Differences in the Dynamics of Parathyroid Hormone Secretion in Hemodialysis Patients With Marked Secondary Hyperparathyroidism[1]

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(J. Am. Soc. Nephrol. 1995; 6:1371–1378)

ABSTRACT

Hemodialysis patients with predialysis intact parathyroid hormone (PTH) levels of more than 500 pg/mL are generally considered to have marked secondary hyperparathyroidism. Because the serum calcium level in these patients varies from low to high, it is not clear whether every hemodialysis patient with a PTH level > 500 pg/mL is part of a uniform group. The dynamics of PTH secretion in 21 hemodialysis patients with predialysis (basal) intact PTH levels > 500 pg/mL (range, 506 to 1978 pg/mL) has been evaluated. The basal/maximal PTH ratio, an indicator of the degree of relative PTH stimulation in the baseline state, was inversely correlated with the maximal PTH ($r = -0.71$), the basal serum calcium ($r = -0.70$), and the difference between the serum calcium at basal and maximal PTH ($r = 0.81$); the latter is the decrement in serum calcium from baseline necessary to maximally stimulate PTH. Because the basal PTH level appeared to be disproportionately influenced by hypocalcemia, the 21 patients were separated into two groups on the basis of the basal serum calcium (Group I < 9 mg/dL and Group II > 9 mg/dL). Basal PTH was not different between the two groups, even though maximally stimulated PTH (1,219 ± 204 *versus* 2,739 ± 412 pg/mL; $P < 0.01$) as induced by hypocalcemia and maximally suppressed PTH (217 ± 37 *versus* 528 ± 104; $P = 0.05$) as induced by hypercalcemia were less in Group I with the low basal calcium; moreover, the ratio of basal/maximal PTH was higher (73 ± 6 *versus* 47 ± 5%; $P < 0.01$) in Group I with the low basal calcium. These results suggest that the reason for a basal PTH > 500 pg/mL may be different among hemodialysis patients. In hypocalcemic patients, the low serum calcium appeared to be a major impetus for the high basal PTH level. In conclusion, (*1*) the maximally stimulated PTH appears to provide a better means of separating patients with marked secondary hyperparathyroidism than the basal PTH and (*2*) hemodialysis patients with basal PTH levels > 500 pg/mL may not be a uniform group.

Key Words: *Calcium hypocalcemia, maximal parathyroid hormone, minimal parathyroid hormone, set point of calcium*

In renal osteodystrophy, the different forms of bone disease are characterized by substantial differences in parathyroid hormone (PTH) (1–4). In osteitis fibrosa, the bone disease associated with marked secondary hyperparathyroidism (2° HPT), PTH levels are considerably higher than in the forms of renal osteodystrophy associated with low bone turnover such as adynamic bone and aluminum bone disease (1–4). In a previous study, we compared the secretory characteristics of the parathyroid gland in different forms of renal osteodystrophy and showed that the basal, maximal, and minimal levels of intact PTH, the set point of calcium, the slope of the PTH-calcium curve, and the ratio of basal to maximal PTH in the basal state were higher in hemodialysis patients with osteitis fibrosa than in hemodialysis patients with adynamic bone or low-turnover aluminum bone disease (1).

Hemodialysis patients with predialysis intact PTH levels higher than 500 pg/mL are considered to have marked 2° HPT, and because osteitis fibrosa is present in this group of patients (2,4), treatment with calcitriol is generally recommended (5–9). However, it is not clear whether every hemodialysis patient with PTH levels exceeding 500 pg/mL should be included as part of a uniform group of patients sharing the same abnormalities in parathyroid gland function (PTH-calcium curve). This concern is especially pertinent considering that the serum calcium level, the main regulator of PTH secretion, varies considerably in this group of patients (5–9) and, as a result, may affect the predialysis PTH level. Thus, it is reasonable to address how the difference in the predialysis serum calcium affects the dynamics of PTH secretion. We have now had the opportunity to evaluate the dynamics of PTH secretion in 21 hemodialysis patients with predialysis PTH levels > 500 pg/mL (range, 506 to 1,978 pg/mL). Our results suggest that considerable differences in PTH secretory patterns are present in hemodialysis patients with low serum calcium as opposed to those with normal or elevated serum calcium.

[1] Received March 9, 1995. Accepted May 23, 1995.

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1046-6673/0605-1371$03.00/0
Journal of the American Society of Nephrology

METHODS

Twenty-one maintenance hemodialysis patients with predialysis levels of intact PTH of more than 500 pg/mL were studied. Ten patients have been reported in a previous study (1). Patients were routinely dialyzed for 3 to 4 h thrice weekly with a dialysate calcium concentration that ranged from 2.5 to 3.5 mEq/L. Their mean age at the time of study was 48.5 ± 2.7 yr (range, 24 to 62 yr), and the mean duration of dialysis was 45.1 ± 8.2 months (range, 6 to 136 months). None of the patients had received any calcitriol or other forms of vitamin D for at least 6 wk before the study.

