Hysteresis of the Parathyroid Hormone Response to Hypocalcemia in Hemodialysis Patients with Low Turnover Aluminum Bone Disease[1,2]

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ABSTRACT

During the study of parathyroid function in 19 hemodialysis patients with low turnover aluminum bone disease, it was observed that serum parathyroid hormone (PTH) levels were higher during the induction of hypocalcemia than during the recovery from hypocalcemia. This type of PTH response has been termed hysteresis. Hypocalcemia was induced during hemodialysis with a calcium-free dialysate. When the total serum calcium level decreased to 7 mg/dL, the dialysate calcium concentration was changed to 3.5 mEq/L and the dialysis session was completed. One week later, hypercalcemia was induced during hemodialysis with a high-calcium dialysate. The mean basal PTH level was 132 ± 37 pg/mL (normal, 10 to 65 pg/mL; immunoradiometric (IRMA), Nichols Institute, San Juan Capistrano, CA) and increased to a maximal PTH level of 387 ± 91 pg/mL during hypocalcemia. For the same ionized calcium concentration, the PTH level was higher during the induction of hypocalcemia than during the recovery from hypocalcemia. Conversely, for the same ionized calcium concentration, the PTH level was greater when hypercalcemia was induced from the nadir of hypocalcemia than when hypercalcemia was induced from basal serum calcium. The set point of calcium (defined as the serum calcium concentration required to reduce maximal PTH by 50%) was greater during the induction of hypocalcemia than during the recovery from hypocalcemia (4.44 ± 0.10 versus 4.25 ± 0.09 mg/dL; $P = 0.03$). The mean basal ionized calcium concentration and the mean ionized calcium concentration at the intersection of the two PTH-calcium curves were the same (4.61 ± 0.13 versus 4.61 ± 0.12 mg/dL). In summary, a hysteretic response of PTH secretion was observed during the induction of and recovery from hypocalcemia; in addition, the basal serum calcium concentration seemed to determine the intersection of the two PTH-calcium curves. Hysteresis was also observed when hypercalcemia was induced from the basal serum calcium and the nadir of hypocalcemia.

Key Words: *Hypercalcemia, maximal PTH inhibition, maximal PTH stimulation, PTH-calcium curve, set point of calcium*

Parathyroid hormone (PTH) secretion is stimulated by hypocalcemia and suppressed by hypercalcemia (1,2). This relationship between PTH and serum calcium is best represented as a sigmoidal curve and has been verified in both *in vivo* and *in vitro* studies (3–8). In normal individuals, the basal PTH level is approximately 25% of the maximally stimulated PTH level and is positioned in the initial part of the steep ascent of the sigmoidal curve (5). Thus, a minimal decrease in serum calcium produces a sharp increase in PTH. In renal failure, secondary hyperparathyroidism is generally observed and has been documented by both increased levels of PTH as measured by RIA (4,6,9) and the increased size of the parathyroid glands (9). In addition, the sigmoidal pattern of the PTH response to hypocalcemia and hypercalcemia is maintained in renal failure; however, PTH levels are generally much higher than normal (4–6).

The increase in PTH secretion in response to progressive acute hypocalcemia has been well characterized both in normal individuals and in patients with renal failure (4–6). Less information is available about PTH secretion during the recovery from acute hypocalcemia. Conceptually, the sigmoidal relationship between PTH and calcium would be expected to remain constant, and a specific serum calcium level would be associated with the same PTH level during the induction of and recovery from hypocalcemia.

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However, results from a recent study in normal volunteers demonstrated that during hypocalcemia, a directional change in the serum ionized calcium concentration produced differences in the PTH concentration (10); thus, for the same serum ionized calcium concentration, the serum PTH concentration was higher during the induction of hypocalcemia than during the recovery from hypocalcemia. In the same study, the reverse was observed during hypercalcemia; the serum PTH level was higher during the recovery from hypercalcemia than during the induction of hypercalcemia. Similar findings were reported recently in hemodialysis patients during hypocalcemia, but not during hypercalcemia (11). As applied to PTH secretion, this phenomenon has recently been termed hysteresis (10).

