The set point of calcium and the reduction of parathyroid hormone in hemodialysis patients

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The set point of calcium and the reduction of parathyroid hormone in hemodialysis patients. Since in some studies in hemodialysis patients calcitriol treatment has resulted in a reduction of both parathyroid hormone (PTH) levels and the set point of calcium, it has been suggested that the set point of calcium reflects a reduction in the magnitude of hyperparathyroidism. However, others have maintained that the set point of calcium is primarily an indicator of the serum calcium at which PTH is secreted and may be dissociated from the magnitude of hyperparathyroidism. The present study was designed to evaluate how a reduction in PTH levels associated with an increase in the predialysis (basal) serum calcium would affect the set point of calcium. Two different treatments were used to produce a reduction in PTH that was associated with an increase in predialysis serum calcium. In the first group, hemodialysis patients received 2 μg of intravenous calcitriol and were dialyzed with a 3.5 mEq/liter calcium dialysate for six weeks; in the second group, hemodialysis patients were dialyzed with a 4 mEq/liter calcium dialysate and had oral calcium supplementation increased for six weeks. In both groups, low and high calcium studies were performed to determine the PTH-calcium relationship before treatment, at the end of six weeks of treatment, and six weeks after the discontinuation of treatment. In the calcitriol group, the predialysis calcium increased from 9.62 ± 0.34 to 10.56 ± 0.31 mg/dl, P < 0.05 and the set point of calcium increased from 9.34 ± 0.23 to 9.79 ± 0.25 mg/dl, P < 0.05 at the same time as maximally stimulated PTH decreased from 2637 ± 687 to 1555 ± 617 pg/ml, P < 0.05. In the high calcium dialysate group, the predialysis serum calcium increased from 9.19 ± 0.31 to 9.84 ± 0.28 mg/dl, P < 0.05, and set point of calcium increased from 9.01 ± 0.26 to 9.39 ± 0.22 mg/dl, P < 0.05 at the same time as maximally stimulated PTH decreased from 1642 ± 450 to 1349 ± 513 pg/ml, P < 0.05. Discontinuation of treatment for six weeks resulted in a return to pretreatment values. In conclusion, our results would suggest that (1) the set point of calcium may not be a reliable indicator of the magnitude of hyperparathyroidism during calcitriol treatment, and (2) PTH secretion may adapt to the ambient serum calcium concentration.

In most studies in hemodialysis patients, calcitriol treatment has resulted in a reduction in parathyroid hormone (PTH) levels [1–4]. However, while calcitriol treatment of dialysis patients with secondary hyperparathyroidism has been shown to reduce PTH levels, the effect of calcitriol on the set point of calcium, defined as the serum calcium concentration at which maximal PTH secretion is reduced by 50% [5], is controversial inasmuch as some studies have reported a reduction in the set point of calcium [3, 6, 7], while in other studies, the set point of calcium did not change despite a reduction in PTH levels [2, 4, 8, 9]. Moreover, it has been suggested that the set point of calcium reflects the reduction in the magnitude of hyperparathyroidism, and thus an inability to reduce the set point of calcium indicates a refractoriness to treatment that may require a parathyroidectomy [3, 7, 9].

The concept that the set point of calcium may be related to the mass of the parathyroid glands was first suggested as a result of a series of in vitro studies by Brown et al [10, 11] and a study in neonatal calves by Keaton et al [12]. As a result of these studies, the concept was generated that the set point of calcium may be an indicator of parathyroid gland mass, or in clinical terms, the magnitude of hyperparathyroidism. However, in vivo, PTH secretion is not only dependent on the serum calcium concentration, but also the serum calcium concentration is a function of the effect of PTH on target organs such as kidney and bone. Moreover, a dissociation between the set point of calcium and the magnitude of hyperparathyroidism may become particularly apparent in the setting of renal failure in which skeletal resistance to the calcemic action of PTH [13], an inability to modulate renal calcium excretion [14], a calcitriol deficiency [15], and hyperphosphatemia [13] are generally present.

Previous studies have shown that the serum calcium concentration is tightly regulated in the normal human [16]. However, the serum calcium concentration varies considerably among dialysis patients. In a recent study in hemodialysis patients, we have observed that the range of serum calcium between maximal and minimal PTH was constant although the basal serum calcium was different [17]. In another study in which the PTH response to hypocalcaemia was evaluated in hemodialysis patients with a broad range of predialysis serum calcium, PTH secretion also appeared to vary according to the serum calcium concentration. Such findings have led to questioning whether PTH secretion in the dialysis patient may be related to the serum calcium concentration.

