The PTH-calcium curve and the set point of calcium in primary and secondary hyperparathyroidism

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Abstract

Background. The regulation of PTH secretion by calcium is altered in patients with primary hyperparathyroidism (HPT). A similar abnormality may occur in secondary HPT, but comparisons of PTH secretion in normal subjects and those with secondary HPT have given contrasting results. Differences in baseline serum ionized calcium (ICa) may partly account for these conflicting results. The aim of the present study was to evaluate whether the regulation of PTH secretion by calcium differs from normal in patients with primary and secondary HPT and to determine whether serum calcium concentration per se can affect the set point of calcium and the PTH-calcium relationship.

Methods. The PTH-ICa relationship and the set point of ICa were evaluated in 19 patients with primary HPT (1-HPT), 16 normocalcaemic patients with secondary HPT (2-HPT; PTH 344 ± 191 pg/ml), 19 hypercalcaemic patients with secondary HPT (3-HPT; PTH 806 ± 254 pg/ml) and 14 healthy volunteers, by inducing hypocalcaemia and hypercalcaemia in order to maximally stimulate or inhibit PTH secretion. In five 1-HPT patients the PTH-ICa curve was restudied after normalization of serum ICa by pamidronate. Parathyroid gland volume was determined by measuring gland size at parathyroidectomy or by means of high-resolution color Doppler ultrasonography.

Results. In 1-HPT patients the PTH-ICa curve, constructed using maximal PTH secretion induced by hypocalcaemia as 100%, was shifted to the right, the set point of ICa was increased, and the slope of the curve was reduced when compared to normal subjects. After normalization of baseline serum ICa by pamidronate, a shift of the PTH-ICa curve towards normal and a reduction in the set point of ICa was observed. However, basal PTH and maximal PTH secretion induced by hypocalcaemia increased, minimal PTH secretion induced by hypercalcaemia remained increased and the slope of the curve did not change significantly. The alterations in the PTH-ICa relationship in hypercalcaemic patients with secondary HPT were similar to those found in 1-HPT patients. In normocalcaemic patients with secondary HPT baseline PTH, maximal and minimal PTH secretion and parathyroid gland size were reduced compared to 3-HPT patients. Compared to normal subjects, 2-HPT patients showed greater calcium-induced minimal PTH secretion. The increase in non-suppressible PTH secretion resulted in a rightward shift of the PTH-ICa curve and an increase in the set point of ICa. A strong correlation was found, in both primary and secondary HPT, between the set point of ICa and baseline serum ICa, and between parathyroid gland size and baseline PTH, maximal PTH and minimal PTH. Multivariate regression analysis showed that baseline serum ICa was the main determinant of the set point of ICa in both primary and secondary HPT.

Conclusions. (i) The regulation of PTH secretion by calcium is abnormal in secondary as well as in primary HPT. (ii) Parathyroid gland enlargement in secondary HPT is associated with reduced sensitivity to serum ICa and resistance of parathyroid gland to calcium-mediated PTH suppression, resulting ultimately in PTH hypersecretion, despite hypercalcaemia. (iii) The set point of calcium is strongly dependent on baseline serum calcium, and the PTH-ICa relationship can be affected by variations in serum ICa concentrations. Thus, when the set point of calcium and the PTH-ICa relationship are evaluated, possible differences in baseline serum ICa concentration among the patients should be taken into account.

Key words: hypercalcaemia; parathyroid hormone; primary hyperparathyroidism; secondary hyperparathyroidism; serum ionized calcium; set point of calcium

Introduction

The extracellular calcium concentration is the primary determinant of parathyroid hormone (PTH) secretion. Mayer and Hurst [1] first demonstrated the inverse sigmoidal relationship between serum calcium and PTH. Their results documented the sensitivity of the parathyroids to small variations in serum calcium over periods of several minutes, slight decreases in serum
Methods

