Dynamics of PTH secretion in hemodialysis patients as determined by the intact and whole PTH assays

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Dynamics of PTH secretion in hemodialysis patients as determined by the intact and whole PTH assays. Background. Renal hyperparathyroidism is assessed by measurement of parathyroid hormone (PTH) levels. The intact PTH assay (I-PTH) not only reacts with 1-84 PTH but also with large, truncated fragments of non-1-84 PTH. Because the whole PTH assay (W-PTH) is specific for 1-84 PTH, non-1-84 PTH is determined by subtracting W-PTH from I-PTH values. These large circulating PTH fragments may exert a hypocalcemic effect by contributing to skeletal resistance to 1-84 PTH.

Methods. The dynamic secretion of both 1-84 PTH and non-1-84 PTH was evaluated during the induction of hypo- and hypercalcemia in eight hemodialysis patients.

Results. The basal ionized calcium concentration was 1.23 ± 0.03 mmol/L at which time I-PTH, W-PTH, and non-1-84 PTH values were 276 ± 78 pg/mL, 164 ± 48 pg/mL, and 102 ± 28 pg/mL, respectively. The induction of hypo- and hypercalcemic changes resulted in a sigmoidal response for all three PTH moieties, I-PTH, W-PTH, and non-1-84 PTH. During hypocalcemia, maximal values of W-PTH were greater than those of non-1-84 PTH. But during hypercalcemia, minimal values of W-PTH and non-1-84 PTH were similar. Neither the set points nor the basal/maximal ratios for W-PTH, I-PTH, and non-1-84 PTH were different. At the baseline ionized calcium concentration, the W-PTH (1-84 PTH)/non-1-84 PTH ratio was 1.53 ± 0.15. Changes in ionized calcium resulted in a sigmoidal relationship with hypocalcemia, increasing this ratio to a maximum of 2.01 ± 0.30 and hypercalcemia decreasing this ratio to a minimum of 1.18 ± 0.15 (P < 0.01 vs baseline for both hypo- and hypercalcemia).

Conclusion. Although acute changes in serum calcium produce similar secretory responses in 1-84 PTH and non-1-84 PTH, the secretory responses are not proportional for these PTH moieties. Changes in the serum calcium concentration modulate the ratio of 1-84 PTH/non-1-84 PTH in a sigmoidal pattern with hypocalcemia maximizing this ratio. Whether changes in the 1-84 PTH/non-1-84 PTH ratio specifically modulate the calcemic action and other biologic effects of 1-84 PTH remain to be determined.

Secondary hyperparathyroidism is commonly observed in dialysis patients. Measurement of parathyroid hormone (PTH) values is used to assess the severity of hyperparathyroidism, to decide whether to start PTH suppressive treatment, and to monitor the effectiveness of treatment. Until recently, the accepted standard for the measurement of PTH has been the assay for "intact" PTH (I-PTH) developed in the late 1980s. But recently, the I-PTH assay was shown to react not only with 1-84 PTH but also with large, truncated fragments of non-1-84 PTH [1–4]. In humans, 20% to 60% of PTH measured with the I-PTH assay corresponds to non-1-84 PTH [1, 3–5]. In dialysis patients, the percent of non-1-84 PTH measured in the I-PTH assay is generally greater than in normals [1–6]. A new assay called whole PTH (W-PTH) has been shown to be specific for 1-84 PTH [4]. Plasma concentrations of large, truncated fragments of non-1-84 PTH can be determined by subtracting the W-PTH (1-84 PTH) value from that measured with the I-PTH assay [7, 8].

Results from recent studies have suggested that the 7-84 PTH fragment antagonizes the calcemic action of 1-84 PTH. In parathyroidectomized rats, the infusion of 7-84 PTH was shown to inhibit the calcemic action of simultaneously infused 1-84 PTH [7]. These results suggest that large, truncated PTH fragments similar to 7-84 PTH may be an important cause of skeletal resistance to 1-84 PTH in uremia [7]. Moreover, in a study in hemodialysis patients, the 1-84 PTH/non-1-84 PTH ratio was less than 1 only in those patients with low bone turnover, a result that also suggests that large carboxy-terminal fragments may antagonize the skeletal effects of 1-84 PTH [8]. Finally, it was shown that the 7-84 PTH fragment, like other carboxy-terminal fragments, binds only...
to the carboxyl PTH (C-PTH) receptor and does not affect the binding of 1-84 PTH to the PTH/parathyroid hormone related peptide (PTHrP) receptor [9–11]. Thus, it would appear that the 7-84 PTH fragment may decrease the calcemic action of 1-84 PTH through its interaction with the C-PTH receptor.