The goal of the present study was to evaluate in a group of hemodialysis patients with basal PTH levels > 250 pg/ml, the effect that intentionally increasing the serum calcium by two different methods had on the set point of calcium and PTH secretion. Serum calcium was increased either by treatment with (1) calcitriol and a high normal dialysate calcium concentration.
were maintained on their respective protocols for six weeks and be different than a calcium increase based on dialysate calcium in the predialysis serum calcium would have on the PTH-calcium hemodialysis.

During each of the three low and high calcium dialysis studies, repeated measures ANOVA was used followed by the Fisher LSD test for multiple comparisons. For comparisons between the two randomized groups, the unpaired Student’s t-test was used. A P value less than 0.05 was considered significant. Results are expressed as the mean ± SE.

Results

At the start of the study the mean KT/V was 1.31 ± 0.08, and the mean predialysis hematocrit, albumin, creatinine, and serum aluminum were 28.3 ± 1.0%, 4.0 ± 0.1 g/dl, 12.8 ± 0.1 mg/dl, and 19.9 ± 4.5 μg/liter, respectively. After randomization, Groups I and II were similar with respect to age (I, 47 ± 6 vs. II, 51 ± 7 years), sex (I, 3 males and 2 females vs. II, 3 males and 3 females) and duration of dialysis (I, 65 ± 21 vs. II, 55 ± 13 months). As shown in Table 1, the predialysis serum calcium, PTH, phosphorus, and alkaline phosphatase levels were not different between the two groups after randomization, after treatment with calcitriol or a high calcium dialysate, and after discontinuation of these treatments.
As shown in Table 2 and Figure 1, calcitriol treatment combined with a dialysate calcium of 3.5 mEq/liter (Group I) resulted in an increase in the basal calcium from 9.62 ± 0.34 to 10.56 ± 0.31 mg/dl, P < 0.05. Treatment with calcitriol resulted in a decrease in maximal PTH (P < 0.05) and tended to decrease basal (P = 0.08 by repeated measures ANOVA) (Fig. 2). Despite this reduction in PTH, the set point of calcium increased (P < 0.05; Fig. 1). Discontinuation of calcitriol resulted in a return of the basal calcium, the set point of calcium, and the maximal PTH to values similar to baseline.

As shown in Table 3, results in the high calcium dialysate group (Group II) were similar to those of the calcitriol treatment group (Group I). An increase in the dialysate calcium concentration and oral calcium supplementation increased the basal calcium from 9.19 ± 0.31 to 9.84 ± 0.28, P < 0.05 (Fig. 1). A high calcium dialysate combined with oral calcium supplementation resulted in a decrease (P < 0.05) in maximal PTH (Fig. 2). Despite the decrease in maximal PTH, the set point of calcium increased (P < 0.05; Fig. 1). Discontinuation of the high calcium dialysate and oral calcium supplementation resulted in a return of the basal calcium, the set point of calcium, and the maximal PTH to baseline values.

Since the results of the studies on the effect of increasing the predialysis (basal) serum calcium were similar in both groups, the groups were combined to increase the power of analysis. After either calcitriol treatment or an increased calcium dialysate with oral calcium supplementation, the basal serum calcium increased from 9.39 ± 0.24 to 10.17 ± 0.24 mg/dl, P < 0.001 (Fig. 1). At the same time as the serum calcium increased, both basal PTH (P < 0.02) and maximal PTH (P < 0.005) decreased (Fig. 2). Despite the reduction in basal and maximal PTH, the set point of calcium increased (P < 0.001; Fig. 1). The discontinuation of calcitriol and a high calcium dialysate with oral calcium supplementation resulted in a return of the basal calcium, the set point of calcium, and the basal and maximal PTH to values not different than baseline.

**Discussion**

In the present study in hemodialysis patients with secondary hyperparathyroidism, treatment with either calcitriol or a high calcium dialysate increased the predialysis (basal) serum calcium. Both treatments also resulted in a decrease in PTH levels, but
The finding that the set point of calcium increased at the same time as PTH levels decreased would suggest that the set point of calcium may not necessarily be an indicator of the magnitude of hyperparathyroidism and is likely influenced by the ambient serum calcium concentration.

The meaning of the set point of calcium has been debated since the term was first popularized by Brown et al more than a decade ago. In an elegant series of in vitro studies, Brown et al demonstrated that the set point of calcium was greater in adenomatous and hyperplastic than normal parathyroid glands [10, 11]. Thus, the concept evolved that the set point of calcium was an indicator of the mass of the parathyroid gland. However, it should be emphasized that the in vitro testing of the PTH-calcium relationship is performed in a closed system that is not influenced by factors other than the externally manipulated calcium concentration. In normal humans and animals, the ability of PTH to modulate serum calcium is affected by calcium absorption from the gut, calcium deposition and release from bone, and renal excretion of calcium. Moreover, differences in the potency of PTH become apparent when normal individuals and hemodialysis patients are compared; for the same serum calcium concentration, the PTH level in the hemodialysis patient may be 20 to 40 times greater [5, 21]. Thus, it is our opinion that in the in vivo setting, the set point of calcium may best be considered to be an indicator of the serum calcium concentration at which PTH secretion is stimulated [5]. In a recent publication, Brown has also arrived at a similar conclusion for the meaning of the set point of calcium in in vivo studies [22].