As described in our previous studies (1,5,6,10), the PTH response to hypocalcemia and hypercalcemia was evaluated. Briefly, a low calcium hemodialysis (1 mEq/L) was performed to induce hypocalcemia and maximally stimulate PTH and a high calcium hemodialysis (4 mEq/L) was performed to induce hypercalcemia and maximally inhibit PTH. Blood for PTH and calcium was obtained at the start of the low calcium dialysis and every 15 min until the serum calcium decreased to 7.5 mg/dL or the dialysis treatment was finished. The following week, a high calcium dialysis was performed and blood for PTH and calcium was obtained at the start and every 15 to 30 min throughout the hemodialysis.

From the data obtained during dialysis-induced hypocalcemia and hypercalcemia, the following terms were defined: (*1*) **basal PTH** was the predialysis PTH level; (*2*) **maximal PTH** was the highest PTH level observed in response to hypocalcemia, and an additional reduction of the serum calcium did not further increase the PTH value; (*3*) **minimal PTH** was the lowest PTH level during suppression by hypercalcemia, and a further increase in the serum calcium did not result in any additional decrease in PTH; (*4*) **the ratio of basal to maximal PTH** was the basal PTH divided by the maximal PTH, and this fraction was multiplied by 100 to provide a percentage; in normals, this ratio is 20 to 25% (11); (*5*) **the ratio of minimal to maximal PTH** was the minimal PTH divided by the maximal PTH, and this fraction was multiplied by 100 to provide a percentage; in normals, this ratio is 3 to 5% (11); (*6*) **the set point of calcium** was defined as we have done previously (1,5,6) as the serum calcium concentration at which maximal PTH secretion was reduced by 50%; **the set point of calcium** was also calculated as defined by Brown (12,13), i.e., the serum calcium concentration at the midrange between the maximal and minimal PTH; (*7*) **the basal serum calcium** (Ca_{basal}) was the serum calcium concentration at the basal (predialysis) PTH; (*8*) **the serum calcium at maximal PTH** (Ca_{max}) was the serum calcium concentration at which the PTH level was first observed to be maximal or within 10% of the maximal PTH. This definition was used because the PTH-calcium curve is sigmoidal and as the PTH value approaches the asymptotic portion of the curve, considerable variation in serum calcium can be observed during small changes in PTH; similarly, for the same reason, (*9*) **the serum calcium at minimal PTH** (Ca_{min}) was the serum calcium concentration at which the PTH level was first observed to be minimal or within 10% of the minimal PTH; (*10*) **the slope of the PTH-calcium curve** was the PTH concentration at 90% of the maximal PTH (transformed to 100%) minus the PTH concentration at the minimal PTH plus 10% divided by the difference in the serum calcium at these two levels of PTH; 10% was subtracted from the maximal PTH and 10% was added to the minimal PTH to be on the linear portion of the PTH-calcium curve and to avoid the asymptotic segments at both ends. When the PTH concentration is represented as a percentage of the maximal PTH, the slope should indicate the sensitivity of the parathyroid cells (defined as the change in PTH for a change in serum calcium). Other parameters analyzed included: (*11*) **the difference between the Ca_{basal} and the Ca_{max}**, which is the reduction in serum calcium necessary to maximally stimulate PTH; (*12*) **the difference between the Ca_{basal} and the Ca_{min}**, which is the increase in serum calcium necessary to maximally inhibit PTH; and (*13*) **the difference between the serum Ca_{min} and the serum Ca_{max}**, which is the range of serum calcium between the maximal and the minimal PTH.

Intact PTH was measured with an immunoradiometric assay for PTH (Allegro; Nichols Institute, San Juan Capistrano, CA). Normal values are 10 to 65 pg/mL, and the range of the standard curve is 0 to 1,400 pg/mL; when values were higher than 1,400 pg/mL, appropriate dilutions were performed. Serum calcium was measured at bedside with an automated calcium analyzer (Calcette, Precision Systems Inc, Natick, MA).

For comparisons between two groups, the nonparametric Mann-Whitney test was used. Linear regression analysis was performed to evaluate the potential association between two variables. Stepwise regression was used when more than one independent variable was included to test the association with the dependent variable. Comparisons among three variables were performed with the nonparametric Kruskal-Wallis test. Results are expressed as the mean ± SE, and significance was defined as a P value <0.05.

RESULTS

Between the patients studied previously ($N = 10$) and more recently ($N = 11$), no significant differences in maximal, basal, and minimal PTH (1,952 ± 519 *versus* 2,119 ± 400, 1,075 ± 179 *versus* 999 ± 148, and 321 ± 85 *versus* 458 ± 123 pg/mL, respectively) were observed. As shown in Figure 1, the correlation between basal and maximal PTH was $r = 0.76$ and $P < 0.001$ (Figure 1A), and between minimal and maximal PTH, it was $r = 0.85$ and $P < 0.001$ (Figure 1B). Correlations between the basal PTH and the basal serum calcium ($r = 0.43$, $P = 0.05$) and the maximal PTH and the basal serum calcium ($r = 0.64$, $P < 0.005$) were more modest but significant. However, the correlations between basal PTH and the set point of calcium and between maximal PTH and the set point of calcium did not reach statistical significance.