While studying PTH secretion in hemodialysis patients with low turnover aluminum bone disease (LTAABD), we observed that serum PTH levels were higher during the induction of hypocalcemia than during the recovery from hypocalcemia. It is our purpose to report our findings of hysteresis in a group of hemodialysis patients with low turnover aluminum bone disease. The mean PTH level in these patients is higher than that in normal individuals (5,12). However, when compared with the majority of dialysis patients, this group of patients is characterized by a relative deficiency of PTH (12–14).

METHODS

The parathyroid function of 19 maintenance hemodialysis patients with bone biopsy-proven LTAABD was studied. The majority of these patients have been reported previously as part of a study evaluating the effect of desferrioxamine treatment on parathyroid function and bone histology (12). Three patients had a previous subtotal parathyroidectomy. Some of the patients had a bone biopsy performed because of symptoms suggestive of LTAABD, but the majority were discovered during routine bone biopsies in our hemodialysis population. Of the 19 patients, 6 were males and 13 were females; their mean age was 55 ± 3 yr, and the mean time on hemodialysis was 44 ± 10 months. In two patients, diabetic nephropathy was the cause of renal failure. At the time of evaluation, three patients, two of whom had a previous subtotal parathyroidectomy, were receiving 0.25 μg of oral calcitriol daily.

Parathyroid function, defined as the PTH-calcium curve, was evaluated before desferrioxamine therapy and not longer than 3 months after the bone biopsy. A calcium-free hemodialysis and a high-calcium hemodialysis were performed on separate days, 1 week apart. During the calcium-free hemodialysis, blood samples for the measurement of total and ionized calcium and PTH were obtained every 15 to 30 min. The decrease in total serum calcium was monitored at the bedside with an automated calcium analyzer (Calcette; Precision Systems Inc, Sudsbury, MA). When the serum calcium decreased to less than 7.0 mg/dL, hypocalcemia was reversed by changing the dialysate calcium to 3.5 mEq/L. The usual time required to decrease the serum calcium to less than 7.0 mg/dL was 30 to 90 min. For the remainder of the 3.5- to 4-h hemodialysis, the patient was dialyzed with a 3.5-mEq/L dialysate calcium concentration. During the hemodialysis with a high-calcium dialysate (calcium concentration, 3.5 to 4 mEq/L), blood samples for the measurement of total and ionized calcium and PTH were obtained every 15 to 30 min throughout the dialysis.

Individual sigmoidal PTH-ionized calcium curves were constructed for each patient with the data obtained from the calcium-free and high-calcium dialysis treatments. A separate PTH-calcium curve was generated after the reversal of hypocalcemia, when the dialysate calcium was changed to 3.5 mEq/L at the nadir of the hypocalcemia. After the change to a 3.5-mEq/L calcium dialysate, the serum ionized calcium concentration progressively increased until the end of hemodialysis. As we have done previously, composite PTH-calcium curves were compiled from the individual curves (6,12). For the analysis of the PTH-calcium curve, the following terms are defined and illustrated in Fig. 1: *maximal PTH stimulation* was the highest PTH level observed in response to hypocalcemia and which additional lowering of the serum ionized calcium concentration did not further

