal, was slightly lower than in patients in group 2 (1.15 *v* 1.18 mmol/L, $P < .01$). The mean postoperative serum levels of $1,25(OH)_2D_3$ (25 *v* 55 pg/mL, $P < .01$), $1,25(OH)_2D_3/25(OH)D_3$ ratio (1.1 *v* 2.7, $P < .01$), and $1,25(OH)_2D_3$/PTH ratio (0.31 *v* 1.76, $P < .01$) were clearly and significantly lower in patients in group 1 than in those in group 2 (Table 1).

When various parameters studied were compared before and after parathyroidectomy within each group, there was no significant difference in BMD (lumbar or femoral neck), serum levels of magnesium, creatinine, or $25(OH)D_3$ in both groups 1 and 2. In addition, there was no difference in calcium or vitamin D supplementation between the groups before and after parathyroidectomy during follow-up, as it has been our policy to not place eucalcemic patients after parathyroidectomy on these supplements. However, there was a significant and comparable decrease in serum PTH, ionized calcium, alkaline phosphatase, chloride/phosphate ratio and a significant increase in serum phosphorus in both groups 1 and 2 after parathyroidectomy. Interestingly, however, we found a significant decrease in $1,25(OH)_2D_3$ levels (54 *v* 25 pg/mL, $P < .01$), $1,25(OH)_2D_3/25(OH)D_3$ ratio (2.6 *v* 1.1, $P < .05$), and $1,25(OH)_2D_3$/PTH

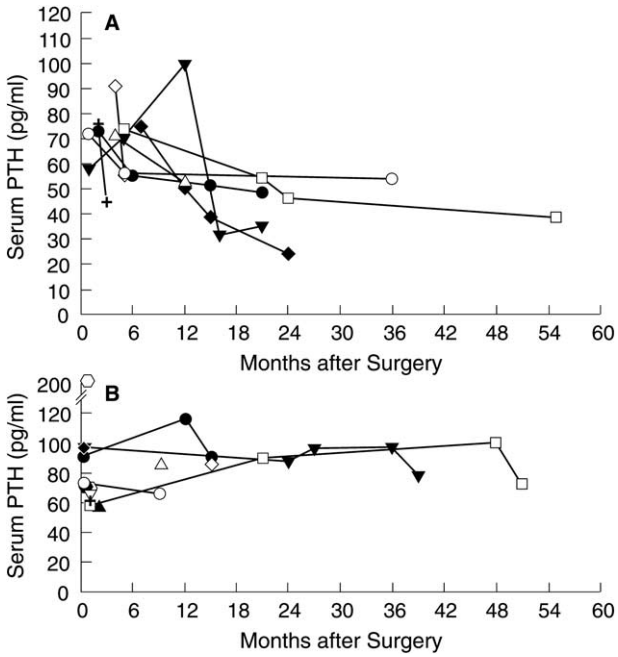

Fig 1. Change in serum PTH over time in patients with elevation in serum PTH and eucalcemia after parathyroidectomy (group 1). (A) Serum PTH in the 8 patients in group 1 who eventually normalized serum PTH after parathyroidectomy (group 1A). (B) Serum PTH in the 13 patients in group 1 who continued to have elevated serum PTH after parathyroidectomy throughout observation period (group 1B).

ratio (0.71 *v* 0.31, $P < .05$) after parathyroidectomy in group 1, but not in group 2 (Table 1).