As shown in Figure 2, the basal/maximal PTH ratio was inversely correlated with the maximal PTH ($r = -0.71$, $P < 0.001$) (Figure 2A), the basal serum calcium ($r = -0.70$, $P < 0.001$) (Figure 2B), and the difference between the serum Ca_{basal} and Ca_{max} ($r = -0.81$, $P < 0.001$) (Figure 2C). The finding that the basal/maximal PTH ratio was higher when the maximal PTH, the basal serum calcium, and the difference between the serum Ca_{basal} and Ca_{max} were in the lower range would suggest that a relative stimulation of the basal PTH level was present and that this relative stimulation of basal PTH was most likely due to the lower serum calcium concentration. When a stepwise linear correlation was performed with the difference between serum Ca_{basal} and Ca_{max}, a marker of the degree of relative PTH stimulation, added to the

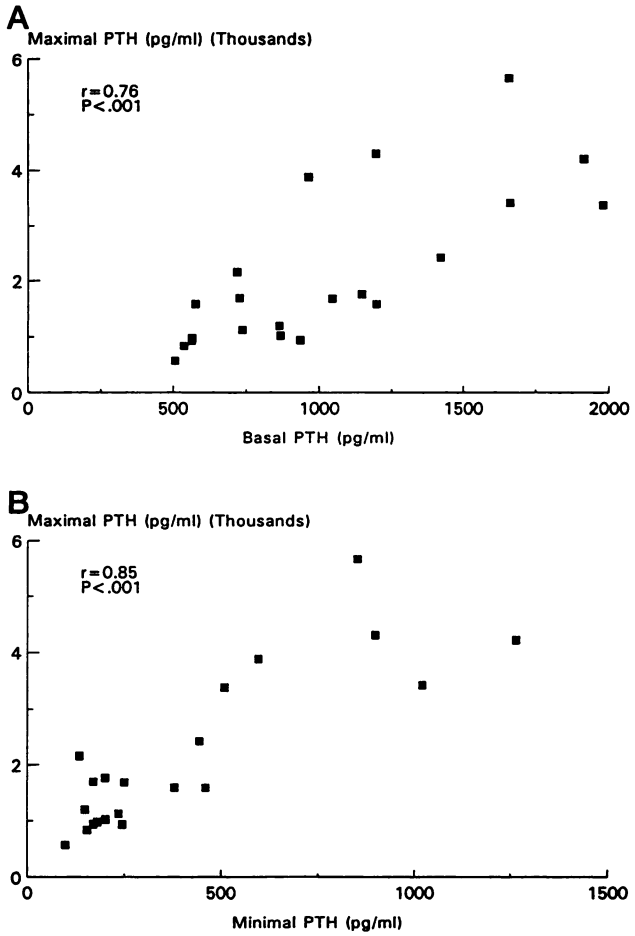

Figure 1. (A) The correlation between the basal and the maximal PTH levels is shown. (B) The correlation between the minimal and maximal PTH levels is shown. The terms are defined in the Methods.

correlation between basal and maximal PTH, the *r* value increased from 0.76 to 0.92.

Traditionally, the predialysis (basal) PTH level is used to characterize the magnitude of 2° HPT; however, our findings presented in Figures 1 and 2 indicate that the basal PTH level not only was dependent on the secretory capacity of the parathyroid gland, but also was affected by the serum calcium concentration. To further analyze the effect of the basal serum calcium on the dynamics of PTH secretion, the patients were separated into two groups, first, based on differences in the maximal PTH and, second, based on differences in the basal serum calcium. As opposed to the basal PTH, the maximal PTH, which represents the maximal secretory capacity of the parathyroid gland during hypocalcemia, is unaffected by the basal serum calcium. The separation according to basal serum calcium was performed to determine whether differences in parathyroid gland function were present despite the absence of any difference in basal PTH levels.

