

Cinacalcet Reduces the Set Point of the PTH-Calcium Curve

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ABSTRACT

The calcimimetic cinacalcet increases the sensitivity of the parathyroid calcium-sensing receptor to calcium and therefore should produce a decrease in the set point of the parathyroid hormone (PTH)-calcium curve. For investigation of this hypothesis, nine long-term hemodialysis patients with secondary hyperparathyroidism were given cinacalcet for 2 mo, the dosage was titrated per a protocol based on intact PTH and plasma calcium concentrations. Dialysis against low- and high-calcium (0.75 and 1.75 mM) dialysate was used to generate curves describing the relationship between PTH and calcium. Compared with precinacalcet levels, cinacalcet significantly reduced mean serum calcium, intact PTH and whole PTH (wPTH; all $P < 0.001$). The set points for PTH-calcium curves were significantly reduced, and both maximum and minimum levels of PTH (intact and whole) were significantly decreased. The calcium-mediated inhibition of PTH secretion was more marked after cinacalcet treatment. In addition, cinacalcet shifted the inverse sigmoidal curve of wPTH/non-wPTH ratio *versus* calcium to the left (*i.e.*, less calcium was required to reduce the wPTH/non-wPTH ratio). In conclusion, cinacalcet increases the sensitivity of the parathyroids to calcium, causing a marked reduction in the set point of the PTH-calcium curve, in hemodialysis patients with secondary hyperparathyroidism.

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Calcimimetics are widely accepted for the treatment of secondary hyperparathyroidism, commonly observed in dialysis patients. They are effective in decreasing parathyroid hormone (PTH), phosphorus, calcium, and the calcium-phosphorus product, even in patients with advanced disease.¹ Decreased expression of the parathyroid calcium-sensing receptor (CaR) in severe parathyroid hyperplasia² may reduce the sensitivity of the parathyroid cell to extracellular calcium, leading to an increase in the set point of the PTH-calcium curve. It is generally accepted that a left shift of the set point indicates an increase in the sensitivity of the parathyroid gland to calcium.³ Thus, if calcimimetics increase parathyroid CaR sensitivity to calcium, then they should produce a decrease in the set point of the PTH-calcium curve.

An immunometric assay for the measurement of intact PTH (iPTH) was, until recently, the accepted standard for the measurement of PTH; however,

the iPTH assay has been shown to react not only with the bioactive form of PTH (whole PTH [wPTH]) but also with large, truncated fragments of non-wPTH,^{4–7} with 20 to 60% of PTH measured in normal individuals corresponding to non-wPTH.^{4,6–8} In dialysis patients, the percentage of non-wPTH measured in the iPTH assay is generally greater than that in healthy control subjects.^{4–9} A newer assay, called “whole” or “full” PTH, has been shown to be specific for wPTH.⁷ Plasma concentra-

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tions of non-wPTH can be determined by subtracting the wPTH value from that measured with the iPTH assay.^{10,11}

The proportional secretion of wPTH and non-wPTH may be modified by the predialysis plasma calcium concentration in hemodialysis patients.^{10,11} In one study,¹² we showed that although acute changes in plasma calcium produce similar secretory responses in wPTH and non-wPTH, the secretory responses are not proportional for these PTH moieties. Changes in the plasma calcium concentration modulate the ratio of wPTH/non-wPTH in a sigmoidal pattern with hypocalcemia maximizing this ratio.

The aim of this study was to evaluate the effect of cinacalcet on the dynamics of wPTH and non-wPTH secretion and also on the wPTH/non-wPTH ratio in response to the induction of hypo- and hypercalcemia during hemodialysis. The set point of the PTH-calcium curve was compared in the same hemodialysis patients before and after treatment with cinacalcet.