After parathyroidectomy, 8 of 21 (38%) patients in group 1 normalized their serum PTH levels (group 1A). In these 8 patients, the shortest time to normalization of serum PTH was 3 months and the longest time to normalization was 21 months (Fig 1). Among the remaining 13 patients with continued elevation of PTH in group 1 (group 1B), the longest duration of postoperative elevation in serum PTH with normal serum calcium has been recorded to be 51 months (Fig 1). The average duration of follow-up was 18 months in group 1A and 11 months in group 1B. In 6 of the 8 patients in group 1A, we have documented $1,25(OH)_2D_3$ and $25(OH)D_3$ levels before and after normalization of serum PTH. There was a significant increase in $1,25(OH)_2D_3$ (16 *v* 38 pg/mL, $P < .01$), $1,25(OH)_2D_3$/PTH ratio (0.18 *v* 0.94, $P < .001$), $25(OH)D_3$ (26 *v* 37 ng/mL, $P < .05$), and a trend towards higher $1,25(OH)_2D_3/25(OH)D_3$ ratio (0.62 *v* 1.07, $P = .86$) with decrease and normalization in serum PTH in group 1A (Fig 2). In comparing vitamin D profile between groups 1A and 1B, the mean serum $1,25(OH)_2D_3$ (38 *v* 24 pg/mL, $P < .05$) and $1,25(OH)_2D_3$/PTH ratio (0.94 *v* 0.30, $P < .001$) were significantly higher in group 1A than the corresponding values in group 1B (Fig 3). There was a trend towards higher serum $25(OH)D_3$ in group 1A than in group 1B (37 *v* 27 ng/mL, $P = .14$), but there was no difference in $1,25(OH)_2D_3/25(OH)D_3$ ratio between groups 1A and 1B (1.1 *v* 1.1, $P = .85$).

DISCUSSION

We observed that elevation in serum PTH after parathyroidectomy in eucalcemic patients occurs in 43% of patients. This finding is not an indication of recurrent or persistent hyperparathyroidism, nor does it suggest the likelihood of subsequent occurrence of hyperparathyroidism; none of our patients developed hypercalcemia during an average follow-up of 9 months. This phenomenon of elevated serum PTH in eucalcemic patients postparathyroidectomy can be transient, resolving as soon as 3 months after parathyroidectomy, or it can persist for more than 4 years with consistently normal calcium levels and renal function (Fig 1).

Some previous studies have suggested that the high serum PTH in such patients is a response to diminished calcium reserve from excessive bone demineralization, renal impairment, or osteomalacia. Others have reported an association of this phenomenon with larger tumor mass, older age, African-

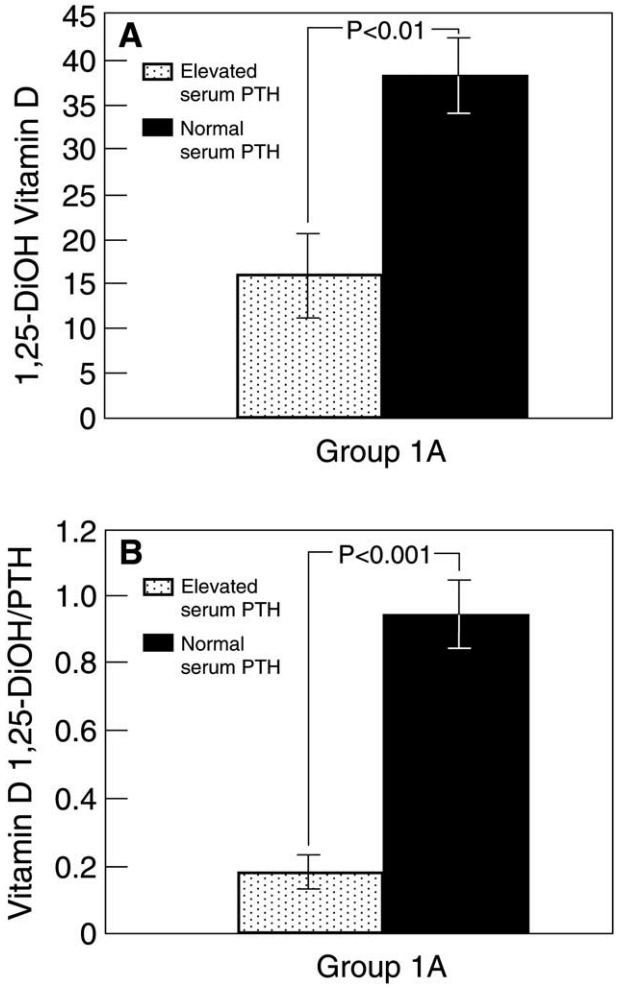

Fig 2. Vitamin D profile in subset of group 1 patients with eventual normalization in serum PTH after parathyroidectomy (group 1A). (A) and (B) Compare 1,25-DiOH vitamin D and vitamin D 1,25-DiOH/PTH ratio, respectively, in group 1A patients before and after normalization of serum PTH postparathyroidectomy demonstrating significant increase in these parameters with normalization of serum PTH.