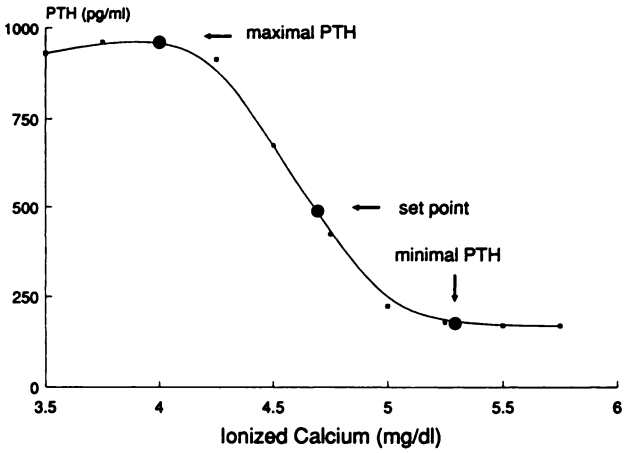

Figure 1. Shown is a graphic representation of the sigmoidal curve depicting the interrelationship between PTH and ionized calcium. During hypocalcemia, PTH secretion was maximally stimulated and maximal PTH represents the ionized calcium level at which maximal PTH stimulation was first observed. During hypercalcemia, PTH secretion was maximally inhibited and minimal PTH represents the ionized calcium level at which maximal PTH inhibition was first observed. The set point is the ionized calcium concentration at which maximal PTH was reduced by 50%.

increase the PTH level; *maximal PTH inhibition* was the lowest PTH level during suppression by hypercalcemia and which an additional increase in serum ionized calcium did not produce further inhibition of PTH; and *the set point of calcium* was the serum ionized calcium concentration at which maximal PTH secretion was reduced by 50%.

Because of the wide dispersion of PTH values, basal ionized calcium levels, and the ionized calcium concentration at which maximal PTH was observed, the mean PTH-calcium curve of the 19 patients did not adequately depict the phenomenon of hysteresis observed in the individual curves of each patient. Because a minimal decrease from the basal calcium concentration produces a marked increase in PTH, the calcium concentration at which the maximal PTH is observed may vary greatly because of the wide dispersion in the basal calcium concentration between the 19 patients. As shown in Figure 2, this difference is illustrated as the patients were divided

