Evidence for adaptation of the entire PTH–calcium curve to sustained changes in the serum calcium in haemodialysis patients

M. J. Borrego¹, A. J. Felsenfeld², A. Martin-Malo¹, Y. Almaden¹, M. T. Concepción³, P. Aljama¹ and M. Rodriguez¹

¹Servicio de Nefrología and the Unidad de Investigación, Hospital Universitario Reina Sofía, Córdoba Spain; ³Hospital Universitario, Tenerife, Spain; and ²Department of Medicine, West Los Angeles VA Medical Center and UCLA, Los Angeles, CA, USA

Abstract

Background. Based on in vitro studies, the set point of calcium has often been considered to represent an intrinsic property of parathyroid gland function. However, in the dialysis patient, the serum calcium does not consistently reflect the magnitude of hyperparathyroidism; in addition, little information is available on whether the PTH–calcium curve is modified by sustained changes in the serum calcium. The present study in hemodialysis patients was designed to evaluate whether the set point of calcium and the dynamics of PTH secretion were modified by sustained changes in the serum calcium.

Methods. To accomplish the goal of the study and obtain a wide range of changes in the serum calcium, hemodialysis patients were dialyzed with either a 1.75 mM (group I) or a 1.25 mM (group II) calcium dialysate for 2 weeks, and were then changed to a 1.25 mM (group I) or a 1.75 mM (group II) calcium dialysate for an additional 2 weeks. At the end of the first and second 2-week periods, low and high calcium studies were performed to obtain PTH–calcium curves.

Results. In group I, the serum ionized calcium decreased with the lower calcium dialysate (P<0.02) and the set point of calcium was reduced (P<0.02); in group II, the serum calcium did not change and the set point of calcium was not modified. When both groups were evaluated together, the delta serum calcium correlated directly with the delta set point of calcium (r=0.87, P<0.001) and inversely with the delta PTH (r=-0.73, P<0.005); at the same time, an inverse correlation was observed between the delta PTH and the delta set point of calcium (r=-0.67, P<0.01). Moreover, the delta serum calcium correlated with both the delta ratio of basal/maximal PTH (r=-0.71, P<0.005) and the change in predialysis serum calcium necessary to maximally stimulate PTH (r=0.84, P<0.001); these latter two are indicators of the position of PTH along the PTH–calcium curve. Finally, in group I the entire PTH–calcium curve shifted to the left on the 1.25 mM calcium dialysate as compared with the 1.75 mM calcium dialysate.

Conclusion. The findings of the present study indicate that: (1) the set point of calcium followed sustained changes in the serum calcium independently of PTH secretion, and (2) the parathyroid gland was able both to adjust the position of PTH secretion on the PTH–calcium curve and to adapt PTH secretion to the existing serum calcium concentration.

Key words: calcium; PTH; set point of calcium; PTH–calcium curve; hemodialysis

Introduction

In vitro studies of parathyroid glands from azotaemic patients have suggested that an increase in the set point of calcium may represent an intrinsic abnormality of PTH secretion by the parathyroid gland [1–3]. Moreover, subsequent studies have suggested that an intrinsic abnormality of PTH secretion associated with secondary hyperparathyroidism in renal failure could be due to a reduction in the vitamin D receptor [4] and hyperplasia of the parathyroid gland, especially nodular hyperplasia which may be associated with monoclonal proliferation of parathyroid cells [5,6]. As a result of these studies the concept of set point abnormalities has been extrapolated to studies in dialysis patients in which an increased set point of calcium has often been equated with increased PTH secretion by an abnormal parathyroid gland [7–9]; however, while some studies in dialysis patients have suggested that calcitriol treatment of secondary hyperparathyroidism simultaneously reduced both PTH levels and the set point of calcium [7,10], this finding has not been confirmed in other studies [11–14].

While in normal humans the serum calcium is tightly regulated [15,16], considerable variation of the serum...
calcium is observed in dialysis patients [8,11,17]; this latter is probably due to the inability to regulate calcium via the kidneys, and the presence of different forms of osteodystrophy [18], as well as the fact that the dialysis patient is exposed to variable degrees of calcium loading during dialysis sessions and receives calcium-containing phosphate binders. In previous studies we have observed that the set point of calcium correlated with the predialysis serum calcium but not with the serum PTH level [8,17]. Moreover, in one study in haemodialysis patients we noted that in two groups of patients with different maximal PTH levels, the basal PTH was similar because of the presence of hypocalcaemia in one group; the difference in serum calcium was also associated with different set points of calcium [17]. In addition, the range of calcium between the maximally stimulated PTH and the maximally suppressed PTH was similar in the two groups despite the marked difference in the predialysis serum calcium; these observations led us to question whether the entire PTH–calcium curve could shift as a result of a change in the predialysis serum calcium.