During hypocalcemia, the proportional increase in middle and late carboxy terminal fragments is less than that of 1-84 PTH [12–14]. Conversely, during hypercalcemia, the proportional decrease in these carboxy terminal fragments is less than that of 1-84 PTH [12–14]. In hemodialysis patients, the percent of non-1-84 PTH was shown to directly correlate with the predialysis serum calcium concentration [7] with an increase in the serum calcium concentration associated with a reduction in the ratio of 1-84 PTH/non-1-84 PTH [8]. While the proportional secretion of 1-84 PTH and non-1-84 PTH may be modified by the predialysis serum calcium concentration [7], there is limited information showing the dynamics of secretion of non-1-84 PTH during the induction of hypo- and hypercalcemia in the same hemodialysis patient.

The goals of the present study were (1) to evaluate the dynamic secretion of both 1-84 PTH and non-1-84 PTH in the same hemodialysis patient during the induction of hypo- and hypercalcemia; (2) to assess the acute regulation and proportional secretion of PTH fragments; and (3) to compare the 1-84 PTH-calcium curve with the I-PTH-calcium and non-1-84 PTH-calcium curves.

METHODS

The criteria for inclusion of chronic hemodialysis patients were (1) clinically stable with no recent illnesses; (2) an I-PTH value between 150 and 600 pg/mL; (3) a normal serum calcium concentration; (4) a serum phosphorus concentration less than 6 mg/dL during the 2 months before study; and (5) no calcitriol treatment during the previous 6 months. Eight patients, four males and four females, agreed to participate in the study. All patients had been on hemodialysis for more than 12 months and no patient was diabetic. The protocol was approved by the Institutional Review Board at the Hospital Universitario Reina Sofia in Cordoba, Spain. The mean age of the patients was 62.8 years (range, 55 to 69 years). The mean duration of hemodialysis was 98 months (range, 15 to 319 months). The primary phosphorus binder was calcium carbonate.

Maximal secretion and suppression of W-PTH and I-PTH were determined by performing a hemodialysis with a low (0.75 mmol/L) and high (1.75 mmol/L) calcium dialysate separated by 1 week [15–18]. In one half of the patients, dialysis with the high calcium dialysate preceded that with the low calcium dialysate. Blood was drawn at regular intervals (basal, 10, 20, 30, 45, 60, 90, 120, 150, 180, and 210 minutes from the beginning of the hemodialysis session) for measurement of ionized calcium and W-PTH and I-PTH. From the data obtained during dialysis-induced hypo- and hypercalcemia, the following terms were defined for W-PTH, I-PTH, and non-1-84 PTH: (1) basal PTH was the predialysis PTH level; (2) maximal PTH was the highest PTH level observed in response to hypocalcemia; the designation of maximal PTH also required that an additional reduction of the serum calcium concentration did not further increase the PTH value; (3) minimal PTH was the lowest PTH level during suppression by hypercalcemia; the designation of minimal PTH also required that a further increase in the serum calcium concentration did not result in any additional decrease in the PTH value; (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 normal volunteers, this ratio is 20 to 25% [19]; 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 we have done previously as the serum calcium concentration at which maximal PTH secretion was reduced by 50% [15–18]; moreover, as was done in other studies, the set point of calcium was also calculated by the method of Brown [20] in which the set point of calcium is the serum calcium at the midrange between the minimal and maximal PTH [21, 22]; (6) the basal serum calcium was the serum calcium concentration at the basal (predialysis) PTH; (7) the serum calcium at maximal PTH secretion was the serum calcium level at which maximal PTH secretion was achieved; and (8) the serum calcium at minimal PTH secretion was the serum calcium level at which minimal PTH secretion was achieved. To assess the calcium-dependent changes in the three PTH moieties, the plasma PTH concentration and the percent of maximal PTH stimulation were plotted against the calcium values extrapolated from the parathyroid function curve of each patient. Finally, as was done in previous studies [5, 8], the ratio of W-PTH (1-84 PTH) to non-1-84 PTH was calculated at baseline and during changes in the ionized calcium concentration.