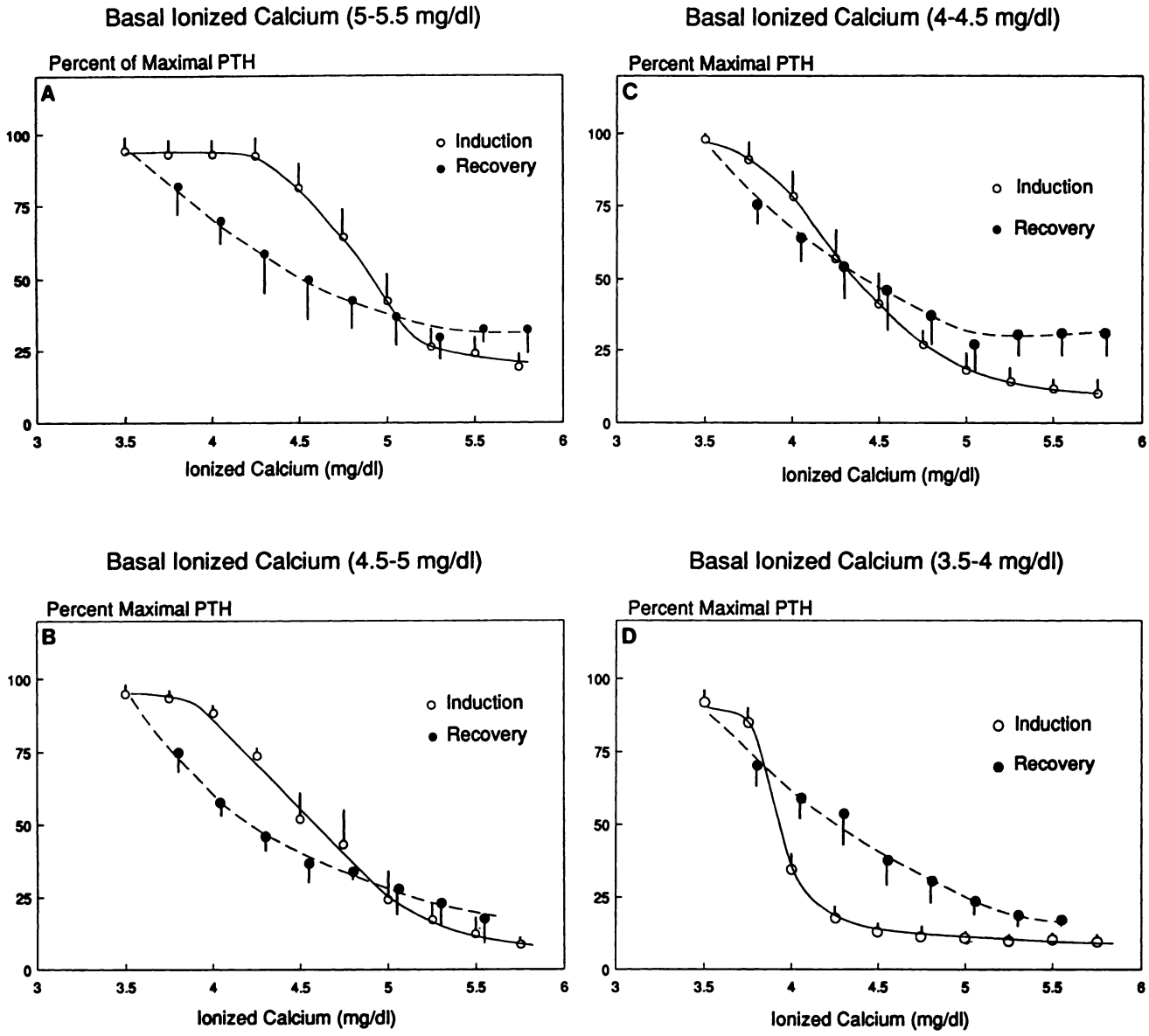

Figure 2. Because of the wide dispersion of basal ionized calcium concentrations and, as a consequence, the level of ionized calcium at which maximal PTH stimulation was observed, the PTH-calcium curves were divided according to the basal ionized calcium concentration. Figures 2A through D illustrate how the basal calcium concentration, with its effect on both the ionized calcium level at maximal PTH stimulation and the PTH-calcium curve developed during the recovery from hypocalcemia, influences the configuration of the mean PTH-calcium curve. The number of patients in Figures 2A through D is six, five, four, and four, respectively. Values are mean ± SE.

according to their basal ionized calcium concentration. To factor for the wide dispersion of PTH values among the patients, the maximal PTH level was transformed to 100% in Figures 2 through 4. In addition, because of the wide dispersion of the ionized calcium level at which maximal PTH was observed, the mean maximal PTH was not 100% at any ionized calcium concentration.

PTH was measured by RIA with an IRMA assay, which is specific for intact PTH (Allegro; Nichols Institute, San Juan Capistrano, CA). The range of

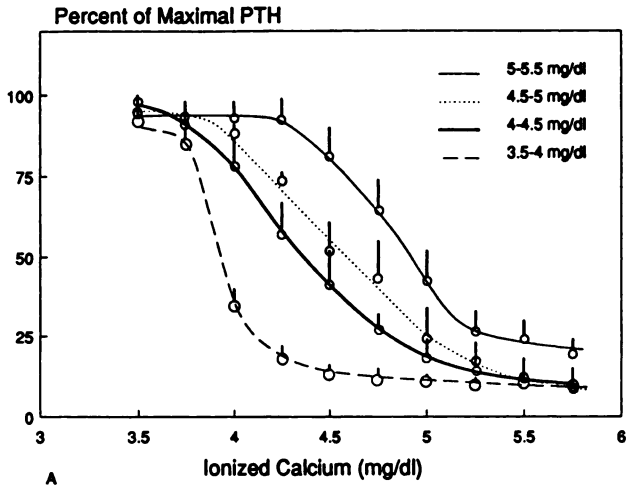

Figure 3. Panel A is a composite of the PTH-calcium curves obtained during the induction of hypocalcemia. As the range of basal serum calcium decreases, the PTH-calcium curves shift further to the left. However, as demonstrated in panel B, the PTH-calcium curve obtained during the recovery from hypocalcemia does not appear to be influenced by the PTH-calcium curve obtained during the induction of hypocalcemia. Values are mean ± SE.

