Are there any differences in the parathyroid response in the different types of renal osteodystrophy?

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Abstract
With the purpose of studying the curve of parathyroid hormone (PTH) secretion. The mathematical model which best relates PTH and serum calcium to variations of serum calcium during dialysis, we studied 20 patients on haemodialysis: 10 women and 10 men, with different forms of bone disease diagnosed by bone biopsy (adynamic bone disease, mild hyperparathyroidism, severe hyperparathyroidism). In all patients, we performed parathyroid stimulation by 4 h dialysis with 1 mEq/l of Ca$^{2+}$ in the dialysate, and an inhibition test in another dialysis session with 4 mEq/l of Ca$^{2+}$, with a 48 h interval. Ca$^{2+}$ and intact parathyroid hormone (iPTH) were measured prior to dialysis and every hour subsequently, to obtain a Ca$^{2+}$–iPTH for each patient. The analysis of the curves was made using Brown’s four-parameter model. Stimulation and inhibition levels were similar in all groups, but basal iPTH and the response profiles obtained varied in the different histological groups. Basal, maximal and minimal iPTH were lower in adynamic forms than in the other two groups ($P<0.04$), and basal calcium was higher than basal calcium of severe hyperparathyroidism, expressing a basal inhibition status. In severe hyperparathyroidism, basal calcium was lower than the set-point, showing a permanent stimulation, and the slope was higher than in other groups, showing more sensitivity to serum calcium variations. The set-point of severe hyperparathyroidism was significantly higher than the set-point of mild and adynamic forms. In conclusion, the functional parathyroid study showed a different response in the different forms of renal osteodystrophy.

Key words: adynamic bone disease; calcium; haemodialysis; hyperparathyroidism; iPTH

Introduction
It has been known for >30 years that serum calcium concentration is the most important factor regulating parathyroid hormone (PTH) secretion. The mathematical model which best relates PTH and serum calcium is a sigmoidal curve, which has been described for many years in ‘in vitro’ and ‘in vivo’ studies [1–7].

Haemodialysis patients show different baseline intact PTH (iPTH) concentrations that correlate with different histological forms of bone disease. With this aim, the use of immunoradiometric assays to measure iPTH has resulted in an important advance in the predictive value of histological forms of high and low bone turnover. There is still a group of patients with low iPTH in which different pathogenic forms overlap, such as adynamic bone disease and mild hyperparathyroidism [8–10].

The existence of more than one histological form with low iPTH could suggest different modes of response in the target organ or different responses of the parathyroid gland to calcium variations.

Basal iPTH may vary according to serum calcium; therefore, it would provide information only about hormone secretion at this calcium concentration but not about the maximal secretory capacity of parathyroid gland [10].

Calcium–iPTH curves seem to be a better way to evaluate parathyroid function and to compare different forms of histological bone disease.

The aim of this study was to investigate the correlation between plasma ionic calcium and iPTH in haemodialysis patients with different forms of renal osteodystrophy, by the analysis of parathyroid gland function.

Patients and methods
We studied 20 patients on chronic haemodialysis (66±53 months), 10 men and 10 women, aged 58±14 years. The aetiology of chronic renal failure was: chronic glomerulopathy ($n=5$), polycystic renal disease ($n=4$), nephroangiosclerosis ($n=6$), reflux nephropathy ($n=1$), hereditary diseases ($n=2$) and unknown ($n=2$). None of them had been parathyroidectomized or treated with desferrioxamine or calcitriol. There were no diabetic patients in the population studied.
All patients were haemodialyzed 12 h per week using a reverse osmosis system or deionizer for water treatment, and with 3.5 mEq/l of Ca\(^{2+}\) in the dialysate.

Seventeen patients had bone biopsy, with prior double tetracycline labelling, and were processed without decalcification with current technics and a histochemical stain for aluminium (Aluminon) [11].

Patients were classified as mild hyperparathyroidism (MHPT) \((n=5)\), severe hyperparathyroidism (SHPT) \((n=7)\) and adynamic bone disease (ABD) \((n=8)\) according to bone histologic forms and or clinical and humoral parameters. Seven of the eight patients with adynamic bone disease had aluminium in the bone.

In all patients, we used a functional stimulation test and an inhibition test of parathyroid glands. Both tests were performed during dialysis as has been described [10]. Initially, we performed a 4 h dialysis with 1 mEq of Ca\(^{2+}\) in the dialysate producing hypocalcaemia and maximal gland stimulation. The inhibition test was carried out in the following dialysis using a dialysate with 4 mEq of Ca\(^{2+}\) for 4 h, inducing hypercalcaemia and maximal gland inhibition.