Laboratory measurements

During the low and high calcium dialysis studies, ionized calcium was measured with a calcium selective electrode (Bayer Diagnostics, Barcelona, Spain) and measurements were performed immediately after the sample was obtained. Otherwise, serum calcium as well as phosphorus, alkaline phosphatase, albumin, and aluminum were measured using standard laboratory techniques. PTH was measured using the Duo PTH Kit (Scantibodies Laboratory, Santee, CA, USA). The kit contains two immunoradiometric assays. Both assays share a polyclonal antibody (anti-PTH 39-84) coated on to the sur-
face of polystyrene beads as a solid-phase. The immuno-
radiometric assay for W-PTH utilizes 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 [4]. The immunoradiometric assay for I-PTH
uses a specific polyclonal antibody directed against 7-34
PTH. With this antibody both 1-84 PTH and large, trun-
cated fragments of non-1-84 PTH are detected. For the
I-PTH and W-PTH assays, the normal reference ranges
are 14 to 66 pg/mL and 7 to 36 pg/mL, respectively. The plasma
concentration of non-1-84 PTH was determined by sub-
tracting the 1-84 PTH (whole) assay value from the
I-PTH assay value.

Statistics
Results are expressed as mean ± SE. When 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. The Friedman and Wilcoxon
tests were used when data were not normally distributed.
Differences were considered significant when the P value
was less than 0.05.

RESULTS
At entry, the serum calcium and phosphorus values
were 9.9 ± 0.3 mg/dL and 4.6 ± 0.9 mg/dL, respectively.
All patients had serum aluminum levels below 35 µg/L,
with a mean value of 15 ± 7 µg/L. Serum albumin and
alkaline phosphatase concentrations were 3.6 ± 0.4 g/dL
and 217 ± 69 IU/L, respectively.
The basal ionized calcium concentration was 1.23 ±
0.03 mmol/L at which I-PTH, W-PTH, and non-1-84 PTH
values were 276 ± 78 pg/mL, 164 ± 48 pg/mL, and 102 ±
28 pg/mL, respectively (Table 1). At baseline, W-PTH
was 60% ± 3% of the I-PTH value while non-1-84 PTH
was 40% ± 6% of I-PTH. Hemodialysis with a low and
high calcium dialysate resulted in sigmoidal PTH-cal-
cium curves for all three PTH moieties (Fig. 1). Hypocalce-
emia increased I-PTH, W-PTH, and non-1-84 PTH val-
ues and the three PTH assay values reached maximal
levels at an ionized calcium concentration of 1.08 ± 0.03
mmol/L. As would be expected, maximal values of
I-PTH were greater than W-PTH values. The latter were
also greater than the non-1-84 PTH value. Hypercalce-
mia decreased values of I-PTH, W-PTH, and non-1-84 PTH.
Maximal inhibition of the three assay values
was achieved at similar ionized calcium concentrations:
1.35 ± 0.02 mmol/L (I-PTH), 1.36 ± 0.02 mmol/L
(W-PTH), and 1.33 ± 0.01 mmol/L (non-1-84 PTH).
At minimal PTH, the concentrations of W-PTH and non-
1-84 PTH were similar (Table 1) (Fig. 1). The W-PTH
concentration was greater than that of non-1-84 PTH
from ionized calcium values of 0.95 to 1.20 mmol/L. In
the hypercalcemic range, no differences were observed
between W-PTH and non-1-84 PTH values.
The relationship between the ionized calcium concen-

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Table 1. Dynamics of parathyroid hormone (PTH) secretion during the induction of hypo- and hypercalcemia