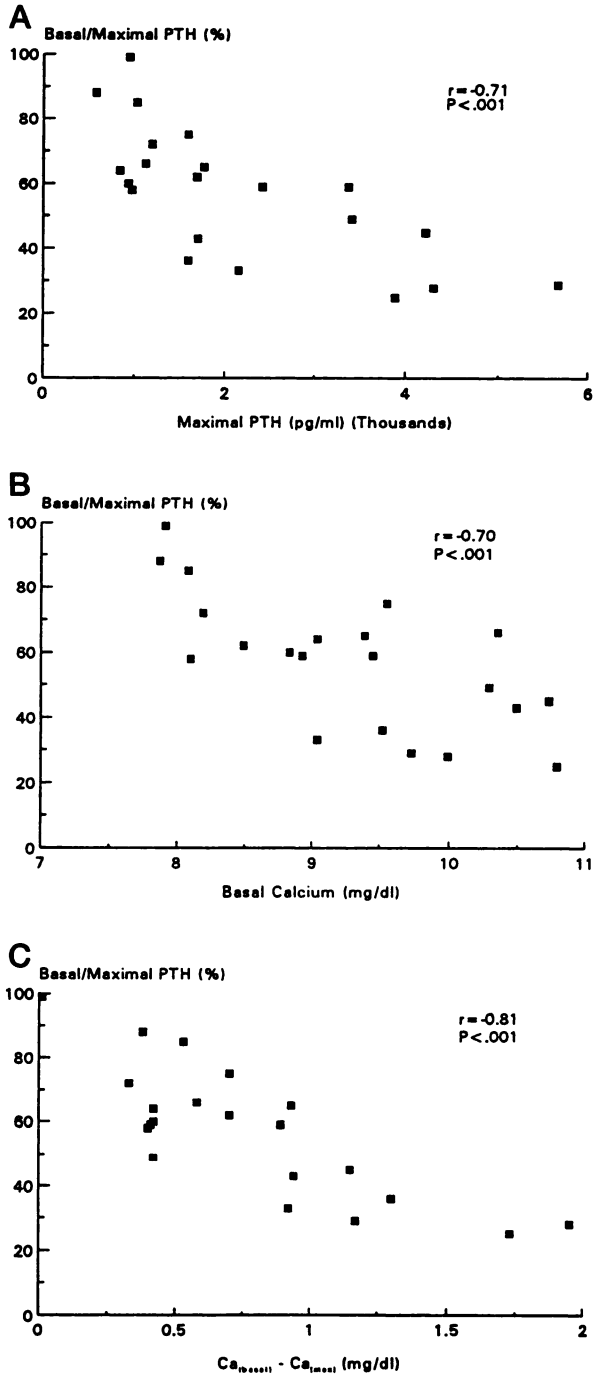

Figure 2. The correlations between the basal/maximal PTH ratio and the maximal PTH (A), the basal serum calcium (B), and the difference between the serum calcium at basal PTH (Ca_{basal}) and the serum calcium at maximal PTH (Ca_{max}) (C) are shown. The terms are defined in the Methods.

The 21 patients were first separated into two groups according to the maximal PTH: Group I, with maximal PTH levels <1,200 pg/mL (N = 8), and Group II, with maximal PTH levels >1,500 pg/mL (N = 13); no

patient had a maximal PTH level between 1,200 and 1,500 pg/mL. The mean age of the patients was similar in both groups (Group *versus* I, 51.5 ± 2.8 *versus* Group II, 46.4 ± 4.0 yr); however, the duration of dialysis was longer in Group II (25.6 ± 6.2 *versus* 59.3 ± 11.5 months; $P < 0.02$). Comparisons of the parameters of the PTH-calcium curve are shown in Table 1. The difference in maximal PTH between the two groups was present because maximal PTH was used to separate the groups. However, it should be noted that although the maximal and minimal PTH levels were more than threefold higher in Group II, the basal PTH level was less than twofold higher in Group II. As shown in Figure 3A, the difference between the maximal and minimal PTH and the basal PTH was the result of a lower basal/maximal PTH ratio ($P < 0.001$) in Group II. The minimal/maximal PTH ratio was similar in the two groups (Table 1). As shown in Figure 4, the basal serum calcium concentration was less ($P < 0.005$) in Group I, as were the serum Ca_{max} ($P = 0.05$), the serum Ca_{min} ($P < 0.02$), and the difference between serum Ca_{basal} and Ca_{max} ($P < 0.001$); the difference between the serum Ca_{basal} and Ca_{min} tended to be greater in Group I ($P = 0.08$). The overall range in serum calcium between the serum Ca_{basal} and Ca_{min} was similar between the two groups (Group I, 2.17 ± 0.24 *versus* Group II, 2.21 ± 0.18 mg/dL), as was the slope of the PTH-calcium curve. The set point of calcium as calculated by our method and the method of Brown tended to be higher in Group II but did not attain significance ($P = 0.09$ and $P = 0.08$, respectively).

The 21 patients were also divided in two groups according to the basal serum calcium—Group I <9 mg/dL ($N = 8$) and Group II >9 mg/dL ($N = 13$). The mean age (Group I, 48.0 ± 3.6 *versus* Group II, 48.9 ± 3.8 yr) and the duration of dialysis (Group I, 33.8 ± 9.8 *versus* Group II, 53.4 ± 11.5 months) were not different. The comparison of the parameters of the PTH-calcium curve is shown in Table 2. By definition, the basal serum calcium was less in Group I than in Group II (8.30 ± 0.14 *versus* 9.87 ± 0.17 mg/dL). Despite the fact that the basal PTH level was not different between the two groups, both maximal PTH ($P < 0.01$) and minimal PTH ($P = 0.05$) were higher in Group II. As shown in Figure 3B, the basal/maximal PTH ratio was higher ($P < 0.02$) in Group I. The minimal/maximal PTH ratio was similar in the two groups (Table 2). As shown in Figure 5, the PTH-calcium curve was shifted to the left in Group I. The serum Ca_{max} ($P < 0.001$), the serum Ca_{min} ($P < 0.001$), the difference between serum Ca_{basal} and Ca_{max} ($P < 0.003$), and the set point of calcium, calculated by both methods ($P < 0.001$), were less in Group I. The difference between Ca_{min} and Ca_{basal} was higher in Group I ($P < 0.04$). The overall range of the PTH-calcium curve (2.27 ± 0.26 *versus* 2.15 ± 0.17 mg/dL) and the slope of the PTH-calcium curve were not different between the two groups.