We studied 19 patients with primary HPT (1-HPT) and 35 patients undergoing regular dialysis affected by secondary HPT (PTH > 200 pg/ml). The uraemic patients were divided into two groups (2-HPT and 3-HPT) according to baseline serum calcium concentration: 16 normocalcaemic patients (12 on haemodialysis, four on CAPD) were allocated in the 2-HPT group, whereas 19 hypercalcaemic (ionized calcium > 1.28 mmol/l) patients (14 on haemodialysis, five on CAPD), were considered as affected by tertiary HPT and allocated in the 3-HPT group. All dialysis patients underwent a bone biopsy. The patients showed either mild lesions of secondary HPT or overt ostesitis fibrosa. None of the patients had evidence of bone aluminium deposition as assessed by histochemical staining and none were taking aluminium-containing medications. Most of the dialysis patients had previously been treated with calcitriol, but vitamin D therapy was discontinued for at least 1 month prior to study. The patients affected by 1-HPT were hypercalcaemic and were studied before parathyroidectomy. All later had surgically documented primary HPT, due to parathyroid adenoma, with postoperative normalization of serum calcium levels. Also 16 of 19 patients with 3-HPT and one patient with 2-HPT underwent total or subtotal parathyroidectomy after parathyroid gland function was investigated by dynamic tests. The patient with 2-HPT underwent parathyroidectomy because of very high PTH levels (805 pg/ml) and calcaemia in the upper normal range (1.26 mmol/l).

The dynamic tests of parathyroid gland function were performed in the 19 1-HPT, 16 2-HPT and 19 3-HPT patients by inducing acute changes in serum ionized calcium (ICa) in order to maximally stimulate (PTH stimulation test) or inhibit (PTH inhibition test) PTH secretion. Fourteen volunteer subjects with normal renal function (N) were also evaluated. In five patients with 1-HPT, the dynamic tests of parathyroid secretion were repeated when a stable reduction of serum ICa was achieved by pamidronate therapy (30–60 mg i.v.), in order to evaluate whether changes in serum calcium concentration could affect the PTH-ICa relationship. Pamidronate infusion reduced serum ICa in all patients within 3–7 days; dynamic parathyroid tests were performed after 2–4 days of stable ICa levels. The baseline characteristics and laboratory data of the patients are summarized in Table 1.

The PTH stimulation test was performed by inducing hypocalcaemia by infusing NaEDTA (20 mg/kg/h for 150 min). PTH inhibition test was performed, 1 week later, by inducing hypercalcaemia by infusing CaCl2 (4 mg/kg/h for 15 min). PTH and ICa were determined at baseline, and after 10, 20, 30 and 60 min and then every 15 min. For the analysis of the PTH-ICa relationship the following terms were used: (i) maximal PTH stimulation (PTHmax), that is the highest level of PTH induced by hypocalcaemia; this level was reached in all patients between 75 and 120 min and thereafter PTH levels remained stable or decreased. (ii) Maximal PTH inhibition (PTHmin), that is the lowest level of PTH induced by hypercalcaemia; this level was reached in all patients between 60 and 105 min and thereafter PTH levels remained stable. (iii) The set point of calcium, which was calculated as either the ICa value at the midrange between PTHmin and PTHmax, as defined by Brown et al. [4], or the ICa value at which PTHmax was reduced by 50% [12]. The sensitivity of parathyroid cells to ICa variations was determined by calculating the slope of the sigmoidal curve, according to Messa et al. [9]. The PTH-ICa curves were constructed using PTHmax as 100% to factor for differences in absolute PTH levels between the patients, and to provide an assessment of individual parathyroid cell function. From the data obtained by PTH stimulation and inhibition tests, individual PTH-ICa curves were constructed for each patient using both the four-parameter model as described by Brown et al. [4] and the...
Results

The parathyroid secretory parameters of patients with 1-HPT, 2-HPT and 3-HPT compared to normal subjects are reported in Table 2.

Primary HPT (1-HPT)