Ionized calcium (Ca\(^{2+}\)) and iPTH were determined before the beginning of dialysis and every hour during dialysis. Serum Ca\(^{2+}\) was determined by selective electrode (Analyzer Electroyte, AVL 984-S) (normal range: 1–1.3 mmol/l) and iPTH by IRMA (ELSA-PTH, CIS BIO International Laboratory, France) (normal values: 8–76 pg/ml). Informed consent was obtained from all patients.

Using Ca\(^{2+}\) and iPTH values from each patient, we defined individual Ca\(^{2+}\)-iPTH response curves, and one curve for each group was defined from the former. The curves were corrected with a statistical programme (Sigma Plot Scientific Graphing System) and they were analysed according to the four-parameter model described by Brown (maximal PTH, minimal PTH, set-point and slope) [6].

Our group defined the set-point as the serum calcium corresponding to 50% inhibition of maximal iPTH without taking account of non-suppressible secretion. The slope was calculated at the linear segment of the curve by eliminating the asymptotic portions at both ends by subtracting 10% from the maximal PTH and adding 10% to the minimal PTH for diminishing error factors, as has been pointed out by Felsenfeld and co-workers [8]. All these parameters were analysed by expressing PTH percentages to allow a comparative analysis between different groups. Results were expressed as mean ± standard deviation.

Statistical analysis was carried out using the Student \(t\)-test for non-dependent samples and linear correlation analysis; a \(P\) value < 0.05 was considered significant.

### Results

As can be seen in Table 1, basal iPTH showed significant differences between the three groups according to histological type.

Basal Ca\(^{2+}\) was higher in the adynamic group when compared with the severe hyperparathyroid group. Maximal and minimal Ca\(^{2+}\) levels reached during the tests, as well as maximal and minimal variations of serum calcium in relation to basal calcium, were comparable in all groups. However, in spite of similar calcium levels, maximal and minimal iPTH were significantly different in the three groups (Table 1, Figure 1).

The programme used to correct curves and to calculate the four parameters showed an excellent correlation between observed and theoretical iPTH values \((r=0.99)\).

The set-point was higher in hyperparathyroid patients than in the adynamic group, and it was higher in SHPT than in mild forms (Table 1, Figure 2). The comparison between basal Ca\(^{2+}\) and set-point in each group showed that in the basal situation the SHPT group had lower calcium levels than at the corresponding set-point; on the contrary, the adynamic group had basal serum calcium higher than its own set-point (Table 1, Figure 1).

The slope was greater in the hyperparathyroid groups than in the adynamic group \((P<0.05)\), but no significant differences were observed between MHPT and SHPT (Table 1, Figure 1).

The linear correlation analysis between basal, minimal and maximal iPTH of each group showed a good

### Table 1. Ca\(^{2+}\), iPTH, set-point and slope of all groups

<table>
<thead>
<tr>
<th></th>
<th>ABD ((n=8))</th>
<th>MHPT ((n=5))</th>
<th>SHPT ((n=7))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Ca(^{2+}) (mmol/l)</td>
<td>1.2 ± 0.14(^a)</td>
<td>0.99 ± 0.23</td>
<td>1.12 ± 0.07(^b)</td>
</tr>
<tr>
<td>Min. Ca(^{2+}) (mmol/l)</td>
<td>0.85 ± 0.08</td>
<td>0.83 ± 0.23</td>
<td>0.97 ± 0.04</td>
</tr>
<tr>
<td>Max. Ca(^{2+}) (mmol/l)</td>
<td>1.46 ± 0.13</td>
<td>1.34 ± 0.4</td>
<td>1.42 ± 0.17</td>
</tr>
<tr>
<td>Amin Ca(^{2+}) (mmol/l)</td>
<td>0.34 ± 0.18</td>
<td>0.33 ± 0.15</td>
<td>0.45 ± 0.15</td>
</tr>
<tr>
<td>Amax Ca(^{2+}) (mmol/l)</td>
<td>0.26 ± 0.05</td>
<td>0.36 ± 0.36</td>
<td>0.30 ± 0.04</td>
</tr>
<tr>
<td>Basal iPTH (pg/ml)</td>
<td>81 ± 82(^e)</td>
<td>461 ± 209(^d)</td>
<td>898 ± 375(^b)</td>
</tr>
<tr>
<td>Basal iPTH (% max PTH)</td>
<td>35 ± 16(^f)</td>
<td>56 ± 9(^h)</td>
<td>67 ± 3(^b)</td>
</tr>
<tr>
<td>Max. iPTH (pg/ml)</td>
<td>286 ± 284(^g)</td>
<td>866 ± 598(^g)</td>
<td>1350 ± 519(^h)</td>
</tr>
<tr>
<td>Min. iPTH (pg/ml)</td>
<td>35 ± 19(^b)</td>
<td>159 ± 153(^m)</td>
<td>278 ± 94(^b)</td>
</tr>
<tr>
<td>Min. iPTH (% max PTH)</td>
<td>19 ± 11</td>
<td>16 ± 10</td>
<td>22 ± 7</td>
</tr>
<tr>
<td>Slope (abs. value)</td>
<td>−356 ± 407(^d)</td>
<td>−2185 ± 2318(^b)</td>
<td>−2262 ± 1353(^j)</td>
</tr>
<tr>
<td>Slope (%)</td>
<td>−99 ± 25(^a)</td>
<td>−172 ± 97(^f)</td>
<td>−142 ± 47(^g)</td>
</tr>
</tbody>
</table>