The set point of calcium was calculated by two different methods—the serum calcium concentration at 50% the maximal PTH and the serum calcium concentration at the midrange between the minimal and the maximal PTH. Because the mean minimal PTH for the 21 patients was 18% of the maximal PTH, the set point of calcium by the second method was lower than the set point of calcium as calculated by the first method. However, the correlation between the two methods for the calculation of the set point of calcium was significant and approached unity ($r = 0.98$, $P < 0.001$).

TABLE 1. A comparison of the PTH-calcium curve in two groups divided according to the maximal PTH[a]

Parameter	Group I[b] ($N = 8$)	Group II[c] ($N = 13$)	*P* Value
Basal PTH (pg/mL)	697 ± 62	1,245 ± 126	<0.004
Maximal PTH (pg/mL)	952 ± 67	2,904 ± 368	
Minimal PTH (pg/mL)	179 ± 17	552 ± 99	<0.007
Minimal/Maximal PTH (%)	18 ± 1	18 ± 2	NS
Basal/Maximal PTH (%)	74 ± 5	47 ± 5	<0.004
Set Point (mg/dL)	9.08 ± 0.25	9.58 ± 0.16	=0.09
Set Point 1 (mg/dL)	8.89 ± 0.26	9.39 ± 0.16	=0.08
Ca_{max} (mg/dL)	8.16 ± 0.27	8.71 ± 0.18	=0.05
Ca_{min} (mg/dL)	10.34 ± 0.19	10.91 ± 0.16	<0.02
Basal Calcium (mg/dL)	8.55 ± 0.30	9.72 ± 0.20	<0.005
$Ca_{basal} - Ca_{max}$ (mg/dL)	0.38 ± 0.06	1.02 ± 0.13	<0.001
$Ca_{min} - Ca_{basal}$ (mg/dL)	1.79 ± 0.27	1.19 ± 0.20	=0.08
$Ca_{min} - Ca_{max}$ (mg/dL)	2.17 ± 0.24	2.21 ± 0.18	NS
Slope (% PTH/mg of calcium)	−61 ± 6	−54 ± 6	NS

[a] Values are the mean ± SE. NS, not significant.
[b] Group I, maximal PTH < 1,200 pg/mL.
[c] Group II, maximal PTH > 1,500 pg/mL. No patient had a value between 1,200 and 1,500 pg/mL.
[d] Difference based on definition of the groups.

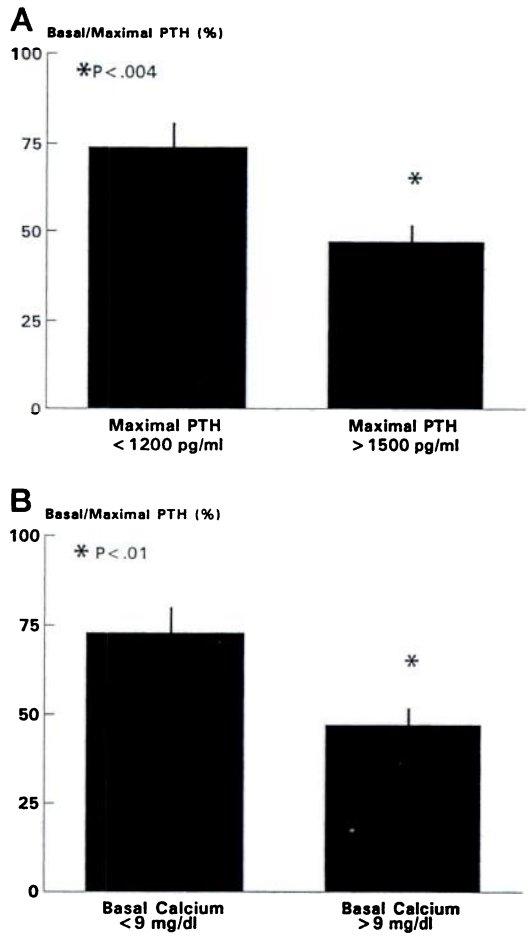

Figure 3. When the 21 hemodialysis patients were divided into two groups on the basis of the maximal PTH level (<1,200 and >1,500 pg/mL, no patient had a maximal PTH between 1,200 and 1,500 pg/mL) and the basal/maximal PTH ratio was higher in the group with the lower maximal PTH (A). When they were divided on the basis of the basal serum calcium (<9 mg/dL and >9 mg/dL), the basal/maximal PTH ratio was higher in the group with the lower basal calcium (B).