The goal of the present study was to evaluate whether the set point of calcium and the dynamics of PTH secretion were modified by sustained changes in serum calcium in a group of haemodialysis patients. To change the serum calcium and maximize the range of the change in serum calcium, we attempted to change the serum calcium in both directions in the two groups of patients that were studied; in one group, the dialysate calcium concentration was decreased from 1.75 mM to 1.25 mM and in the other group, the dialysate calcium was increased from 1.25 mM to 1.75 mM. In both groups, patients were dialysed with the initial calcium dialysate for 2 weeks and with the second calcium dialysate for an additional 2 weeks. Low and high calcium studies were performed both after 2 weeks of the initial calcium dialysate and after 2 weeks on the second calcium dialysate. We observed that changes in the set point of calcium directly correlated with changes in the serum calcium and were inversely correlated with changes in PTH.

**Methods**

This study was performed in 13 maintenance haemodialysis patients with predialysis PTH levels less than 500 pg/ml; this range of PTH was selected because these patients were not receiving calcitriol and it was believed that it would be easier to modify the predialysis serum calcium during a short time period [8]. The mean age of the patients was 56 ± 4 years, seven patients being female and six male; the mean duration of haemodialysis was 33 ± 6 months. The patients were randomly divided into two groups. In group I (n = 7), the patients were dialysed with a 1.75 mM calcium dialysate for 2 weeks and then changed to a 1.25 mM calcium dialysate for 2 weeks. In group II (n = 6), the patients were dialysed with a 1.25 mM calcium dialysate for 2 weeks and then changed to a 1.75 mM calcium dialysate for 2 weeks. In both groups, low and high calcium studies were performed to obtain a PTH–calcium curve at the end of the first 2 weeks before the change to either the lower or higher calcium dialysate and a second PTH–calcium curve was performed after 2 weeks on the second calcium dialysate.

The PTH–calcium curve was performed as we have described previously [8,11,12,17]. To determine maximal PTH secretion and suppression, a low calcium (0.5 mM) haemodialysis and a high calcium (2 mM) haemodialysis were performed on separate dialysis days. Samples were obtained every 15–30 min during the low and high calcium studies. From the data obtained during dialysis-induced hypo- and hypercaemia, 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 hypercaemia and where 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 hypercaemia and where 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. This ratio should indicate the relative degree of PTH stimulation in the basal state; in normal volunteers, this ratio is 20–25% [19]; (5) the set point of calcium was defined as we have done previously [8,12,17] as the serum calcium concentration at which maximal PTH secretion was reduced by 50%; the set point of calcium was also calculated by the method of Brown [2], in which the set point of calcium is at the mid-range PTH between the minimal and maximal PTH; (6) the basal serum calcium was the serum calcium concentration at the basal (predialysis) PTH; (7) the serum calcium at maximal PTH (Cmax) 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, (8) the serum calcium at minimal PTH (Cmin) was the serum calcium concentration at which the PTH level was first observed to be minimal or within 10% of the minimal PTH; and (9) the difference between the basal calcium and the Cmax was the reduction in serum calcium necessary to maximally stimulate PTH; this value should provide similar information as the basal/maximal PTH ratio because it indicates the relative degree of PTH stimulation in the basal state.

Intact PTH was measured with an immunoradiometric assay for parathyroid hormone (Allegro, Nichols Institute, San Juan Capistrano, CA, USA). Normal values are 10–65 pg/ml and the range of the standard curve is 0–1400 pg/ml. During the low- and high-calcium studies, serum ionized calcium was measured at bedside with a selective ionized calcium electrode (Ciba–Corning SA, Madrid, Spain); the normal range for serum calcium using this method is from 1.19 to 1.28. At all other times, serum calcium, phosphorus, alkaline phosphatase, albumin, and bicarbonate were measured by standard laboratory techniques. Serum calcitriol (Nichols Institute, San Juan Capistrano, CA, USA) was measured at the completion of the 2 weeks with the 1.25 mM calcium dialysate and the 2 weeks with the 1.75 mM calcium dialysate and was less than 12 pg/ml (normal 25–60 pg/ml) in all patients at both intervals.