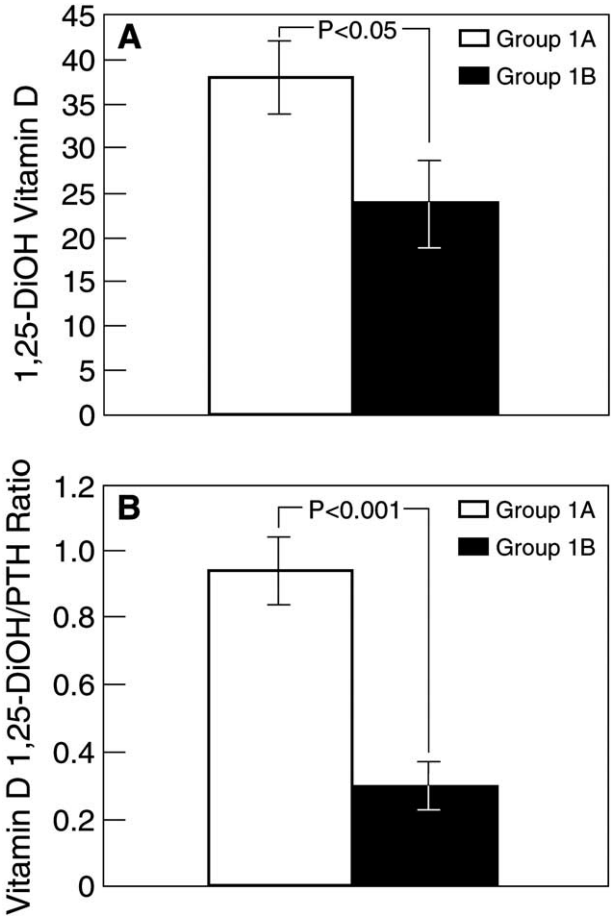

Fig 3. Comparison of vitamin D profile between subset of group 1 patients with normalization in serum PTH (group 1A) and patients with continued elevation of serum PTH after parathyroidectomy (group 1B). (A) and (B) Compare 1,25-DiOH vitamin D and vitamin D 1,25-DiOH/PTH ratio, respectively, between group 1A and group 1B patients demonstrating significant increases in both parameters with normalization in serum PTH.

American descent, and female sex.[5,7,8,10,12] However, in our study, we observed no significant difference in BMD, alkaline phosphatase, age, sex, race, excised parathyroid mass, renal function, or $25(OH)D_3$ levels between eucalcemic patients with elevated serum PTH after parathyroidectomy (group 1) and those with normal serum PTH after parathyroidectomy (group 2) to suggest a "mild" form of Hungry Bone Syndrome, vitamin D deficiency, or impaired renal function as causes of elevation of serum PTH after parathyroidectomy. However, there was a trend towards a greater mass of parathyroid tissue excised and significantly higher preoperative serum PTH level in group 1 patients, suggesting more severe or prolonged state of hyperparathyroidism in patients in group 1 versus those in group 2.