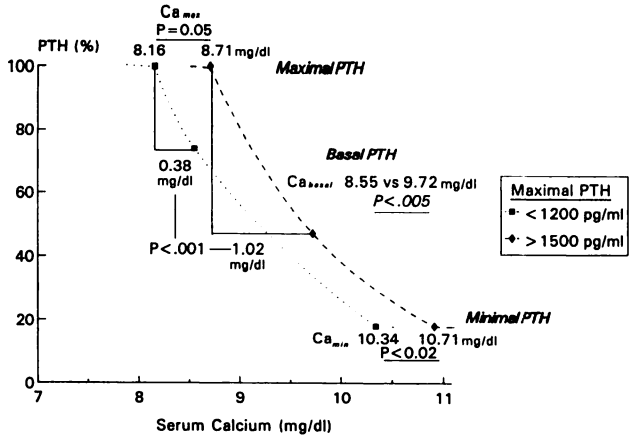

Figure 4. Shown are the PTH-calcium curves for the two groups separated on the basis of the maximal PTH (<1,200 and >1,500 pg/mL); maximal PTH was transformed to 100% for each patient. The serum calcium at maximal PTH (Ca_{max}), basal PTH (Ca_{basal}), and minimal PTH (Ca_{min}) was less in the group with a maximal PTH < 1,200 pg/mL. The decrement in serum calcium from basal PTH necessary to maximally stimulate PTH (maximal PTH) was less in the group with the lower maximal PTH (0.38 versus 1.02 mg/dL). Although not shown, the difference in serum calcium between the serum calcium at minimal (Ca_{min}) and at maximal (Ca_{max}) PTH was not different between the two groups (2.17 ± 0.24 *versus* 2.21 ± 0.18 mg/dL).

DISCUSSION

Dynamic testing of PTH secretion was performed in 21 maintenance hemodialysis patients with a predialysis PTH of more than 500 pg/mL. Because the relationship between PTH and serum calcium is best expressed as a sigmoidal curve, dynamic testing allows the matching of PTH for a specific serum calcium level; thus, the effect that any change in predialysis serum calcium may have on the PTH level is removed. In this study, it was possible to appreciate how a reduction in predialysis (basal) serum calcium in the hypocalcemic group resulted in basal PTH levels similar to those in the normocalcemic group; however, distinct differences in the maximal PTH secretory capacity, the degree of relative PTH stimulation in the baseline state (ratio of basal/maximal PTH), and the difference in serum calcium between basal and maximal PTH ($Ca_{basal} - Ca_{max}$) were still present between the two groups. At the same time, dynamic testing of PTH secretion showed that although the range of serum calcium between maximal and minimal PTH was similar between the hypocalcemic and normocalcemic groups, the PTH-calcium curve was shifted to the left in the hypocalcemic group, suggesting the possibility that PTH secretion in the hemodialysis patient may adapt to the ambient serum calcium. Finally, dynamic PTH testing allowed for the determination of the relative degree of PTH stimulation in the baseline state (basal/maximal PTH ratio) and the ability to maximally suppress PTH during hypercalcemia (minimal/maximal PTH ratio). As was shown in this study, hypocalcemia resulted in an increase in the basal/maximal PTH ratio, thus demonstrating that basal PTH was stimulated relative to maximal PTH in the hypocalcemic group. The minimal/maximal PTH ratio was similar in the hypocalcemic and normocalcemic groups, indicating that despite marked differences in maximal PTH levels between the two groups, PTH suppression was proportionally similar between the two groups.

The correlation between minimal and maximal PTH was better than that between basal and maximal PTH. This result was likely because the minimal/maximal PTH ratio was constant while the basal/maximal PTH ratio varied inversely with the basal serum calcium

TABLE 2. A comparison of the PTH-calcium curve in two groups divided according to basal calcium[a]

Parameter	Group I[b] (N = 8)	Group II[c] (N = 13)	P Value
Basal PTH (pg/mL)	846 ± 108	1,153 ± 140	NS
Maximal PTH (pg/mL)	1,219 ± 204	2,739 ± 412	<0.01
Minimal PTH (pg/mL)	217 ± 37	528 ± 104	=0.05
Minimal/Maximal PTH (%)	18 ± 1	19 ± 2	NS
Basal/Maximal PTH (%)	73 ± 6	47 ± 5	<0.01
Set Point (mg/dL)	8.78 ± 0.10	9.76 ± 0.15	<0.001
Set Point 1 (mg/dL)	8.62 ± 0.12	9.56 ± 0.15	<0.001
Ca_{max} (mg/dL)	7.90 ± 0.14	8.87 ± 0.18	<0.001
Ca_{min} (mg/dL)	10.18 ± 0.19	11.02 ± 0.11	<0.003
Basal Calcium (mg/dL)[d]	8.30 ± 0.14	9.87 ± 0.17	
$Ca_{basal} - Ca_{max}$ (mg/dL)	0.40 ± 0.07	1.01 ± 0.13	<0.001
$Ca_{min} - Ca_{basal}$ (mg/dL)	1.87 ± 0.27	1.14 ± 0.18	<0.04
$Ca_{min} - Ca_{max}$ (mg/dL)	2.27 ± 0.26	2.15 ± 0.17	NS
Slope (% PTH/mg of calcium)	−66 ± 9	−51 ± 3	NS

[a] Values are the mean ± SE. NS, not significant.
[b] Group I, basal calcium <9 mg/dL.
[c] Group II, basal calcium >9 mg/dL.
[d] Difference based on definition of the groups.