RESULTS

Nine patients (five men, four women) who aged 27 to 63 yr (mean 49) and had spent 18 to 240 mo on hemodialysis were included in the study. Causes of renal disease included nephroangiosclerosis ($n = 1$), polycystic kidney disease ($n = 1$), interstitial nephritis ($n = 1$), glomerulonephritis ($n = 2$), hemolytic uremic syndrome ($n = 1$), and unknown ($n = 3$).

Treatment with cinacalcet led to a significant reduction in mean plasma ionized calcium and phosphorus levels ($P < 0.001$ and $P < 0.020$, respectively; Table 1). There was no significant change in the mean serum albumin and alkaline phosphatase concentrations after cinacalcet treatment (Table 1).

There was a significant decrease in basal iPTH and basal wPTH levels after the 2-mo treatment with cinacalcet (both $P < 0.001$; Table 1). Before cinacalcet treatment, the mean

wPTH level was $56 \pm 12\%$ of the iPTH value; after cinacalcet treatment, wPTH accounted for $62 \pm 10\%$ of the iPTH value (NS *versus* precinacalcet treatment).

Set Point of the PTH-Calcium Curve

Changes in plasma ionized calcium concentration induced by hemodialysis with low and high concentrations of calcium in the dialysate produced a sigmoid-shaped response of iPTH and wPTH (Figure 1). Set points measured from iPTH-calcium and wPTH-calcium curves were not statistically different. Before treatment with cinacalcet, the set point of the iPTH-calcium curve was 1.21 ± 0.02 ; after treatment with cinacalcet, the set point decreased significantly to 1.10 ± 0.01 ($P < 0.001$). Similar results were obtained from the wPTH-calcium curve (Table 1). Results obtained when the set point was calculated as the plasma calcium midrange between the minimal and maximal PTH led to similar results (Table 1).

Maximal and Minimal PTH

Hemodialysis with a low concentration of calcium in the dialysate produced an increase in iPTH and wPTH to their maximal levels. Cinacalcet produced a significant decrease in the maximal iPTH and wPTH levels ($P < 0.001$ and $P < 0.020$, respectively; Table 1). The degree of decrease in maximal PTH was similar for iPTH and wPTH (24 and 26%, respectively). Similarly, hemodialysis-induced hypercalcemia produced a decrease in iPTH and wPTH to minimal levels (Table 1). Cinacalcet treatment led a significant decrease in the minimal iPTH and wPTH levels ($P < 0.001$ and $P < 0.020$, respectively). Again, the degree of decrease in minimal PTH was similar for iPTH and wPTH (64 and 59%, respectively).

Mean plasma calcium concentrations required to stimulate iPTH and wPTH maximally were higher before (1.075 ± 0.020 and 1.070 ± 0.002) than after (0.98 ± 0.04 and 0.95 ± 0.03) treatment with cinacalcet (both $P < 0.01$). Plasma calcium

Table 1. Levels of calcium, phosphorus, albumin, alkaline phosphatase, iPTH, and wPTH before and after cinacalcet treatment^a

Parameter	Before Cinacalcet	After Cinacalcet	P
Basal calcium (mM)	1.190 ± 0.110	1.110 ± 0.200	<0.001
Phosphorus (mM)	1.740 ± 0.160	1.410 ± 0.090	<0.020
Albumin (g/dl)	3.960 ± 0.400	4.030 ± 0.500	NS
Alkaline phosphatase (IU/L)	117.000 ± 20.000	134.000 ± 28.000	NS
Basal iPTH (pg/ml)	645.000 ± 86.000	336.000 ± 55.000	<0.001
Maximal iPTH (pg/ml)	997.000 ± 116.000	762.000 ± 107.000	<0.001
Minimal iPTH (pg/ml)	148.000 ± 29.000	53.000 ± 10.000	<0.001
iPTH basal/maximal ratio	0.640 ± 0.060	0.460 ± 0.070	<0.050
iPTH set point	1.210 ± 0.020	1.100 ± 0.010	<0.001
iPTH set point (midrange)	1.190 ± 0.020	1.090 ± 0.010	0.001
Basal wPTH (pg/ml)	358.000 ± 46.000	181.000 ± 11.000	<0.010
Maximal wPTH (pg/ml)	624.000 ± 93.000	467.000 ± 65.000	<0.020
Minimal wPTH (pg/ml)	56.000 ± 14.000	23.000 ± 5.300	<0.020
wPTH basal/maximal ratio	0.530 ± 0.050	0.430 ± 0.050	<0.050
wPTH set point	1.190 ± 0.020	1.075 ± 0.010	<0.001
wPTH set point (midrange)	1.180 ± 0.010	1.060 ± 0.010	<0.001