Interestingly, we noted a significant relationship between $1,25(OH)_2D_3$ levels and PTH elevation in normocalcemic patients after parathyroidectomy. PTH is known to promote the 1-α hydroxylation of $25(OH)D_3$.[11] Because the postoperative mean serum PTH level was significantly higher in patients in group 1 than group 2, one would expect higher postoperative $1,25(OH)_2D_3$ levels and a higher $1,25(OH)_2D_3/25(OH)D_3$ ratio in patients in group 1 than group 2. However, we observed the opposite phenomenon, a significantly lower postoperative $1,25(OH)_2D_3$, $1,25(OH)_2D_3/25(OH)D_3$, and $1,25(OH)_2D_3$/PTH ratio in group 1 than in group 2. The data suggest that the elevation of serum PTH after parathyroidectomy observed in group 1 patients may be a compensatory adjustment for decreased renal response to PTH-mediated 1-α hydroxylation of $25(OH)D_3$ to $1,25(OH)_2D_3$, which in turn, may result in decreased absorption of calcium by the gastrointestinal tract. Because serum $25(OH)D_3$ levels were comparable and clearly normal in groups 1 and 2 patients, the data suggest that PTH in group 1 may be less effective in promoting 1-α hydroxylation of $25(OH)D_3$ to $1,25(OH)_2D_3$ and is not a compensatory response to deficiency of vitamin D.

Renal resistance to PTH in group 1 patients is further supported by comparing vitamin D profile between patients in group 1 in whom serum PTH has normalized (group 1A) with those patients in group 1 with continued elevation of serum PTH (group 1B). We found that there was a significant increase in $1,25(OH)_2D_3$ and $1,25(OH)_2D_3$/PTH ratio with normalization of serum PTH in group 1A patients. Similarly, we found significantly higher $1,25(OH)_2D_3$ and $1,25(OH)_2D_3$/PTH ratio in patients in group 1A compared with patients in group 1B (with continued elevation in serum PTH during duration of follow-up). The increase in serum $1,25(OH)_2D_3$ that occurs with the decrease of serum PTH to normal is consistent with the notion that elevation in serum PTH after parathyroidectomy in eucalcemic patients is related to renal resistance to PTH, as a decrease in serum PTH would be expected to lead to a decrease in $1,25(OH)_2D_3$ levels. That the above-mentioned resistance to PTH in group 1 patients can be transitory is suggested by the normalization of serum PTH with time in 38% of group 1 patients. As patients in group 1A were followed on average for a longer duration of time after parathyroidectomy than those in group 1B (18 months *v* 11 months, respectively), it seems possible that most, if not all, patients in group 1B may ultimately normalize their serum PTH.

If elevation in serum PTH in eucalcemic patients after parathyroidectomy (group 1) and low $1,25(OH)_2D_3$ levels were related, as is suggested by our data, these patients would be expected to have decreased calcium absorption by the gastrointestinal tract. This inference is supported by a recent study by Westerdahl et al.[7] This study observed that patients with elevated serum PTH and normal calcium levels after parathyroidectomy given an oral load of 1,500 mg calcium demonstrated significantly less increase in serum calcium and urinary excretion of calcium than patients with normal serum PTH and calcium after parathyroidectomy. Vitamin D profile was not evaluated in their study. Interestingly, patients with high serum PTH and normal calcium levels after parathyroidectomy, comparable to our group 1 patients, demonstrated a decrease in serum PTH to normal levels after oral calcium load,[7] suggesting that PTH elevation is a reversible condition and is related to decreased calcium absorption in these patients.

Downregulation of receptor production or postreceptor second messenger system is a well-known phenomenon in circumstances where there is excess stimulation of the biochemical system involved. As mentioned in the recent study by Norden-