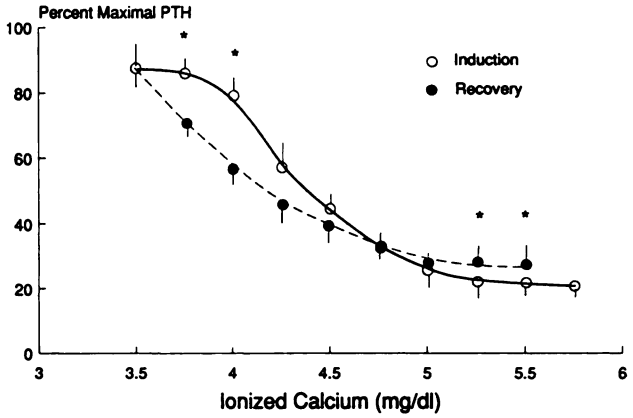

Figure 4. The mean sigmoidal PTH-calcium curve (±SE) developed during the induction of hypocalcemia and hypercalcemia from baseline (solid line) is contrasted with the mean PTH-calcium curve developed as the ionized calcium concentration was increased during the recovery from the nadir of hypocalcemia (broken line). The maximal PTH level is represented as 100%. The difference in the two PTH-calcium curves is known as hysteresis. * $P < 0.05$.

TABLE 1. Biochemical data[a]

	Patients	Normal Range
Serum calcium (mg/dL)	9.5 ± 0.2	8.5–10.5
Serum phosphorus (mg/dL)	5.3 ± 0.2	2.5–4.5
Serum alkaline phosphatase (U/L)	107 ± 9	40–115
Serum albumin (g/dL)	3.8 ± 0.1	3.5–5.0
Serum aluminum (μg/L)	139 ± 23	<5

[a] Values are mean ± SE.

PTH for this assay in normal individuals is 10 to 65 pg/mL (5,6,10,12). All samples from an individual patient were measured in the same assay. Intra-assay variation was less than 5%. Ionized calcium was measured with an ICA1 ionized calcium analyzer (Radiometer A/S, Copenhagen, Denmark). Serum aluminum was measured by flameless atomic absorption spectrophotometry by a previously described method (12). Serum phosphorus, albumin, and alkaline phosphatase were measured with a Technicon SMA II autoanalyzer (Technicon Instruments Corporation, Tarrytown, NY).

Bone biopsies were obtained after 2 days of oral tetracycline was administered twice, at a 10-day interval. The bone specimens were processed and quantified as described previously (6,12). Patients were considered to have LTAABD if the osteoblast surface was less than 5%, the aluminum surface was greater than 20%, and the bone formation rate was less than 106 $\mu m^2/mm^2/day$ (12).

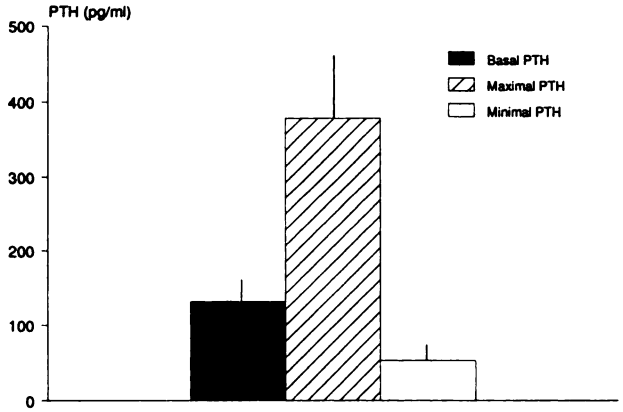

Figure 5. Shown are the mean values (±SE) for basal PTH, maximal PTH, and minimal PTH in the 19 patients.

Data were evaluated by using analysis of variance for repeated measures. The paired and unpaired *t* tests for single comparisons were used when applicable. A *P* value of <0.05 was considered significant. Results are expressed as the mean ± SE.