**Statistics**

The non-parametric Wilcoxon test was used to compare the paired data from the two groups. Regression analysis was
Adaptation of PTH secretion in haemodialysis patients

used to evaluate the potential association between two or more parameters; partial correlation analysis was used to assess the effect of each one of the dependent variables. Since in one group the dialysate calcium was decreased and in the other group the dialysate calcium was increased, the data resulting from the change from baseline observed after the dialysate calcium was changed contains both negative and positive values. A *P* value less than 0.05 was considered to be significant. The data are expressed as the mean ± SE.

**Table 1.** Demographic and biochemical data

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=7)</th>
<th>Group II (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 6</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>Time on dialysis (months)</td>
<td>26 ± 6</td>
<td>41 ± 10</td>
</tr>
<tr>
<td>Sex</td>
<td>4M/3F</td>
<td>2M/4F</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.25 mM calcium dialysate</td>
<td>5.01 ± 0.27</td>
<td>6.48 ± 0.77</td>
</tr>
<tr>
<td>1.75 mM calcium dialysate</td>
<td>5.17 ± 0.23</td>
<td>5.97 ± 0.86</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (IU)</td>
<td>58 ± 6</td>
<td>74 ± 18</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.25 mM calcium dialysate</td>
<td>3.8 ± 0.2</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>1.75 mM calcium dialysate</td>
<td>3.9 ± 0.1</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/l)</td>
<td>20.7 ± 1.7</td>
<td>19.6 ± 1.9</td>
</tr>
<tr>
<td>1.25 mM calcium dialysate</td>
<td>20.5 ± 1.8</td>
<td>19.4 ± 1.7</td>
</tr>
</tbody>
</table>

Mean ± SE.

**Results**

As shown in Table 1, the age of the patients, the duration of haemodialysis and the sex distribution were not different between the two groups. The serum phosphorus, alkaline phosphatase, albumin, and bicarbonate levels were not different between the two groups at the start of the study and also were not different within each group at the end of the 2 weeks on the 1.25 or the 1.75 mM dialysate calcium.

As shown in Figure 1 and Table 2, the predialysis serum ionized calcium decreased (*P*<0.02) in group I after the change to a lower calcium dialysate (Figure 1A); however, in group II, the change to a higher calcium dialysate did not result in an increase in the predialysis serum calcium. The set point of calcium decreased in group I (*P*<0.02), but did not change in group II (Figure 1B). In two patients in group II, the serum calcium did not increase after 2 weeks on a 1.75 mM calcium dialysate and in these same two patients, the set point of calcium also did not change (Figures 1A and 1B). Moreover, when the set point of calcium was calculated by the method of Brown [2], similar results were observed, with the set point of calcium decreasing in group I (*P*<0.02) but not in group II (Table 2). The change in the predialysis (basal) PTH was not significant in either group (Figure 1C). As shown in Table 2, the maximal PTH did not change in the two groups, but minimal PTH

**Fig. 1.** Effect that a change in the dialysate calcium had on (A) the serum ionized calcium, (B) the set point of calcium, and (C) the PTH level is shown for each of the patients in group I (closed circles) and group II (open circles). In group I, patients were dialysed with a 1.75 mM calcium dialysate for 2 weeks and then changed to a 1.25 mM calcium dialysate for an additional 2 weeks; in group II, the sequence was reversed. The two patients represented by an interrupted line in each panel did not increase their serum ionized calcium or set point of calcium, nor decrease their PTH level after the calcium dialysate was increased. The dark bars in each panel represent the mean value for the group.
and the delta predialysis basal calcium was $r = 0.87$, $P < 0.001$; however, both the delta set point of calcium and the delta serum calcium were inversely correlated with the delta basal PTH (Figures 4B and C, $r = -0.67$, $P < 0.01$ and $r = -0.73$, $P < 0.005$ respectively). The set point of calcium was also calculated by the method of Brown [2] and similar results were observed. The correlation between the delta set point and the delta predialysis basal calcium was $r = 0.82$, $P < 0.001$ and between the delta set point and delta PTH was $r = -0.79$, $P = 0.001$. Although delta PTH correlated with both delta serum calcium and delta set point separately, multiple regression followed by stepwise regression analysis with delta PTH as dependent variable and delta serum calcium and delta set point as independent variables showed that delta set point did not contribute significantly to the correlation ($r = 0.086$ for delta set point).