strom et al,[13] resistance to serum PTH has been demonstrated in the human osteoblasts of patients with end-stage renal disease with secondary hyperparathyroidism by demonstrating decreased production of PTH receptor mRNA in response to chronic exposure to elevated levels of PTH.[15] Therefore, our finding of significantly lower $1,25(OH)_2D_3$ levels observed in group 1 patients may reflect downregulation (ie, resistance) of PTH receptors or the enzyme involved in 1-α-hydroxylation of $25(OH)D_3$ to $1,25(OH)_2D_3$ at the level of the kidneys due to chronic elevation in serum PTH. Additionally, the study by Nordenstrom et al[13] has demonstrated resistance to PTH in patients with elevated serum PTH with eucalcemia after parathyroidectomy (equivalent to our group 1 patients) by infusing PTH intravenously and showing a significantly smaller increase in ionized calcium compared with patients with eucalcemia and normal serum PTH levels after parathyroidectomy (equivalent to our group 2). Although they were not able to achieve statistical significance, their data showed a trend towards lower urinary cyclic adenosine monophosphate (cAMP) excretion per glomerular filtration rate (GFR) (142 *v* 433 pmol $\times$ min/cc^2, $P = .57$) and a smaller increase in $1,25(OH)_2D_3$ levels (18 *v* 23 pmol/L, $P = 88$) in response to infused PTH in patients equivalent to our group 1 compared with their control patients (group 2 equivalent).[12] These results are consistent with our findings of peripheral resistance to PTH. However, our study suggests that resistance to PTH occurs primarily at the level of the kidneys as our group 1 patients clearly have significantly lower $1,25(OH)_2D_3$ levels after parathyroidectomy compared with patients in group 2, and have a significant increase in $1,25(OH)_2D_3$ levels after normalization in serum PTH in these patients.

Teleologically, renal resistance to PTH may serve as a protective mechanism that results in lower serum calcium in response to persistently elevated PTH in primary hyperparathyroidism. Therefore, it may be severity of hyperparathyroidism or duration of disease that promotes development of renal resistance and the associated increase in PTH observed in patients within group 1. This notion is supported by our observation of significantly higher preoperative PTH levels, ionized calcium, and a tendency toward larger parathyroid tumor mass in patients who develop this disorder (group 1) compared with those who do not (group 2). Tisell et al[12] also demonstrated a significantly higher preoperative serum PTH and serum calcium levels, and Westerdahl et al[7] showed a significantly higher mass of parathyroid tissue excised in patients with elevated serum PTH with eucalcemia after parathyroidectomy compared with patients who do not develop this phenomenon. However, the role of the duration of hyperparathyroidism in the proposed renal resistance to PTH cannot be assessed, as the onset of hypercalcemia could not be reliably determined.

Elevation in serum PTH in eucalcemic patients (group 1) may conceivably be explained, in part, by a state of vitamin D deficiency. However, none of the patients in group 1 or 2 had subnormal levels of $25(OH)D_3$, and $1,25(OH)_2D_3$ levels were high normal to supranormal. In addition, $25(OH)D_3$ levels were comparable in both groups 1 and 2, and therefore vitamin D deficiency cannot explain the postoperative elevation in serum PTH in group 1 patients. However, as indicated in the Results, there was a significant increase in $25(OH)D_3$ levels in the subset of patients in group 1 in whom serum PTH eventually normalized during follow-up (group 1A). This subset of patients also had a trend towards higher $25(OH)D_3$ levels when compared with the subset of patients in group 1 who had persistently elevated serum PTH levels during the duration of follow-up (group 1B); however this difference was not statistically significant. Alternatively, high serum PTH measured in group 1 patients may reflect biologically inactive PTH. Because our PTH assay measured intact PTH, this possibility appears unlikely, but it should be addressed in a more detailed analysis in future studies.

Our study has been a retrospective chart analysis, and not all parameters could be measured in all patients. However, given our highly significant findings and supporting data from the study by Nordenstrom et al[13] confirming peripheral resistance to PTH, we feel that there is a resistance to PTH in patients with high serum PTH and eucalcemia after parathyroidectomy, and that the resistance occurs at the level of the kidney as demonstrated by the significant reduction in the active vitamin D metabolite $1,25(OH)_2D_3$ in group 1 patients postoperatively and a significant increase in $1,25(OH)_2D_3$ after normalization in serum PTH in these same patients.

In summary, elevation in PTH after parathyroidectomy in normocalcemic patients is (1) a common occurrence observed in about 43% of patients; (2) a transient and a reversible phenomenon frequently resolving in several months, but may persist for over 4 years in some patients; (3) associated with decreased renal conversion of $25(OH)D_3$ to its active form $1,25(OH)_2D_3$; and (4) not an indication of persistent hyperparathyroidism.

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