The volume of parathyroid adenoma ranged from 0.07 to 8.9 cm³, the gland weight from 0.05 to 14 g. As expected baseline ICa, baseline PTH, PTHmax, PTHmin, and the serum ICa levels at which maximal and minimal PTH secretion occurred were greater in 1-HPT than in N. Although 1-HPT patients displayed a spectrum of PTH suppressibility, as a group, their minimal PTH secretion induced by hypercalcaemia, evaluated as either absolute value (Table 2) or per cent of maximal PTH secretion (range: 8–51%, mean: 21 ± 12%) was greater than in N (range: 6–13%, mean: 8 ± 2, P < 0.001) (Figure 1). Moreover, minimal and maximal PTH secretion were achieved at greater ICa levels than in N. Thus, in 1-HPT the PTH-ICa curve, constructed using PTHmax as 100%, was shifted to the right and upward and the set point was increased in comparison to N, as shown in Figure 1, in which the set point of ICa, the serum ICa levels at maximal PTH secretion and inhibition for each individual patient are reported. The set point of ICa (calculated as midpoint) corresponded to a PTH level of 62 ± 8% of maximal PTH, compared to 55 ± 3% in N (P < 0.001). The slope of the curve was significantly reduced in 1-HPT (298 ± 107%, range: 155–438%) compared to N (475 ± 86%, range: 335–647%), suggesting a reduced sensibility of the glands to serum ICa changes.

In the five patients treated with pamidronate, baseline serum ICa decreased from 1.45 ± 0.04 to 1.25 ± 0.06 mmol/l. The reduction of serum ICa stimulated parathyroid gland and induced a significant increase in baseline PTH and maximal PTH secretion (Table 3). The modifications of minimal PTH (as either absolute value or per cent of PTHmax) were not significant. The ICa concentrations at maximal PTH secretion and inhibition decreased. As a consequence of these secretory parameter changes, a leftward shift of the sigmoidal PTH-ICa curve in one of our patients is reported in Figure 2. Figure 3 shows the shift to the left of the composite regression line between probit PTH and ICa, after reduction of baseline serum ICa in the five patients treated with pamidronate. The set point of ICa, calculated after probit transformation of per cent PTH secretion, decreased from 1.42 ± 0.05 to 1.19 ± 0.07 mmol/l (P < 0.05) after normalization of basal serum ICa.

### Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Ionized Ca (mmol/l)</th>
<th>PTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>range (mean)</td>
<td>M/F</td>
<td>range (mean)</td>
<td>range (mean)</td>
</tr>
<tr>
<td>Normal</td>
<td>14</td>
<td>23–74 (52)</td>
<td>6/8</td>
<td>1.15–1.23 (1.21)</td>
</tr>
<tr>
<td>1-HPT</td>
<td>16</td>
<td>28–75 (54)</td>
<td>7/12</td>
<td>1.31–1.75 (1.41)</td>
</tr>
<tr>
<td>2-HPT</td>
<td>16</td>
<td>26–73 (53)</td>
<td>7/9</td>
<td>1.16–1.25 (1.21)</td>
</tr>
<tr>
<td>3-HPT</td>
<td>19</td>
<td>18–71 (51)</td>
<td>9/10</td>
<td>1.30–1.44 (1.36)</td>
</tr>
</tbody>
</table>
Set point 50, mmol

Set point mid, mmol

Set point 50% = 21 ± 12

γ

Gland volume, cm³

Gland volume, cm³

Gland volume, cm³

ICa at maximal PTH inhibition is reported for each individual patient and midrange between PTHmax and PTHmin; ICam and ICamin = ICa level at PTHmax and PTHmin.

***P = <0.001 vs N and 2-HPT; **P = <0.001 among the groups; *P = <0.01 vs 3-HPT; t = P < 0.001 and f = P < 0.05 vs N; *P = <0.01 vs 2-HPT; b = P < 0.001 vs 2-HPT and 3-HPT.

Secondary HPT (2-HPT and 3-HPT)

Patients with secondary HPT were divided into two groups according to serum ICa. Compared to N, normocalcaemic patients with secondary HPT (2-HPT) showed increased baseline, maximal and minimal PTH secretion (Table 2). The increase in per cent minimal PTH secretion resulted in a rightward shift of the curve and an increase in the set point of ICa in comparison to N (Table 2 and Figure 4). Hypercalcaemic patients with secondary HPT (3-HPT) had greater parathyroid gland size, and greater baseline, maximal and minimal PTH levels than 2-HPT (Table 2). Serum phosphate was not significantly different in 2- and 3-HPT. Parathyroid gland volume ranged from 0.6 to 5.5 cm³ in 3-HPT and from 0.1 to 1.2 cm³ in 2-HPT. The serum ICa levels at which maximal and minimal PTH secretion occurred and the minimal PTH secretion induced by hypercalcaemia (as a per cent of maximal PTH secretion) were greater than in N and 2-HPT. Thus, the PTH-ICa curve, constructed using PTHmax as 100%, was shifted to the right and upward and the set point was increased in comparison to N and 2-HPT (Figure 4). The slope of the curve was significantly reduced in 3-HPT (range: 151–400%/mmol/l), compared to N and 2-HPT (range: 270–652%/mmol/l) (Table 2).