RESULTS

In Table 1, the biochemical data of the 19 hemodialysis patients with LTAABD are presented. Total serum calcium and serum albumin were normal. Serum alkaline phosphatase was at the upper limits of normal. Serum aluminum and phosphorus were elevated.

As shown in Figure 5, the mean basal, maximal, and minimal PTH levels were 132 ± 37, 387 ± 91, and 53 ± 21 pg/mL, respectively. In addition, the ratio of basal to maximal PTH was 33 ± 5%. When contrasted with values reported in normal volunteers (5), the minimal, basal, and maximal PTH levels were approximately four to five times greater than normal; the basal to maximal PTH ratio was increased by approximately 10%. Finally, although not shown, there was no correlation between either serum aluminum or stainable trabecular bone aluminum and maximal PTH, minimal PTH, and basal PTH.

In Figures 2A through D, the patients are grouped according to their basal ionized calcium concentration. In general, the higher the basal ionized calcium concentration, the higher the ionized calcium concentration at which the intersection of the two PTH-calcium curves (induction of and recovery from hypocalcemia) was observed. In the group with the lowest basal ionized calcium concentration (Figure 2D), the intersection of the two PTH-calcium curves was observed at an ionized calcium concentration less than 4 mg/dL. In addition, as the basal ionized calcium decreased from a range of 5 to 5.5 to 3.5 to 4.0 mg/dL, the PTH-calcium curve during the induction of hypocalcemia shifted progressively to the left (Fig. 3A). However, the PTH-calcium curve during the recovery from hypocalcemia appeared to remain constant despite changes in the PTH-calcium curve observed during the induction of hypocalcemia (Figure 3B).

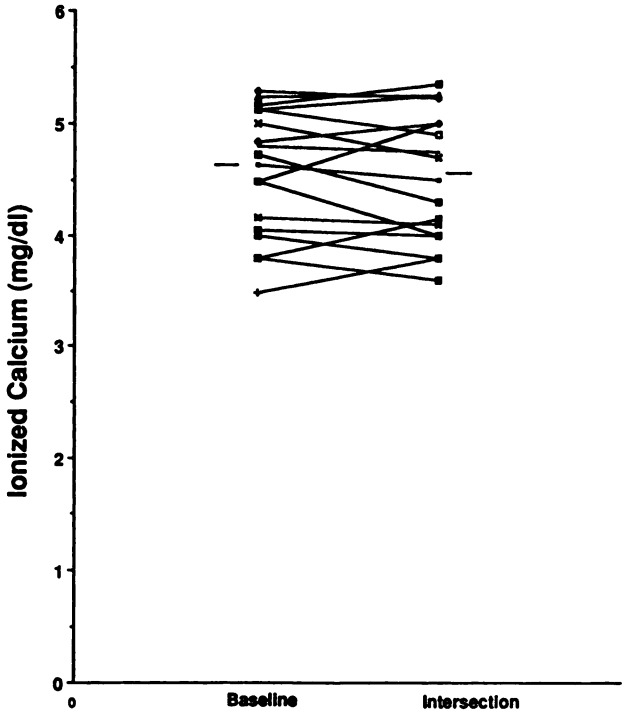

Figure 6. Shown are the individual values in each patient for baseline ionized calcium and the ionized calcium concentration at which the two PTH-calcium curves intersect. The lines connect the two points for each patient. The line to the left of the baseline calcium and to the right of the intersection calcium are the mean values for each.

In Figure 4, the maximal PTH value was transformed to 100% to factor for differences in absolute PTH values between patients. For the same ionized calcium concentration during hypocalcemia, the PTH concentration was greater during the induction of hypocalcemia than during the recovery from hypocalcemia. However, after the intersection of the two PTH curves, the serum PTH concentration was less for the same serum calcium concentration when hypercalcemia was induced from the basal serum calcium than when hypercalcemia was induced from the nadir of hypocalcemia. The set point of calcium, derived from the individual PTH-calcium curves of the 19 patients, was higher during the induction of hypocalcemia than during the recovery from hypocalcemia, 4.44 ± 0.10 versus 4.25 ± 0.09 mg/dL (P = 0.03).