In Figure 5 the delta serum ionized calcium which resulted from the change in dialysate calcium was compared with the delta basal/maximal PTH ratio (Figure 5A) and the delta difference between the basal calcium and the CAm (Figure 5B). An increase in the basal/maximal PTH ratio and a reduction in the difference between the basal calcium and the CAm both would indicate an increase in PTH stimulation in the baseline state. As shown in Figures 4A and 4B, the correlations between the delta ionized calcium and the delta basal/maximal PTH ratio (4A) and the delta difference between basal calcium and CAm (4B) were both significant ($r = -0.71$, $P < 0.005$ and $r = 0.84$, $P < 0.001$ respectively).

### Discussion

The present study was designed to evaluate whether the PTH–calcium curve was modified by sustained changes in the predialysis serum calcium concentration. As such, two groups of haemodialysis patients were studied; in one group, the dialysate calcium was decreased from 1.75 to 1.25 mM and in the other

---

**Table 2. Parameters of the PTH–calcium curve before and after the change in dialysate calcium**

<table>
<thead>
<tr>
<th></th>
<th>Group I ($n=7$)</th>
<th>Group II ($n=6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean $\pm$ SE</td>
<td>Mean $\pm$ SE</td>
</tr>
<tr>
<td>Basal calcium (B) (mM)</td>
<td>$1.21 \pm 0.04$</td>
<td>$1.15 \pm 0.02$</td>
</tr>
<tr>
<td>Basal calcium (A)</td>
<td>$1.12 \pm 0.03$</td>
<td>$1.21 \pm 0.04$</td>
</tr>
<tr>
<td>Set point of calcium (B) (mM)</td>
<td>$1.16 \pm 0.03$</td>
<td>$1.08 \pm 0.04$</td>
</tr>
<tr>
<td>Set point of calcium (A)</td>
<td>$1.12 \pm 0.03$</td>
<td>$1.12 \pm 0.04$</td>
</tr>
<tr>
<td>Set point of calcium-1 (B) (mM)</td>
<td>$1.13 \pm 0.02$</td>
<td>$1.06 \pm 0.04$</td>
</tr>
<tr>
<td>Set point of calcium-1 (A)</td>
<td>$1.13 \pm 0.02$</td>
<td>$1.06 \pm 0.04$</td>
</tr>
<tr>
<td>Basal PTH (B) (pg/ml)</td>
<td>$194 \pm 59$</td>
<td>$193 \pm 37$</td>
</tr>
<tr>
<td>Basal PTH (A)</td>
<td>$258 \pm 51$</td>
<td>$144 \pm 45$</td>
</tr>
<tr>
<td>Maximal PTH (B) (pg/ml)</td>
<td>$481 \pm 112$</td>
<td>$571 \pm 130$</td>
</tr>
<tr>
<td>Maximal PTH (A)</td>
<td>$553 \pm 81$</td>
<td>$460 \pm 84$</td>
</tr>
<tr>
<td>Minimal PTH (B) (pg/ml)</td>
<td>$71 \pm 14$</td>
<td>$80 \pm 15$</td>
</tr>
<tr>
<td>Minimal PTH (A)</td>
<td>$87 \pm 12$</td>
<td>$68 \pm 11$</td>
</tr>
<tr>
<td>CAm (B) (mM)</td>
<td>$0.04 \pm 0.03$</td>
<td>$0.27 \pm 0.05$</td>
</tr>
<tr>
<td>CAm (A)</td>
<td>$0.00 \pm 0.03$</td>
<td>$0.07 \pm 0.03$</td>
</tr>
<tr>
<td>CAm (B) (mM)</td>
<td>$1.21 \pm 0.02$</td>
<td>$1.18 \pm 0.04$</td>
</tr>
<tr>
<td>CAm (A)</td>
<td>$1.17 \pm 0.02$</td>
<td>$1.20 \pm 0.02$</td>
</tr>
<tr>
<td>CAm (B) (mM)</td>
<td>$0.17 \pm 0.03$</td>
<td>$0.18 \pm 0.06$</td>
</tr>
<tr>
<td>CAm (A)</td>
<td>$0.12 \pm 0.02$</td>
<td>$0.27 \pm 0.05$</td>
</tr>
<tr>
<td>Basal/maximal PTH (B) (%)</td>
<td>$40 \pm 5$</td>
<td>$35 \pm 3$</td>
</tr>
<tr>
<td>Basal/maximal PTH (A) (%)</td>
<td>$48 \pm 5$</td>
<td>$29 \pm 5$</td>
</tr>
</tbody>
</table>

Mean $\pm$ SE.