Compared to patients with 1-HPT, patients with...
Table 3. Effect of serum ionized calcium reduction by pamidronate therapy on the PTH secretory parameters in five patients with primary hyperparathyroidism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After pamidronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized Ca mmol/l</td>
<td>1.45 ± 0.04*</td>
<td>1.25 ± 0.06*</td>
</tr>
<tr>
<td>PTH, pg/ml</td>
<td>106 ± 97</td>
<td>297 ± 210*</td>
</tr>
<tr>
<td>PTHmax, pg/ml</td>
<td>263 ± 245</td>
<td>644 ± 299*</td>
</tr>
<tr>
<td>PTHmin, pg/ml</td>
<td>81 ± 65</td>
<td>154 ± 142</td>
</tr>
<tr>
<td>PTH %</td>
<td>40 ± 14</td>
<td>49 ± 13*</td>
</tr>
<tr>
<td>PTHmin %</td>
<td>33 ± 11</td>
<td>20 ± 13</td>
</tr>
<tr>
<td>Set point 50, mmol/l</td>
<td>1.43 ± 0.05</td>
<td>1.23 ± 0.08*</td>
</tr>
<tr>
<td>Set point mid, mmol/l</td>
<td>1.34 ± 0.04</td>
<td>1.18 ± 0.09*</td>
</tr>
<tr>
<td>ICamax, mmol/l</td>
<td>1.24 ± 0.04</td>
<td>1.07 ± 0.05*</td>
</tr>
<tr>
<td>ICamin, mmol/l</td>
<td>1.31 ± 0.03</td>
<td>1.45 ± 0.08</td>
</tr>
<tr>
<td>Slope %/mmol/l</td>
<td>246 ± 64</td>
<td>270 ± 85</td>
</tr>
</tbody>
</table>

* = P < 0.001 and * = P < 0.05 vs baseline.

A significant negative linear correlation was also found between parathyroid gland volume and per cent minimal PTH secretion (r = 0.51, P < 0.05 in 1-HPT and 0.54, P < 0.001 in secondary HPT). Moreover, baseline PTH was correlated with both PTHmax (r = 0.91 and 0.902) and PTHmin (r = 0.97 and 0.85). No significant correlation was found between serum phosphate and the other variables in both primary and secondary HPT.

In both primary and secondary HPT the set point of ICa, calculated either as 50% of PTHmax or midpoint between PTHmax and PTHmin, was significantly correlated with baseline ICa, baseline PTH, PTHmax, PTHmin and parathyroid gland volume. Multiple regression analysis (multiple r = 0.949 in 1-HPT and 0.917 in secondary HPT) showed that baseline serum ICa was the strongest predictor of the set point of ICa (P < 0.0002 and < 0.00001), whereas the effect of baseline PTH, serum phosphate and parathyroid gland size was not statistically significant. The correlation between the set point of ICa and baseline ICa in patients with primary and secondary HPT is reported in Figure 5. The slope of the regression line between serum ICa and set point of ICa was not different in primary and secondary HPT, suggesting that the relationship between the set point of ICa and basal serum ICa is independent from the type of HPT.

A significant negative linear correlation was found in secondary HPT between the slope of the PTH-ICa curve and baseline ICa (r = −0.69), baseline PTH (r = −0.44), PTHmax (r = −0.43), PTHmin (r = −0.62) and parathyroid gland volume (r = −0.40). However, multiple regression analysis (multiple r = 0.74,
Fig. 3. Composite plots of individual regression lines between probit PTH and ICa before (squares, dotted line, \( y = -6.4 \times +14.2 \)) and after (circles, continuous line, \( y = -6.2 \times +12.2 \)) treatment with pamidronate in five patients with primary HPT. PTH data are given as probit PTH and the percentage of maximal PTH secretion. Pamidronate decreased baseline ICa from 1.45 ± 0.04 to 1.25 ± 0.06 mmol/l, shifting the regression line to the left and downward. The set point of ICa, calculated after probit transformation of per cent PTH secretion, decreased from 1.42 ± 0.05 to 1.19 ± 0.07 mmol/l (\( P < 0.05 \)) after normalization of basal serum ICa. * = \( P < 0.001 \) and # = \( P < 0.05 \) vs values observed after reduction of baseline serum ICa.