The mean ionized calcium concentration at baseline (4.61 ± 0.13 mg/dL) and the mean ionized calcium concentration at the intersection of the two PTH-calcium curves (4.61 ± 0.12 mg/dL) were the

same. In Figure 6, it can be observed that in each patient, the basal ionized calcium concentration was similar to the ionized calcium concentration at the intersection of the two PTH-calcium curves. In addition, a regression analysis performed between the ionized calcium concentration at baseline and the ionized calcium concentration at the intersection of the two PTH-calcium curves showed a significant correlation with the slope approaching unity: $y = 0.435 + 0.91x$ ($r = 0.87$; $P < 0.001$).

DISCUSSION

This study demonstrated that for the same serum calcium concentration, the serum PTH level was higher during the induction of hypocalcemia than during the recovery from hypocalcemia. This phenomenon is known as hysteresis and, as applied to PTH secretion, was recently introduced by Conlin *et al.* (10) to characterize the influence of directional changes of the serum calcium on PTH secretion. In their study, directional changes in the serum calcium affected PTH secretion during both hypocalcemia and hypercalcemia. Our results were similar to those observed by Conlin *et al.* (10) in normal volunteers and by Cunningham *et al.* (11) in hemodialysis patients. Others have found by using a calcium clamp technique that hypocalcemia maximally stimulated PTH, but PTH levels gradually declined after 15 min even though the magnitude of hypocalcemia was maintained constant (15,16). Thus, the results of our study are in agreement with those of previous studies that have evaluated the effect of directional changes in the serum calcium on PTH secretion during hypocalcemia.

In the study by Cunningham *et al.* in hemodialysis patients, the hysteretic response to hypocalcemia was not altered by the serum aluminum concentration (11). The findings in our study would serve to confirm this observation. Furthermore, as we have reported previously (12), most of our patients were treated with desferrioxamine for 1 yr. Treatment with desferrioxamine reduced stainable trabecular bone aluminum from 44 ± 4 to 13 ± 3%, even though the serum aluminum level did not change. When parathyroid function was reevaluated after desferrioxamine treatment, the hysteresis of the PTH-calcium curve was similar to that observed before treatment with desferrioxamine.

In the study presented here, the PTH level for the same serum calcium concentration was greater when hypercalcemia was induced from the nadir of hypocalcemia than when hypercalcemia was induced from basal serum calcium. In our study, the sequence of hypercalcemia was different from that in other studies, in which the hypercalcemia was induced first and then the serum calcium concentration was decreased. Adami *et al.*, (17) in both dialysis patients and patients with vitamin D deficiency, and Conlin *et al.*, (10) in normal volunteers, found that PTH levels were lower during the induction of hypercalcemia than during the recovery from hypercalcemia. However, Cunningham *et al.*, (11) in hemodialysis patients, did not find any difference in PTH levels during the induction of and recovery from hypercalcemia. Perhaps more surprising were the results of an animal study in which serum PTH levels were greater during the induction of hypercalcemia than during the reduction of the serum calcium (18).