(B) = Before; (A) = After.

Group I = 1.75 to 1.25 mM calcium dialysate.

Group II = 1.25 to 1.75 mM calcium dialysate.

Set point of calcium-1 as calculated by the method of Brown (PTHmax – PTHmin/2).
Adaptation of PTH secretion in haemodialysis patients

The observation that the entire PTH–calcium curve shifted to the left as the predialysis serum calcium was reduced suggests the parathyroid gland may be capable of adapting to the existing serum calcium.

The patients in the present study had mild hyperparathyroidism and were selected because it was not necessary to treat them with calcitriol and it was believed that the serum calcium could be manipulated more easily than in haemodialysis patients with more severe hyperparathyroidism [18]. Our results demonstrate that the set point of calcium, as calculated by two different methods, changed in the same direction as the predialysis serum calcium while the change in PTH was inversely correlated with both the delta serum calcium and the delta set point of calcium. Thus, at least in a group of haemodialysis patients with mild secondary hyperparathyroidism, the set point of calcium did not appear to represent a fixed property of the parathyroid gland; if it had, it would be expected that the set point of calcium would have changed in the same direction as the PTH. Moreover the finding that the set point of calcium changed in the same direction as the serum calcium would suggest that the set point of calcium may be able to adapt to sustained changes in the existing serum calcium. Such a conclusion is also in agreement with our previous results in haemodialysis patients with more severe secondary hyperparathyroidism [20].

An interesting observation in the present study was that the delta basal/maximal PTH ratio was inversely correlated with the delta serum calcium induced by decreasing or increasing the dialysate calcium (Figure 5). A direct correlation was observed between the set point of calcium and the change in PTH; this is the basal serum calcium minus serum calcium at maximal PTH (CAmax). These results would suggest that PTH secretion adapted to the sustained change in the serum calcium not only by shifting the PTH–calcium curve but also by adjusting its position along the PTH–calcium curve. These concepts are illustrated in the present study in Figure 2A, in which the PTH–calcium curve and the set point of calcium shift to the left, but at the same time the increase in the basal PTH from 40 to 48% was not as great as would be anticipated from the original PTH–calcium curve in which the same serum calcium would have produced a PTH value that was approximately 70% of the maximal PTH. Thus, due to the leftward shift of the PTH–calcium curve and the set point in our patients, the reduction in the predialysis serum calcium was associated with a less than expected increase in the basal/maximal PTH ratio and reduction in the difference between the basal calcium and the CAmax. In normal humans, it is not possible to shift the set point of calcium because an efficient calcium homeostatic mechanism effectively responds to any deviation from a normal serum calcium and restores the serum calcium to normal [19,21]. However, in the haemodialysis patient, for whom it is difficult to

![Graph A](image1.png)

**Fig. 2.** PTH–calcium curve obtained after 2 weeks on the first calcium dialysate and after 2 weeks on the second calcium dialysate is shown (A) for group I and (B) for group II. The calcium dialysate shown at the top of each figure was the first to be used for the group, 1.75 mM for group I and 1.25 mM for group II. The asterisk represents a significant difference (P<0.05).
Fig. 3. PTH–calcium curves in each patient from group I. PTH is represented as percentage change from the PTHmax. Values for PTHmax (pg/ml) are also given for each patient.

precisely modulate the serum calcium because of the lack of kidney function and bone alterations, the PTH–calcium curve appears to be able to adapt to sustained changes in the serum calcium by changing both the set point of calcium and the position of PTH secretion along the PTH–calcium curve. These adaptations may be important for the parathyroid gland to be able to maintain a secretory reserve to protect against a further reduction in the serum calcium. It is important to note that our study was 2 weeks and thus
Adaptation of PTH secretion in haemodialysis patients

Fig. 4. Correlations between (A) the change (delta) in the ionized calcium and the delta set point of calcium, (B) the delta PTH and the delta set point of calcium, and (C) the delta PTH and the delta ionized calcium. Both negative and positive values were obtained since a reduction in dialysate calcium generally reduced the ionized calcium and increased the PTH and an increase in the dialysate calcium had the opposite effect.