<table>
<thead>
<tr>
<th></th>
<th>Intact PTH</th>
<th>Whole PTH</th>
<th>Non-1-84 PTH</th>
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<tbody>
<tr>
<td>Basal PTH pg/mL</td>
<td>276 ± 78</td>
<td>164 ± 48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>102 ± 28&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maximal PTH pg/mL</td>
<td>721 ± 101</td>
<td>477 ± 59&lt;sup&gt;b&lt;/sup&gt;</td>
<td>253 ± 47&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>Minimal PTH pg/mL</td>
<td>112 ± 16</td>
<td>58 ± 8&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>52 ± 9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Basal/maximal PTH %</td>
<td>37 ± 7</td>
<td>34 ± 6</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>Calcium at PTH maximum mmol/L</td>
<td>1.08 ± 0.03</td>
<td>1.08 ± 0.03</td>
<td>1.08 ± 0.04</td>
</tr>
<tr>
<td>Calcium at PTH minimum mmol/L</td>
<td>1.35 ± 0.02</td>
<td>1.36 ± 0.02</td>
<td>1.33 ± 0.01</td>
</tr>
<tr>
<td>Set point (50%) mmol/L</td>
<td>1.19 ± 0.03</td>
<td>1.18 ± 0.03</td>
<td>1.20 ± 0.03</td>
</tr>
<tr>
<td>Set point (midrange) mmol/L</td>
<td>1.17 ± 0.03</td>
<td>1.17 ± 0.03</td>
<td>1.17 ± 0.03</td>
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Mean ± SE.
<sup>a</sup>P < 0.05 as compared with intact PTH; <sup>b</sup>P < 0.05 as compared with whole PTH.

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Fig. 1. Changes in the secretion of intact parathyroid hormone (I-PTH), whole PTH (W-PTH), and non-1-84 PTH are shown in relation to the ionized calcium concentration. Horizontal lines at the top of the figure indicate the range of ionized calcium concentration at which differences were significant.
tration and the percent of maximal PTH stimulation for I-PTH, W-PTH, and non-1-84 PTH is shown in Figure 2. With ionized calcium concentrations ranging from 0.95 to 1.25 mmol/L, values of the three PTH moieties as a percent of maximal stimulation were similar indicating that during hypocalcemia, the degree of stimulation for W-PTH and I-PTH was not different. During PTH suppression between ionized calcium values from 1.30 to 1.50 mmol/L, non-1-84 PTH as a percent of its maximal value was greater than that of both W-PTH and I-PTH. The set points for the three PTH moieties were not different (Table 1). Also the basal/maximal ratios for W-PTH, I-PTH, and non-1-84 PTH were not different (Table 1).

In Figure 3, the W-PTH/non-1-84 PTH ratio is plotted against the ionized calcium concentration. At baseline ionized calcium concentration, the W-PTH/non-1-84 PTH ratio was $1.53 \pm 0.15$ (range, 1.03 to 1.65). Hypercalcemia resulted in a progressive decrease in the W-PTH/non-1-84 PTH ratio (minimum value less than baseline, $1.53 \pm 0.15$, $P < 0.01$). Hypocalcemia produced a progressive increase in the W-PTH/non-1-84 PTH ratio (maximum value greater than baseline, $2.01 \pm 0.30$ vs. $1.53 \pm 0.15$, $P < 0.01$). The minimum W-PTH/non-1-84 PTH ratio was observed at an ionized calcium of $1.38 \pm 0.03$ mmol/L, a value not different from the ionized calcium concentration required to produce minimum levels of the three PTH moieties. However, the maximum W-PTH/non-1-84 PTH ratio was observed at an ionized calcium of $1.14 \pm 0.03$ mmol/L, a value significantly greater than the ionized calcium concentration needed to produce maximum levels of the three PTH moieties.

From the basal serum calcium concentration of 1.23 mmol/L, the concentration of W-PTH relative to I-PTH progressively increased during hypocalcemia and decreased during hypercalcemia (Fig. 4). At an ionized calcium of 1.40 mmol/L, W-PTH as percent of I-PTH was $53.6\% \pm 1.7\%$ but this ratio was $66\% \pm 2.2\%$ at an ionized calcium of 1.0 mmol/L ($P < 0.001$). Between 0.95 and 1.0 mmol/L there was no change in the W-PTH/I-PTH ratio.

**DISCUSSION**

The present study was designed to evaluate calcium-induced changes in I-PTH, W-PTH, and non-1-84 PTH in hemodialysis patients. Our results show that the dynamic secretion of the three PTH moieties have several interesting similarities. All three PTH moieties were stimulated by hypocalcemia and suppressed by hypercalcemia.
and each of the PTH moieties was best expressed as a sigmoidal curve. As a percent of maximal PTH induced by hypocalcemia, the values during the induction of hypocalcemia were remarkably similar (Fig. 2).