^aData are means \pm SE.

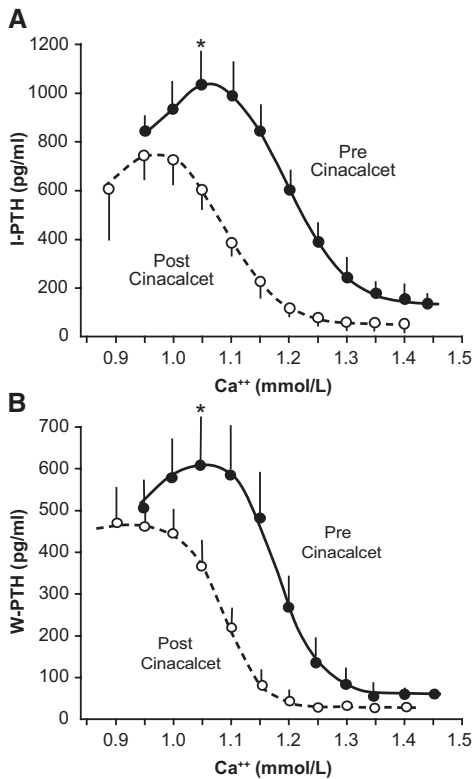


Figure 1. (A) PTH-calcium curve for iPTH before and after treatment with cinacalcet. ●, before cinacalcet; ○, after cinacalcet. (B) PTH-calcium curve for wPTH before and after treatment with cinacalcet (* $P < 0.05$ for both iPTH and wPTH before and after cinacalcet treatment for ionized calcium concentrations >1.05 mM). ●, before cinacalcet; ○, after cinacalcet.

concentrations required to achieve minimal iPTH and wPTH were lower after (1.25 ± 0.04 and 1.22 ± 0.03) than before (1.39 ± 0.05 and 1.33 ± 0.03) cinacalcet therapy (both $P < 0.001$).

The relationships between iPTH and wPTH secretion, measured as a percentage of maximal PTH stimulation, and ionized calcium concentrations are shown in Figure 2. The reduction of PTH secretion (iPTH and wPTH) by calcium was more marked after treatment with cinacalcet than before. Before cinacalcet, for a plasma ionized calcium concentration of 1.15 mM, both iPTH and wPTH were stimulated at 70 to 80% of the maximal PTH; however, after cinacalcet, the same calcium concentration produced almost total inhibition of PTH secretion. For ionized calcium concentrations >1.05 mM, the values for iPTH and wPTH were significantly lower ($P < 0.05$) after than before treatment with cinacalcet (Figure 1).

Ratio of Basal To Maximal PTH

One important observation is a greater decrease in set point (0.11 mmol/L) than in basal serum calcium (0.08 mmol/L) levels, resulting in a lower basal/maximal PTH ratio. The ratio of basal to maximal PTH for iPTH and wPTH decreased after treatment with cinacalcet (both $P < 0.05$; Figure 2, Table 1).