In the study presented here, PTH was measured with an immunoradiometric assay that is specific for intact hormone (19). In previous studies, this PTH assay has proven to be reliable and sensitive to changes in the serum calcium concentration (5,6,10,12). Thus, the PTH results do not appear to be artifactual. Possible explanations to be considered for hysteresis include the following. As suggested by some, hypocalcemia may accelerate the peripheral metabolism of PTH (20); however, this has not been observed by others (15,21). It is also possible that the parathyroid gland could have released PTH fragments (22); however, the PTH assay used for this study is highly specific for intact hormone and should not measure carboxy-terminal or midmolecule fragments of PTH. An intriguing possibility is that the differences in PTH levels during the induction of and recovery from hypocalcemia may be due to PTH stored in the parathyroid gland. Thus, during the induction of hypocalcemia, the higher PTH level would be due to the combination of the production rate of PTH plus the release of stored hormone. Then, during the recovery from hypocalcemia, stored hormone is depleted and PTH levels depend solely on the production rate. However, against this possibility is our finding of the transposition of the PTH curves when hypercalcemia was induced. If depletion of stored PTH were important, it would be difficult to explain the increase of PTH levels when hypercalcemia was induced from the nadir of hypocalcemia, unless the rate of PTH production increased during the course of this study. To evaluate this question, a study should be performed to test the PTH response to the reinduction of hypocalcemia after the recovery from the initial hypocalcemia. Finally, Conlin *et al.* (10) suggested that the shorter duration of the recovery period could have influenced the hysteretic response of PTH. However, our results would suggest that time was not a factor, because the duration of the recovery from hypocalcemia was not shorter than the induction of hypocalcemia.

An interesting finding in our study was that the basal serum calcium concentration seemed to determine the calcium concentration at which the two PTH curves intersected. This finding has been demonstrated in Figures 2 and 6. In addition, the correlation between these two parameters was significant

with a slope that approached unity. The regulation of serum calcium is not as precise in dialysis patients as in the normal individual. Thus, a wider range of basal serum calcium levels is observed in the dialysis patient. However, why the PTH-calcium curve derived from the induction of hypocalcemia and the PTH-calcium curve generated by the recovery from hypocalcemia should intersect in the proximity of the basal serum calcium concentration is not known. In addition, whether this finding is involved with the mechanism of hysteresis remains to be determined. Finally, as demonstrated in Figure 3, the PTH-calcium curve shifted to the left as the basal serum calcium decreased; however, the PTH-calcium curve reflecting the recovery from hypocalcemia remained constant. This finding would suggest that the basal serum calcium may dictate the level at which PTH is stimulated during the induction of hypocalcemia or, conversely, that the level of calcium at which PTH responds determines the basal serum calcium concentration. However, the PTH-calcium curve during the recovery from hypocalcemia, while consistently showing a hysteretic pattern, did not appear to be influenced by the PTH response during the induction of hypocalcemia.

The results of this study and others stress the value of analyzing PTH and calcium as a two-dimensional model with the omission of time (4–6,10,12). By plotting PTH versus calcium, the importance of the sigmoidal relationship between these two parameters is appreciated. Thus, important factors such as the set point and the slope can be defined and analyzed, as well as the ionized calcium concentration at which the intersection of the two PTH-calcium curves is observed. In addition, such an analysis permits a comparison of different PTH-calcium curves obtained in different forms of renal osteodystrophy or after a specific form of treatment, such as calcitriol or desferrioxamine (6,12,23). The plotting of calcium and PTH versus time, as performed in some studies, obscures the sigmoidal relationship between PTH and calcium (11,13,17,18); in addition, even the rapidity of changing the serum calcium concentration may not influence PTH secretion (5).

In summary, the PTH response to hypocalcemia and hypercalcemia was evaluated in 19 maintenance hemodialysis patients with LTAABD. The mean basal serum PTH level was greater than normal, and the pattern of the PTH response to hypocalcemia and hypercalcemia was appropriate. During the recovery from hypocalcemia, PTH levels, for the same serum calcium concentration, were significantly lower than PTH levels during the induction of hypocalcemia. However, during hypercalcemia, the PTH-calcium curves were transposed. This type of PTH response has been termed hysteresis. The observation was also made that the intersection of the two PTH-calcium curves, generated by the induction of and the recovery from hypocalcemia, seemed to be determined by the basal serum calcium concentration. In conclusion, for the same serum calcium concentration, the PTH response to the induction of and the recovery from hypocalcemia was different. Similar findings were observed in hypercalcemia, except that the induction of hypercalcemia from two different levels of serum calcium produced different PTH levels for the same serum calcium concentration. The cause of the hysteresis is not known.

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