Fig. 4. The set point of calcium (calculated as midpoint between maximal and minimal PTH secretion), the serum ICa at maximal PTH secretion and, the serum ICa at maximal PTH inhibition is reported for each individual patient affected by normocalcaemic (\( n = 16, \) triangles) and hypercalcaemic secondary HPT (\( n = 19, \) asterisks) and, for 14 normal subjects (squares). Maximal PTH secretion is transformed to 100%. Polynomial regression analysis was used to calculate the curves. The sigmoidal curve is shifted to the right in hypercalcaemic secondary HPT (thin line, \( y = -6642 \times^4 + 37321 \times^3 - 77896 \times^2 + 71402 \times - 24131, \ r = 0.92 \)) compared to normocalcemic secondary HPT (dotted thick line, \( y = -15704 \times^4 + 81254 \times^3 - 156205 \times^2 + 131996 \times - 41251, \ r = 0.94 \)) and normal subjects (thick line, \( y = -18604 \times^4 + 93286 \times^3 - 175638 \times^2 + 145334 \times - 44477, \ r = 0.97 \)).

\( P < 0.0001 \) showed that only baseline serum ICa was a significant (\( P < 0.001 \)) predictor. In primary HPT the slope of the PTH-ICa curve was correlated with baseline serum ICa (\( r = -0.45, \ P < 0.05 \)) and per cent minimal PTH secretion (\( r = -0.58, \ P < 0.01 \)).

**Discussion**

The results of our study indicate that the regulation of PTH secretion by parathyroid glands, in response to changes in serum ICa, is altered in both primary and
Fig. 5. Correlation between baseline serum ionized calcium and the set point of calcium (calculated as ICa level at which maximal PTH secretion was reduced by 50%) in primary (circles, $y = 0.99 x - 0.02$, $r = 0.92$) and secondary HPT (triangles, $y = 0.94 x + 0.08$, $r = 0.91$).

secondary HPT. Previous in vitro and in vivo studies have documented that the set point of calcium and non-suppressible PTH secretion are greater in patients with primary HPT than in normal subjects [4,6]. In the present study we have evaluated in vivo the entire PTH-ICa curve by inducing maximal stimulation and inhibition of parathyroid gland; our results show that in primary HPT patients there is not only an increase in the set point, but also a rightward shift of the curve and a decrease in the slope of the curve, in comparison with normal subjects. PTH secretion in response to the increase in serum ICa was relatively non-suppressible and the degree of non-suppressibility (minimal PTH secretion) correlated significantly with tumor mass, as reported also by Khosla et al. [6]. The reduction of baseline serum ICa within the normal range by pamidronate therapy resulted in a shifted of the PTH-ICa curve towards normal and in a reduction in the set point of ICa. The decrease in the set point of ICa was directly correlated with the decrease in baseline serum ICa. However, the normalization of baseline serum ICa induced a significant increase in baseline PTH and maximal PTH secretion, whereas non-suppressible PTH secretion remained greater than normal. Since, it is unlikely an increase in parathyroid mass after only a few days of relatively low serum ICa, we can speculate that the increase in PTH secretion is caused by an increase in the per cent of active secretory cells. The activation of parathyroid cells after normalization of serum ICa is in agreement with the Parfitt’s hypothesis that parathyroid cells in adenomas grow until the size of the gland is such that the amount of PTH secreted induces a degree of hypercalcaemia which meets ‘the set point’, so that a steady-state is achieved [20]. So, adenomatous parathyroid glands are ‘set’ to maintain serum ICa at a constant, but higher, level than normal. Interestingly, the slope of the sigmoidal curve, that was reduced in primary HPT compared to normal subjects, did not change significantly after the reduction of baseline serum ICa, suggesting that the sensitivity of parathyroid glands is altered in primary HPT within a wide range of baseline ICa concentrations. Thus, in patients with primary HPT the combination of an increase in gland mass, a decrease in maximal PTH suppressibility, a decrease in parathyroid cell sensitivity, and an increase in the set point of ICa may contribute to inappropriate hypersecretion of PTH in face of hypercalcaemia, as supposed by Brown [4].