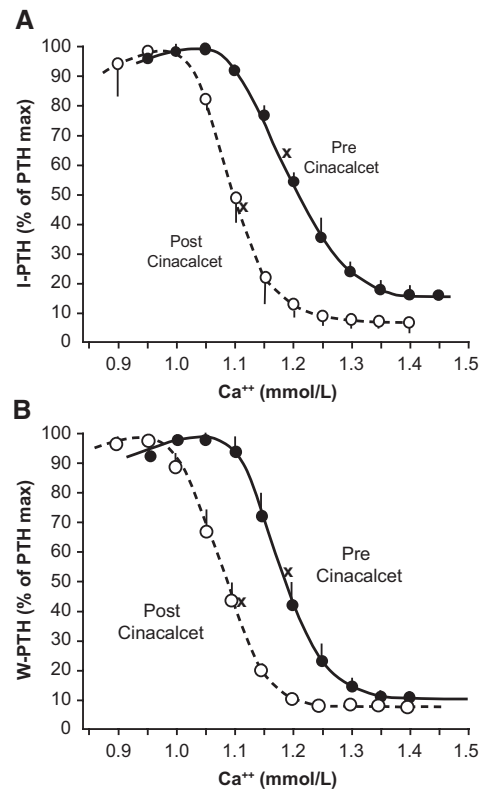


Figure 2. (A) Relationship between the percentage of maximal PTH stimulation for iPTH and the ionized calcium concentration. ●, before cinacalcet; ○, after cinacalcet; x, basal values. (B) Relationship between the percentage of maximal PTH stimulation for wPTH and the ionized calcium concentration. ●, before cinacalcet; ○, after cinacalcet; x, basal values.

Thus, the relative degree of PTH stimulation at the basal plasma calcium concentration was reduced after treatment with cinacalcet.

The wPTH to Non-wPTH Ratio

The relationship between the ratio wPTH/non-wPTH and the plasma ionized calcium concentration before and after treatment with cinacalcet are shown in Figure 3. The wPTH/non-wPTH ratio decreased as the plasma calcium concentration increased. After treatment with cinacalcet, the curve shifted to the left; thus, less calcium was required to reduce the wPTH/non-wPTH ratio. Before treatment, the basal calcium was 1.19 ± 0.11 mM and the corresponding ratio wPTH/non-wPTH was 1.18 ± 0.14 . After treatment with cinacalcet, the plasma calcium decreased to 1.11 ± 0.20 mM; however, the ratio wPTH/non-wPTH remained almost the same (1.12 ± 0.17).

DISCUSSION

Cinacalcet lowers PTH, phosphorus, calcium, and the calcium-phosphorus product¹ and is licensed for the treatment of sec-

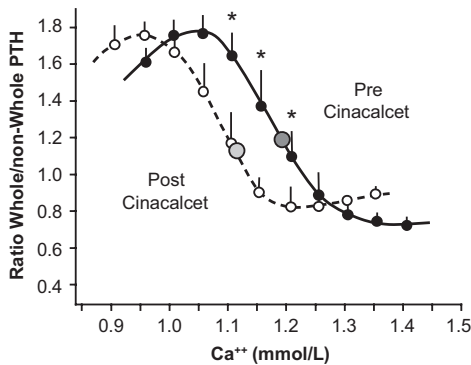


Figure 3. Relationship between wPTH/non-wPTH and serum ionized calcium concentration before and after treatment with cinacalcet. Values of wPTH/non-wPTH were significantly decreased ($*P < 0.05$) after cinacalcet at ionized calcium concentrations of 1.10, 1.15, and 1.20 mmol/L. ●, before cinacalcet; ○, after cinacalcet; ●, basal serum calcium values.

ondary hyperparathyroidism in hemodialysis patients with ESRD. Because cinacalcet targets the parathyroid CaR, increasing sensitivity to extracellular calcium, it was hypothesized that cinacalcet should produce a decrease in the set point of the PTH-calcium curve in patients with secondary hyperparathyroidism.