Patients included in the present study were not on calcitriol treatment and had mild to moderate elevations in PTH levels. Thus, we were not able to compare our results to those in hemodialysis patients with severe hyperparathyroidism. But, results available from a limited number of studies do suggest the possibility of differences [1, 23]. In one study, hemodialysis patients were separated into mild and severe hyperparathyroidism based on the bone histology [23]. Others have used 1-84 PTH values to separate patients [1, 24]. Both groups of investigators reported that the ratio of C-PTH/1-84 PTH was greater in hemodialysis patients with mild than in those with severe hyperparathyroidism.

In our patients, the mean ratio of W-PTH/non-1-84 PTH at baseline was 1.53 ± 0.15 and none of the patients had a ratio <1 even though in some patients, the 1-84 PTH (W-PTH) value was only minimally elevated. Monier-Faugere et al [8] have reported that all their patients with low bone turnover had a W-PTH/non-1-84 PTH ratio <1. But, Coen et al [5] did not find any difference in the W-PTH/non-1-84 PTH ratio among dialysis patients with low turnover osteodystrophy, hyperparathyroid bone disease, and mixed osteodystrophy. Also, Reichel et al [25] have reported that in 141 hemodialysis patients, the ratio of 1-84 PTH to non-1-84 PTH was <1 in only eight patients. Similarly, Salusky et al [26] did not report any difference in the W-PTH/non-1-84 PTH ratio in dialysis patients with different types of bone histology. Thus, whether the W-PTH/non-1-84 PTH ratio is of value in detecting low bone turnover in dialysis patients would seem to be disputed.

Regarding the determination of non-1-84 PTH by the subtraction of W-PTH from I-PTH values, preliminary results from a recent study have suggested a potentially complicating issue [abstract; D’Amour et al, J Bone Miner Res 17 (Suppl 1):S391, 2002]. In that study, it was shown by high-performance liquid chromatography (HPLC) that besides 1-84 PTH, the W-PTH assay recognized a pre 1-84 PTH peak that was not recognized by the I-PTH assay. In dialysis patients, this peak accounted for 22% ± 7% of PTH measured with the W-PTH assay. In the basal state of our patients, such a 22% reduction of the W-PTH determination of 1-84 would mean that non-1-84 PTH would increase by 35 pg/mL. Moreover, if these preliminary results are confirmed, studies would need to be performed to determine whether the induction of hypocalcemia would disproportionately affect the amount of pre-1-84 PTH recognized by the W-PTH assay.

The relationship between ionized calcium and the W-PTH/non-1-84 PTH ratio was a sigmoidal curve with a maximum and minimum suggesting a coordinated regulation in the secretion of 1-84 PTH and non-1-84 PTH. If the calcemic action of PTH is affected by this ratio, it would seem that a greater ratio would be expected with hypocalcemia than with hypercalcemia. It is also of interest that the maximum W-PTH/non-1-84 PTH ratio was achieved with a serum calcium concentration of 1.14 ± 0.03 mmol/L, which was higher than the ionized serum calcium concentration needed to achieve maximum levels of W-PTH and non-1-84 PTH (1.08 ± 0.03 mmol/L). According to previous reports, the calcemic action of the W-PTH may not depend solely on its absolute concentration but also on its concentration relative to that of non-1-84 PTH [7–9, 12]. Thus, even before maximal W-PTH values were achieved, a maximal W-PTH/non-1-84 PTH ratio at a higher ionized calcium concentration might possibly have the potential to optimize the calcemic effect of PTH.

Parameters of the PTH calcium curves for the three PTH moieties were determined and no differences were found in the basal/maximal PTH ratio, ionized calcium concentrations at maximal and minimal PTH, and set point. At every ionized calcium concentration from 1 to 1.30 mmol/L, the correlation coefficient (r value) for the comparison between W-PTH and I-PTH was 0.95 or greater and the P value was <0.001 (data not shown). At ionized calcium concentrations of 1.35 and 1.40 mmol/L, the r values were 0.91 and 0.92, respectively. Thus, it would appear that in previous studies in which only the I-PTH assay was used, conclusions on PTH secretion based on the I-PTH assay do accurately reflect secretion of 1-84 PTH during hypocalcemic stimulation and hypercalcemic suppression of PTH secretion.