\(^a\) vs b: \(P=0.03\); c vs d: \(P<0.005\); d vs e: \(P=0.056\); e vs c: \(P<0.0001\); f vs g: \(P<0.03\); g vs h: \(P<0.02\); f vs h: \(P<0.0001\); i vs j: \(P=0.04\); i vs k: \(P<0.0001\); l vs m: \(P=0.04\); l vs n: \(P<0.0001\); p vs q: \(P<0.03\); o vs q: \(P<0.04\); r vs s: \(P<0.05\); r vs t: \(P=0.002\); u vs v: \(P=0.063\); u vs w: \(P<0.05\).
Ca$^{2+}$–iPTH curves in renal osteodystrophy

Our results showed a good adjustment to a sigmoidal curve, as described previously [9,10]. According to data pointed out in the literature, this sigmoidal relationship between Ca$^{2+}$ and iPTH is defined through four parameters (maximal PTH, slope, set-point and minimal PTH) which would assess the functioning mass of parathyroid cells, its sensitivity to calcium variations and its degree of suppressibility [6,12]. We added the analysis of basal iPTH, basal Ca$^{2+}$, minimal and maximal Ca$^{2+}$ and its respective variations in relation to basal value.

Calcium concentrations in basal conditions and during stimulation and inhibition tests were comparable in all three groups, but this was not so for iPTH concentrations. In basal conditions, iPTH was significantly greater in the SHPT group. This fact, as well as the presence of maximal and minimal iPTH concentrations significantly greater in this group, could be the expression of a larger parathyroid gland mass, as has been described by other authors [9,12]. The presence of a very good correlation between basal and maximal iPTH in all patients would have the same meaning. Felsenfeld et al. have published similar findings [10].

The high level of basal iPTH in the SHPT group would indicate a high stimulation in basal conditions and probably a lower secretory functional reserve in these patients.

The presence of a greater slope in hyperparathyroid groups would point to an increased sensitivity of parathyroid cells to calcium variations independent of the degree of severity of hyperparathyroidism. The difference between slope values of patients with hyperparathyroidism and ABD shows the different response of the parathyroid gland to serum calcium variations in both groups.

Our results showed that the set-point of SHPT is higher than in mild forms and in ABD.

The finding in the SHPT group of a set-point higher than its basal serum calcium would indicate that in the basal situation these patients are stimulated continuously. This finding agrees with basal iPTH levels of 67% of the maximal PTH secretion. On the other hand, the adynamic group showed a basal serum calcium greater than its set-point, showing that in basal conditions the PTH secretion is inhibited, as shown by a basal iPTH of 35% maximal iPTH, as was described by other authors [10]. This would explain, at least in part, the situation of relative hypoparathyroidism and its histological pattern with very poor cellularity and absence of normal bone remodelling. Probably, the lower sensitivity to calcium serum variations, mentioned above, could contribute to the relative hypoparathyroidism found in ABD.

The highest level of basal Ca$^{2+}$ in these patients could be determined by a disturbance in Ca$^{2+}$ incorporation into bone, as was demonstrated by Kurz et al. [13]. In some cases, aluminium could be involved in the poor incorporation of calcium into bone. The
sensitivity of parathyroid glands to changes in ionized calcium is diminished in these patients, as shown by the lower values of the slope in this group when compared with hyperparathyroid patients. Similar findings have been described by Sanchez et al. [14]. In addition to the inhibitory effect of hypercalcaemia, some other factors could be involved, e.g. the inhibitory action of aluminium [15,16].

Therefore, at similar calcium concentrations, we obtained different responses both on stimulation and on inhibition in different forms of renal osteodystrophy.

In conclusion, these results suggest that: (i) there are differences in the parathyroid response to calcium variations in different types of renal osteodystrophy; (ii) the parathyroid gland mass is larger in the SHPT group; (iii) sensitivity to the hypocalcaemic stimulation in SHPT is increased, and probably its functional reserve is decreased; (iv) the set-point in the SHPT group is increased and it is greater than the basal calcium level, explaining the permanent stimulation state of these patients in basal conditions; (v) in ABD, the presence of a basal calcium level higher than its set-point would explain the state of functional parathyroid inhibition which these patients show.

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