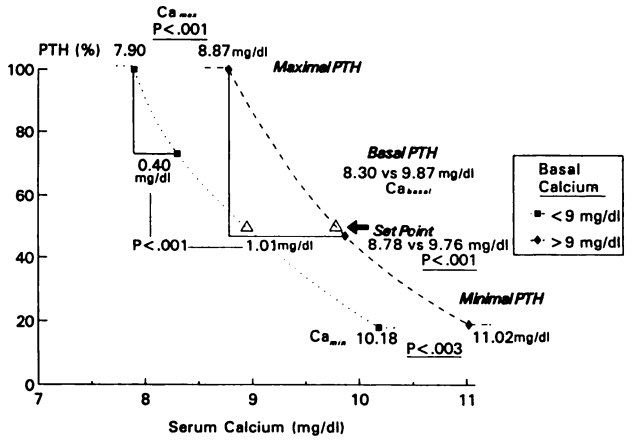

Figure 5. Shown are the PTH-calcium curves for the two groups separated on the basis of the basal serum calcium (<9 mg/dL and >9 mg/dL); maximal PTH was transformed to 100% for each patient. The serum calcium at maximal PTH (Ca_{max}), minimal PTH (Ca_{min}), and the set point of calcium was less in the group with a basal calcium <9 mg/dL. The decrement in serum calcium necessary to maximally stimulate PTH (maximal PTH) was less in the group with the lower basal calcium (0.40 *versus* 1.01 mg/dL). Although not shown, the difference in serum calcium between the serum calcium at minimal (Ca_{min}) and maximal (Ca_{max}) PTH was not different between the two groups (2.27 ± 0.26 *versus* 2.15 ± 0.17 mg/dL).

concentration; thus, the basal PTH level was disproportionately increased in patients with hypocalcemia.

The 21 hemodialysis patients were separated into two groups based both on the maximal PTH and on the basal serum calcium. When the groups were separated according to the maximal PTH, the group with the lower maximal PTH was characterized by a low basal calcium and an increased basal/maximal PTH ratio. However, it should also be noted that even in the group with the lower maximal PTH, the maximal PTH level was approximately 10-fold higher than in normal individuals (11) and still these patients were hypocalcemic; this serves to illustrate the magnitude of the skeletal resistance to PTH present in uremia. When the groups were separated according to the basal calcium, the group with the lower basal calcium was characterized by a higher basal/maximal PTH ratio, which would account for the fact that basal PTH levels were not different between the two groups. Thus, despite a more than twofold difference in the maximal secretory capacity of the parathyroid gland (maximal PTH) between the two groups, the basal PTH levels were not different because hypocalcemia stimulated PTH secretion in the group with the lower basal serum calcium; this difference in the degree of PTH stimulation in the baseline state is shown by the fact that the mean ratio of basal/maximal PTH was 73% in the hypocalcemic group and only 47% in the normocalcemic group. These results indicate that the reason for a basal PTH >500 pg/mL may not be uniform among hemodialysis patients and would also suggest that in patients with a low basal serum calcium, the low serum calcium is a major impetus for the increase in the basal PTH.

The results of this study also suggest that the clinical response to calcitriol treatment may be different in this group of patients. In patients with a low basal calcium, a high basal/maximal PTH ratio, and a lower maximal PTH, a clinical response to calcitriol would be expected because a calcitriol-induced increase in serum calcium should reduce PTH levels. Moreover, calcitriol should have an inhibitory effect on PTH transcription because the lower maximal PTH level would suggest a smaller parathyroid gland mass

(14,15). However, in patients with a normal to increased basal calcium, a moderate increase in the basal/maximal PTH ratio as compared with a normal value of 25% (11), and a markedly increased maximal PTH level, it is conceiveable that calcitriol treatment may not be as effective. Indeed, this latter group may include a significant number of patients with nodular hyperplasia of the parathyroid gland (16–19), which is associated with a decrease in vitamin D receptors (17), decreased responsiveness to increases in calcium (20), and DNA changes indicative of a greater proliferative capacity (21); moreover, it may be associated with acquired genetic changes that may result in autonomous parathyroid cell proliferation (22). Another intriguing clinical question is whether the former group, as the result of the stimulatory effect of the low serum calcium and high basal/maximal PTH ratio, is evolving into the latter group, with a greater parathyroid gland mass and more autonomous PTH secretion. The finding that patients with the lower maximal PTH had a shorter duration of dialysis lends credence to this possibility.