The dynamics of PTH secretion were evaluated using low and high concentrations of calcium dialysate before and after treatment with cinacalcet. After 2 mo of treatment with cinacalcet, there was a left shift of the PTH-calcium curves for both iPTH and wPTH. Thus, cinacalcet reduces the set point of the PTH-calcium curves, and, therefore, the sensitivity of the parathyroid cells to calcium is increased. Previous studies showed there was a greater reduction in PTH levels 4 h after administration of cinacalcet than at the 24-h time point, which was used to monitor the efficacy of treatment^{13,14}; therefore, 24 h after treatment, any acute effect of cinacalcet is absent. In this study, patients received cinacalcet the day before blood sampling. The half-life of the cinacalcet molecule is 34 ± 9 h¹⁵; therefore, the PTH-calcium curve was obtained when serum cinacalcet levels were minimal, and the change in the set point was not the result of an acute calcimimetic effect.

Several reports^{16–18} have shown that there is an “adaptation” of the PTH-calcium curve set point to the prevailing plasma calcium concentration. A decrease in plasma calcium was associated with a reduction in the set point, with an increase in basal minimum and maximum PTH secretion and even in the basal-to-maximal PTH ratio. These changes in PTH secretion are increased responses of parathyroid cells to the low calcium levels. In our study, the decrease in set point was due to increased sensitivity of the receptor to the inhibitory effect of calcium. The decrease in set point after cinacalcet was associated with a decrease in basal minimal and maximal PTH secretion and a decrease in the basal to maximal PTH secretion, which is a clear sign of inhibition of parathyroid gland activity. Possible explanations for an alteration in the set point

of the PTH-calcium curve include changes in the extracellular ionized calcium concentration,^{16,17} which is not supported by this study, or a calcium-independent effect.¹⁹

After cinacalcet treatment, minimal wPTH and iPTH were accomplished with a normal calcium concentration (1.22 and 1.25 mM, respectively). A small increase in plasma calcium concentration within the normal range may produce a marked decrease in PTH and explains the effectiveness of cinacalcet in the treatment of secondary hyperparathyroidism. In addition, basal PTH, maximal PTH, and minimal PTH for wPTH and iPTH were reduced after treatment with cinacalcet.

The patients included in this study had high PTH levels; therefore, they benefited from the treatment with cinacalcet. These patients were not on vitamin D. Because vitamin D can modify basal PTH levels,²⁰ treatment with vitamin D analogs in the 6 mo before and during the study was not permitted, to avoid any possible confounding effect produced by the action of vitamin D receptor activation. The dynamic of PTH secretion was evaluated in the same patients using low- and high-calcium hemodialysis (which effectively decreases and increases plasma calcium, respectively), resulting in a concomitant stimulation and inhibition of PTH secretion. This method has been used by different investigators to assess the dynamics of PTH secretion in hemodialysis patients with secondary hyperparathyroidism.^{16–18,21–23}

The relative degree of PTH stimulation was measured using the ratio of basal to maximal PTH. In normal volunteers, this ratio is 20 to 25%²⁴ and is higher in hemodialysis patients.^{12,16} In this study, the ratio of basal to maximal PTH for wPTH and iPTH was 53 and 64%, respectively, before cinacalcet treatment. After treatment with cinacalcet, the ratio was reduced (43 and 46%), indicating a reduction in PTH stimulation relative to the maximal capacity of the gland.

To our knowledge, no published written report has shown the effect of calcimimetics on set point in dialysis patients. In this study, there was a decrease in the wPTH/non-wPTH ratio as the plasma calcium concentration increased. After treatment with cinacalcet, the wPTH/non-wPTH ratio *versus* calcium curve shifted to the left. Thus, less calcium was required to reduce the wPTH/non-wPTH ratio. Despite the hypocalcemic effect of cinacalcet, the wPTH/non-wPTH ratio was unchanged. The left shift of the wPTH/non-wPTH ratio *versus* calcium curve is an interesting finding. The plasma calcium response to PTH is nearly linear between 0.625 and 1.250 mM; however, above a plasma calcium concentration of 1.25 mM, the response decreases.²⁰ This reduced response is due, in part, to an increase in carboxy-terminal and large truncated amino-terminal PTH fragments.^{25,26} These fragments antagonize the calcemic effect of PTH.^{10,27,28} Some authors proposed that a decrease in wPTH/non-wPTH ratio was associated with decreased turnover.¹¹ Because cinacalcet inhibits parathyroid gland function,¹² a decrease in the wPTH/non-wPTH ratio would have been expected, with a consequent increase in the risk for low bone turnover as a result of a decrease in wPTH relative to non-wPTH; however, cinacalcet treatment shifted the inverse sigmoidal curve of wPTH/non-wPTH–calcium leftward,