While we believe that the set point of calcium is consistently an indicator of the serum calcium concentration at which PTH secretion is stimulated, the set point of calcium may also be in certain situations an indicator of the magnitude of hyperparathyroidism. In individuals with normal renal function, the set point of calcium is increased in patients with primary hyperparathyroidism as compared with normal individuals. In this situation, the higher PTH levels increase the serum calcium by enhancing bone resorption, augmenting renal calcium reabsorption, and increasing gut absorption of calcium through the action of PTH on calcitriol production [23, 24]. In renal failure because of skeletal resistance to PTH [13], diminished renal modulation of calcium excretion [14], and decreased calcitriol levels [15], regulation of serum calcium is more problematic and less precise than in normal individuals. This concept is well-illustrated in the recent study by

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**Table 3. Biochemical data in the high calcium dialysate group.**

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>POST1</th>
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</thead>
<tbody>
<tr>
<td>PTHmax (pg/ml)</td>
<td>1642 ± 450</td>
<td>1349 ± 513†</td>
<td>1744 ± 595</td>
</tr>
<tr>
<td>PTHbase (pg/ml)</td>
<td>810 ± 266</td>
<td>610 ± 265</td>
<td>908 ± 362</td>
</tr>
<tr>
<td>PTHmin (pg/ml)</td>
<td>315 ± 155</td>
<td>279 ± 128</td>
<td>304 ± 136</td>
</tr>
<tr>
<td>Basal/Max PTH (%)</td>
<td>44 ± 6</td>
<td>36 ± 12</td>
<td>45 ± 7</td>
</tr>
<tr>
<td>Min/Max PTH (%)</td>
<td>14 ± 4</td>
<td>18 ± 5</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>Set Point of Calcium</td>
<td>9.19 ± .31</td>
<td>9.84 ± .28†</td>
<td>9.26 ± .26</td>
</tr>
<tr>
<td>CMax (mg/dl)</td>
<td>8.38 ± .33</td>
<td>8.24 ± .26</td>
<td>8.05 ± .21</td>
</tr>
<tr>
<td>CMin (mg/dl)</td>
<td>10.64 ± .28</td>
<td>10.82 ± .22</td>
<td>10.71 ± .32</td>
</tr>
</tbody>
</table>

Mean ± se

*P < 0.05 versus PRE
†P < 0.05 versus PRE and POST
‡PRE—before a high calcium dialysate
§POST—after treatment with a high calcium dialysate
¶POST1—after discontinuation of a high calcium dialysate
Whether the parathyroid gland has a similar adaptive capacity is an important question which deserves further study. In conclusion, the results of the present study in hemodialysis patients have demonstrated that treatment with either calcitriol or a high calcium dialysate can increase the set point of calcium despite a decrease in the PTH level. These results would suggest that the set point of calcium may not be a reliable indicator of the magnitude of hyperparathyroidism during calcitriol treatment in hemodialysis patients. Furthermore, the results of this study suggest the intriguing possibility that PTH secretion by the parathyroid gland may adapt to the ambient serum calcium concentration.

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References


Some studies in hemodialysis patients have suggested that since the calcitriol-induced reduction in PTH levels is accompanied by a reduction in the set point of calcium, the set point of calcium reflects a reduction in the magnitude of hyperparathyroidism [3, 7]. However, a reduction in the set point of calcium has not been observed in all studies in dialysis patients in which calcitriol treatment reduced PTH levels [2, 4, 8, 9] or even in a study in azotemic patients in which phosphorus restriction reduced PTH levels [29].

Messa et al. in which three groups of patients with progressive renal failure were characterized [25]. As expected, PTH levels increased as renal function decreased, but the set point of calcium for the three groups was similar despite more than a sixfold difference in PTH levels. Further complicating the situation in renal failure are the different forms of renal osteodystrophy which are characterized by low or high bone turnover [26]. In dialysis patients with a relative PTH deficiency and low bone turnover such as in adynamic bone or aluminum associated osteomalacia, the set point of calcium tends to be lower than in dialysis patients with markedly increased PTH levels and the high-turnover bone disease, osteitis fibrosa [19]. However, complicating calcium regulation in the dialysis patient is several confounding variables which include an inability to modulate serum calcium when dialysis patients with low bone turnover are challenged with a calcium load [27], the effect of hyperphosphatemia on calcium regulation [15], and marked differences in active and quiescent bone surfaces among patients [28].


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