To evaluate the dynamic of PTH secretion in secondary HPT we selected 35 dialysis patients with PTH levels >200 pg/ml. The patients were divided into two groups according to baseline serum ICa. Calcium-mediated PTH suppression was significantly lower in normocalcaemic patients with secondary HPT (2HPT) than in normal subjects, as reported also by others [8,14,15]. The consequent increase in per cent minimal PTH secretion resulted in a rightward shift of the PTH-ICa curve and an increase in the set point of ICa compared to normal subjects. Our data on the set point of calcium are in contrast with the results of other studies [8–10]. Different criteria of selection of renal patients, as regards the degree of severity of secondary HPT and basal serum ICa levels can, at least partly, explain the divergent results. Messa et al. [9] studied renal patients with a GFR ranging between 12 and 60 ml/min. The patients showed a very mild degree of HPT, since the mean basal PTH and maximal PTH in the subgroup of patients with advanced renal failure were 142 and 312 pg/ml, respectively. The patients studied by Ramirez et al. [8] showed a degree of secondary HPT very close to that of our normocalcaemic secondary HPT patients, as suggested by comparable levels of baseline serum ICa, baseline PTH, and maximal and minimal PTH secretion. Also Ramirez et al. [8] documented an increase in non-suppressible PTH secretion in the patients with secondary HPT.
patients with severe HPT and controls can be blunted associated with reduced sensitivity to serum ICa and the regulation of PTH release by calcium are present thyroid glands and elevated basal calcium concentrations. Moreover, the two patients who underwent parathyroidectomy in Goodman’s study had the highest set point values, suggesting that abnormalities in the regulation of PTH release by calcium are present at least in patients with advanced hyperparathyroidism.

Our hypercalcaemic uraemic patients showed a more severe form of secondary HPT than normocalcaemic patients, as documented also by Felsenfeld et al. [13]. Moreover, the two patients who underwent parathyroidectomy in Goodman’s study had the highest set point values, suggesting that abnormalities in the regulation of PTH release by calcium are present at least in patients with advanced hyperparathyroidism.

We found a significant correlation between parathyroid gland mass, maximal PTH secretion and calcium-mediated minimal PTH secretion in secondary HPT as well as in primary HPT, as reported by others [6,10,15]. Moreover, parathyroid gland size, and minimal and maximal PTH secretion were significantly correlated with baseline serum ICa. These data indicate that hyperplasia of parathyroid gland plays an important role in the development and aggravation of secondary HPT. Our findings provide direct evidence in support of prior prediction [21] that parathyroid gland enlargement or some related factors, such as a reduced expression of vitamin D receptors [22], genetic deletion [23] or parathyroid cell monoclonal growth [24] causes alterations in calcium sensing by parathyroid. The reduced sensitivity to serum ICa and the resistance of parathyroid gland to calcium-mediated PTH suppression induce PTH hypersecretion leading, ultimately, in patients with more advanced hyperparathyroidism, to hypercalcaemia.

Our study demonstrates that the set point of ICa is strongly dependent on basal serum ICa and the PTH-ICa relationship can be affected by variations in serum ICa. The finding that the set point changes in association with the change in serum ICa is supported by the results of recent studies in dialysis patients, showing that the set point of calcium increases after the elevation of basal serum calcium induced by high dialysate calcium [16] or calcitriol therapy [16,25,26], whereas it decreases after the reduction of basal serum ICa induced by low calcium dialysate [17].

In conclusion, our study demonstrated that the regulation of PTH secretion by calcium is abnormal in secondary as well as in primary HPT, and that parathyroid gland enlargement, in secondary HPT, is associated with reduced sensitivity to serum ICa and resistance of parathyroid gland to calcium-mediated PTH suppression, resulting in PTH hypersecretion. These results support the frequent clinical observation of failure of PTH suppression, despite hypercalcaemia and calcitriol therapy, in patients with large parathyroid glands and elevated basal calcium concentration [18].

References


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