The separation of patients into two groups according to maximal PTH and to basal calcium served to illustrate several other noteworthy findings. In the groups with the lower maximal PTH and the lower basal calcium, the difference between the serum Ca_{basal} and Ca_{max} was less; this is in agreement with the finding that the basal/maximal PTH ratio was higher and would emphasize that basal PTH was relatively stimulated. Whether the patients were separated on the basis of maximal PTH or basal calcium, the range of the PTH-calcium curve (difference between the serum Ca_{max} and Ca_{min}) was similar. However, the PTH-calcium curve was shifted to the left in the groups with the lower maximal PTH and the lower basal calcium. These results suggest the intriguing possibility that (*1*) secretion by the parathyroid gland may adapt to the ambient serum calcium; and (2) the range of serum calcium for PTH secretion (sigmoidal PTH-calcium curve) remains constant.

The clinical implications of our findings would suggest that even when only the predialysis (basal) PTH is available, a similar predialysis PTH level between a hypocalcemic patient and a normocalcemic patient would suggest the presence of certain differences. The hypocalcemic patient would be expected to have a decreased maximal PTH, a higher basal/maximal PTH ratio, and a reduced difference between Ca_{basal} and Ca_{max} than his or her normocalcemic counterpart. The lower maximal secretory capacity of the parathyroid gland in the hypocalcemic patient would suggest a smaller parathyroid gland mass. The higher basal/maximal ratio and the reduced difference between Ca_{basal} and Ca_{max} would indicate that the relative degree of PTH stimulation was higher in the hypocalcemic patient; thus, the hypocalcemic patient would be expected to be positioned higher on the steep portion of the PTH-calcium curve. Consequently, an increase in serum calcium should result in a greater proportional decrease in PTH in the hypocalcemic patient than in the normocalcemic patient. Both the smaller secretory capacity of the parathyroid gland and the potential for a greater response in PTH for a change in calcium would suggest the likelihood of a greater response to calcitriol in the hypocalcemic patient.

We and others believe that the set point of calcium as defined in this study provides information on the serum calcium concentration at which PTH is secreted (8,13). Brown has advanced the concept that the set point of calcium should be defined as the midrange between the minimal and the maximal PTH (12,13), whereas we have used the serum calcium concentration at 50% of the maximal PTH to represent the set point of calcium (1,5,6,8). The correlation between the two methods of calculating the set point of calcium approached unity ($r = 0.98$). Although either method should provide similar information, it should be noted that the set point of calcium as calculated by the method of Brown was slightly less (9.20 ± 0.15 *versus* 9.39 ± 0.15 mg/dL) than the set point of calcium as calculated by our method.

In normal humans, serum calcium is tightly regulated in a narrow range through the action of PTH on bone and kidney and the action of calcitriol on gut absorption (23,24). In the dialysis patient, calcium regulation is altered because the kidney is nonfunctional, resistance to the calcemic action of PTH on bone is present (25,26), and intestinal calcium is malabsorbed as the result of a calcitriol deficiency (27). Because marked 2° HPT (basal PTH > 500 pg/mL) was present in the hemodialysis patients studied, it would be expected that these patients would have osteitis fibrosa (2,4); indeed, in the 10 patients studied previously and included as part of this study, a bone biopsy showed osteitis fibrosa (5). Moreover, the extent of cellular activity and the bone formation rate have been shown to correlate with the basal PTH level in several studies (4,28). In this study, the basal serum calcium appeared to have a modest correlation with the basal and the maximal PTH levels. However, in other forms of renal osteodystrophy such as adynamic bone and low-turnover aluminum bone disease—both of which are characterized by decreased cellular activity and bone formation—the serum calcium level does not appear to depend on the PTH level (1). Thus, it would appear that calcium regulation may be more PTH dependent in dialysis patients with marked 2° HPT and osteitis fibrosa than in dialysis patients with a modest PTH elevation and low bone turnover.

In conclusion, when 21 hemodialysis patients with marked 2° HPT were separated into two groups according to maximal PTH levels, distinct differences were observed in the characteristics of PTH secretion and serum calcium regulation. In the group with the lower maximal PTH level, a low serum calcium appeared to be responsible for stimulating PTH in the

baseline state. Similarly, when patients were separated on the basis of differences in serum calcium, basal PTH levels were similar in both groups. However, maximal and minimal PTH levels were lower in the hypocalcemic group, indicating that hypocalcemia disproportionately increased the basal PTH. The range of serum calcium for PTH secretion (sigmoidal PTH-calcium curve) remained constant, even though the PTH-calcium curve was shifted to the left in the groups with the lower maximal PTH and the lower basal calcium; this finding suggests that the PTH-calcium curve may adapt to the ambient serum calcium concentration. Furthermore, the results of this study suggest the possibility of a different clinical response to calcitriol treatment in these two groups of patients and also raises the question of whether hemodialysis patients with lower maximal PTH levels, higher basal/maximal PTH ratios, and lower serum calcium levels are evolving to a stage in which PTH secretion may become more autonomous.

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