Fig. 5. Correlations between the change (delta) in the ionized calcium and (A) the change (delta) in the ratio between basal to maximal PTH, and (B) the change (delta) in the difference in serum calcium between the basal calcium and the calcium at maximal PTH. Since the dialysate calcium was both increased and decreased, both negative and positive values of ionized calcium were obtained.

Various authors have reported different results on the modification of the set point by calcitriol [7,10–14]. Other authors [23,24] have suggested that the reported differences on the effect of calcitriol on the set point are due to the different methods for evaluating the set point (50% of the PTH max versus 50% of the difference between PTHmax and PTHmin). The results of the present study suggest the possibility that the reason for the differences among the studies may not be due to calcitriol nor differences in the methods for evaluating the set point, but rather may be the result of the fact that the PTH–calcium curve is modified by sustained changes in serum calcium.

Various authors have reported different results on the modification of the set point by calcitriol [7,10–14]. Other authors [23,24] have suggested that the reported differences on the effect of calcitriol on the set point are due to the different methods for evaluating the set point (50% of the PTH max versus 50% of the difference between PTHmax and PTHmin). The results of the present study suggest the possibility that the reason for the differences among the studies may not be due to calcitriol nor differences in the methods for evaluating the set point, but rather may be the result of the fact that the PTH–calcium curve is modified by sustained changes in serum calcium.

... it may not be appropriate to extrapolate our findings to a situation of more chronic hypocalcaemia. It is possible that a longer period of low calcium dialysis would induce parathyroid cell proliferation which could separately affect the PTH–calcium curve. In addition, our findings were obtained in patients with moderate hyperparathyroidism, in whom diffuse rather than nodular hyperplasia was more likely to be present. Thus our study patients are probably different from those with nodular hyperplasia who are characterized by markedly increased PTH levels, hypercalcaemia, ...
in the set point which were in the same direction as the change in serum calcium; this observation was valid independent of the method by which the set point was calculated and may also explain why the published results about the effect of calcitriol on the set point are not consistent. As we have previously reported [20], an increase in the serum calcium induced by calcitriol administration may result in increased set point despite a reduction in the PTH level. Results from the present study suggest that it may be difficult to assess a direct effect of calcitriol on the set point unless the serum calcium concentration remains unchanged.

The idea that the PTH–calcium curve is able to adapt to the existing serum calcium is a novel concept; however, this concept is supported by the results of a study performed in dogs with secondary hyperparathyroidism due to chronic vitamin D deficiency in which the maximal PTH level increased approximately 5-fold [25]; after vitamin D repletion restored the serum calcium and the basal PTH level to normal, maximal PTH remained 3-fold greater than normal [26]. Thus, to maintain a normal serum calcium and basal PTH, it was necessary to reduce the basal to maximal PTH ratio to approximately 10% and shift the set point of calcium to the left. Studies of calcitonin secretion by the C-cells of the thyroid gland, which contain the same calcium receptor as the parathyroid gland [27], would tend to lend additional support for the concept that the parathyroid gland may be capable of adapting PTH secretion to the existing serum calcium. Thus, both in animals [28] and hemodialysis patients [29], it has been shown that calcitonin secretion adapts to the existing serum calcium concentration.

In summary, in hemodialysis patients with mild secondary hyperparathyroidism, changes in the set point of calcium directly correlated with changes in the serum ionized calcium, but not PTH. At the same time, the PTH–calcium curve adapted to sustained changes in the serum ionized calcium by both a shift of the entire PTH–calcium curve in the direction of the change in serum ionized calcium and an adjustment in position along the sigmoidal PTH–calcium curve. In conclusion, these findings indicate that parathyroid gland function is able to adapt to sustained changes in the serum calcium.

Acknowledgements. This work was supported by a grant from FISS (93/0630) and Fundacion Reina Sofia–Caja Sur. Dr Arnold J. Felsenfeld was a visiting Professor of Medicine in the Department of Medicine of the University of Cordoba School of Medicine during the 1995–96 academic year.

References

15. Parfitt AM. Bone and plasma calcium homeostasis. Bone 1987; 8 [Suppl 1]: S1–S8

Received for publication: 28.5.96
Accepted in revised form: 1.11.96