and hypocalcemia, induced by cinacalcet, could offset the decreased wPTH/non-wPTH ratio. A previous study by Martin *et al.*²⁹ compared the effect of long-term treatment with cinacalcet or placebo on the ratio of bioactive PTH (biPTH) to iPTH-biPTH in patients with secondary hyperparathyroidism. They found significant variations in this ratio with respect to plasma calcium. Higher plasma calcium levels were associated with a lower ratio of biPTH to iPTH-biPTH in both treatment groups. For any given plasma calcium concentration, the ratio was lower in patients receiving cinacalcet compared with those receiving placebo. This is an interesting observation that does not contradict our results. As depicted in Figure 3, hypercalcemia was associated with a lower ratio of wPTH to non-wPTH, and for serum calcium levels from 1.00 to 1.25 mM, the ratio was lower after cinacalcet treatment than before treatment. In this study, phosphorus levels were reduced after cinacalcet therapy; however, this decrease in serum phosphorus levels is not expected to have a large impact on the set point of the PTH-calcium curve.^{30,31}

The maximal secretion of PTH obtained during hemodialysis with low calcium is a reflection of the size of the parathyroid gland or the number of parathyroid cells that are actively secreting PTH. The parathyroid gland size was not measured in this study; however, it is unlikely that, in such a short period of time, cinacalcet was able to reduce the size of the parathyroid glands. Although it could be that the number of cells secreting PTH has decreased, the minimal PTH may also reflect the total mass of parathyroid cells. In this study, the minimal PTH decreased by as much as 65% after treatment with cinacalcet. We propose that cinacalcet may decrease maximal and minimal PTH secretion by restraining PTH secretion in a significant number of parathyroid cells.

In conclusion, as cinacalcet increases the sensitivity of the CaR to the inhibitory effect of calcium in patients with secondary hyperparathyroidism, a high calcium level is not required to inhibit PTH secretion.

CONCISE METHODS

Five male and four female patients who were younger than 65 yr and met the following criteria were eligible for inclusion in the study: On long-term hemodialysis for >6 mo and clinically stable with no recent illnesses, iPTH 300 to 1000 pg/ml, normal plasma calcium concentration (9.0 to 10.6 mg/dl), serum phosphorus concentration <6 mg/dl, no treatment with vitamin D analogs during the previous 6 mo and not added to treatment during the study period, no diabetes, and serum aluminum levels <35 µg/L. The protocol adhered to the Declaration of Helsinki and was approved by the institutional review board at the Hospital Universitario Reina Sofia (Cordoba, Spain). Informed written consent was obtained before inclusion in the study.

PTH-calcium curves were measured before and after 2 mo of treatment with cinacalcet. Patients were started on cinacalcet 30 mg/d, and iPTH concentration was measured at weekly intervals. The dosage of cinacalcet was increased by 30 mg/d when the PTH was >300 ng/ml

and the plasma calcium concentration was >8.5 mg/dl, whereas the cinacalcet dosage was decreased (withheld) when PTH was <150 ng/ml or plasma calcium was <8.5 mg/dl.