It was first suggested approximately 3 years ago that 7-84 PTH interfered with the calcemic action of 1-84 PTH by competing for PTH receptor binding [7]. But more recent reports have shown that the 7-84 PTH fragment does not directly interfere with the binding of 1-84 PTH to the PTH/PTHrP receptor, but rather acts at the C-PTH receptor in an unspecified manner to interfere with the calcemic action of 1-84 PTH [9–11]. Moreover, it was shown that smaller carboxy-terminal PTH fragments may also interfere with the calcemic and phosphaturic actions of 1-84 PTH [9].

Recently D’Amour has stated that during normal conditions, 1-84 PTH composes only 20% of total secreted PTH with the remainder being composed of a number of different carboxy-terminal PTH fragments [24]. Moreover, of the total carboxy-terminal PTH fragments, perhaps only 10% of these are the large non-1-84 PTH fragment recognized by the I-PTH assay. During hypocalcemia, all forms of PTH are markedly stimulated with 1-84 PTH increasing to 30% and carboxy-terminal PTH fragments decreasing to 70% of total secreted PTH. Conversely, during hypercalcemia, all forms of PTH are sup-

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pressed but carboxy-terminal PTH fragments increase to 90% of total secreted PTH and 1-84 PTH only accounts for 10% [24]. Both the large non-1-84 PTH fragments recognized by the I-PTH assay and the smaller carboxy-terminal fragments not recognized by the I-PTH assay bind to the C-PTH receptor [8]. But, whether the former has a specific effect that is different from the latter requires further study. Another important area needing study is whether the hyperplastic parathyroid gland due to renal failure secretes the same spectrum of PTH moieties and in the same proportion as the normal parathyroid gland during hypo- and hypercalcemia and at normal calcium values. But, even if the secretory ratios of the different PTH moieties are not affected by renal hyperparathyroidism, another factor that would affect these ratios is their metabolism. In renal failure, the metabolism of carboxy-terminal PTH fragments is slower than that of 1-84 PTH [24, 27, 28] and such a response would increase the ratio of carboxy-terminal PTH fragments to 1-84 PTH independent of parathyroid gland secretion. Thus, if indeed the ratio of carboxy-terminal PTH fragments to 1-84 PTH does play an important role in the biologic activity of PTH, many questions remain to be answered, especially in the azotemic patient.

If biologic relevance is affected by the total amount of carboxy-terminal PTH fragments, then just evaluating the large non-1-84 PTH fragments recognized by the I-PTH assay may not provide all the necessary information. Perhaps the reason that a low ratio of 1-84 PTH/non-1-84 PTH was found by some to be helpful for the diagnosis of low bone turnover [8] is that non-1-84 PTH measured by the I-PTH assay has a specific effect independent of other carboxy-terminal fragments or that it does reflect the total amount of carboxy-terminal fragments of PTH present. In one study of hemodialysis patients, it was shown that the ratio of C-PTH (53–84 PTH)/1-84 PTH was greater in dialysis patients with adynamic bone than in dialysis patients with severe osteitis fibrosa [23]. To obtain these results, we used the individual patient data presented in the paper and calculated the ratio of carboxy-PTH/1-84 PTH, which was greater (P < 0.05) in patients with adynamic bone than in those with osteitis fibrosa. The greater proportional increase in carboxy-PTH in patients with adynamic bone suggests that carboxy-PTH may have a biologic effect.

CONCLUSION

Although acute changes in the serum calcium concentration produce a similar secretory response of 1-84 PTH and non-1-84 PTH, the changes in each are not proportional. The ratio of 1-84 PTH/non-1-84 PTH increases with hypocalcemia and decreases with hypercalcemia in a nonlinear and sigmoidal pattern. Thus, the serum calcium concentration seems to modulate the proportional secretion of 1-84 PTH and non-1-84 PTH by the parathyroid glands. Whether changes in the ratio of 1-84 PTH/non-1-84 PTH or the ratio of 1-84 PTH to the total amount of carboxy-terminal PTH fragments specifically modulate the calcemic action and other biologic effects of 1-84 PTH remain to be determined.

ACKNOWLEDGMENTS

The present study was supported by Fundacion Nefrologica de Cordoba and a Grant (BFI 2001-0350) from Spanish Ministry of Science and Technology. Yolanda Almadden is a researcher supported by the Ramon y Cajal Program from the Spanish Ministry of Science and Technology.

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