Maximal secretion and suppression of iPTH and wPTH as well as the entire PTH-calcium curve were determined by performing hemodialysis with low (0.75 mM) and high (1.75 mM) concentrations of calcium dialysate separated by 1 wk.^{16,17,21,22} Blood was drawn at regular intervals (basal and 10, 20, 30, 45, 60, 90, 120, 150, 180, and 210 min from the beginning of the hemodialysis session) for measurement of ionized calcium, iPTH, and wPTH. Patients received cinacalcet the day before blood sampling.

The following terms were defined for wPTH and iPTH, using the data obtained during dialysis-induced hypo- and hypercalcemia: (1) Basal PTH was the mean of the predialysis PTH level with low- or high-calcium dialysate; (2) maximal PTH was the highest PTH level observed in response to hypocalcemia; an additional reduction of the plasma calcium concentration did not further increase the PTH; (3) minimal PTH was the lowest PTH level during suppression by hypercalcemia; a further increase in the plasma calcium concentration did not result in any additional decrease in PTH; (4) ratio of basal to maximal PTH (%) was (basal PTH/maximal PTH) × 100 (this ratio is 20 to 25% in normal volunteers²⁴) by correcting the actual PTH for the overall capacity to produce PTH (maximal PTH), a measure of the relative degree of PTH stimulation is obtained; (5) the set point of calcium was defined as the plasma calcium concentration at which maximal PTH secretion was reduced by 50%.^{16,17,21,22} The method of Brown and colleagues^{32–34} was also used, where the set point of calcium is the plasma calcium at the midrange between the minimal and maximal PTH (curve fitting was achieved using spectral analysis Running-Means software.³⁵); the dependent variable (PTH) was in the form of means of three consecutive serum calcium values, limiting analytical variability; (6) basal plasma calcium was the mean of plasma calcium concentrations at basal (predialysis) PTH with low- or high-calcium dialysate; (7) plasma calcium at maximal PTH secretion was the plasma calcium level at which maximal PTH secretion was achieved; and (8) plasma calcium at minimal PTH secretion was the plasma calcium level at which minimal PTH secretion was achieved.

For assessment of the calcium-dependent changes in iPTH and wPTH, graphs were constructed interpolating the PTH value from the PTH-calcium curve for each patient at the following calcium concentrations: 0.90, 0.95, 1.00, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, and 1.45 mM. After the calculation of individual PTH values, curves were constructed with mean values of interpolated PTH values. The ratio of wPTH to non-wPTH was calculated at baseline and during changes in the ionized calcium concentration.^{8,11}

Laboratory Measurements

During the low- and high-calcium dialysis phases, ionized calcium was measured using a calcium-selective electrode (Bayer Diagnostics, Barcelona, Spain) immediately after the blood sample was obtained. Plasma calcium, phosphorus, alkaline phosphatase, albumin, and aluminum were measured using standard laboratory techniques. PTH was measured using the Duo PTH Kit (Scantibodies Laboratory, San-tee, CA). The kit contains two immunoradiometric assays. Both assays share a polyclonal antibody (anti-PTH 39–84) coated onto the surface of polystyrene beads as a solid phase. The immunoradiometric

assay for wPTH uses a tracer antibody directed against the 1-4 amino-terminal region of PTH. The use of this antibody is designed to be specific for 1-84 PTH.⁷ The immunoradiometric assay for iPTH uses a specific polyclonal antibody directed against 7-34 PTH. With this antibody, both wPTH and non-wPTH are detected. For iPTH and wPTH assays, the normal reference ranges are 14 to 66 and 7 to 36 pg/ml, respectively. The intra- and interassay coefficients of variation were <5 and <7%, respectively, for both assays. The plasma concentration of non-wPTH was determined by subtracting the wPTH assay value from the iPTH assay value.

Statistical Analysis

Results are presented as means \pm SE. When the data were normally distributed, as assessed by the Shapiro-Wilks test, means were compared using paired *t* test or general linear model for repeated measures, followed by the Bonferroni *post hoc* test. Differences were considered significant at $P < 0.05$.

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DISCLOSURES

None.

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