Early identification of risk factors for refractory secondary hyperparathyroidism in patients with long-term renal replacement therapy

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Abstract

Background. Secondary hyperparathyroidism can complicate renal replacement therapy (RRT) in patients with end-stage renal disease. Current medical therapies often result in hypercalcaemia and fail to correct hyperparathyroidism, but might be more effective at an early stage of disease. The aim of this study was to identify prognostic factors at the start and during the first year of RRT for refractory secondary hyperparathyroidism needing parathyroidectomy (PTx) during long-term follow-up.

Methods. A total of 202 consecutive patients starting RRT between August 1988 and August 1996 at our centre with at least 1 year of follow-up were included. Biochemical and treatment data at the start and during the first year of RRT were collected. Univariate and multivariate analyses were used to identify risk factors for PTx during follow-up.

Results. Thirty-three patients (16%) needed PTx after 52±23 months of RRT. Need for PTx was not different between patients undergoing haemodialysis and peritoneal dialysis, but was associated with parameters reflecting calcium and phosphate control at start and after 1 year of RRT. In a Cox multivariate model, serum parathyroid hormone [relative risk (RR): 1.02 per pmol/l; P < 0.001], phosphate (RR: 1.107 per 0.1 mmol/l; P = 0.002) and alkaline phosphatase (RR: 1.004 per U/l; P = 0.049) after 1 year of RRT were independently associated with increased risk for PTx.

Conclusions. Failure of control of calcium–phosphate metabolism at the start of and early during RRT is strongly associated with PTx during long-term follow-up. Given the high prevalence of insufficient phosphate control, patients may benefit from aggressive correction of serum phosphate in the pre-dialysis and early dialysis period.

Keywords: parathyroidectomy; parathyroid hormone; phosphorus; renal replacement therapy

Introduction

Secondary hyperparathyroidism develops in chronic renal insufficiency as a consequence of disturbances in calcium, phosphate and vitamin D metabolism. It causes renal osteodystrophy and soft tissue calcification and contributes significantly to the cardiovascular morbidity and mortality in patients with end-stage renal disease (ESRD) [1]. Despite improvements in medical treatment and dialysis therapy, the parathyroidectomy (PTx) rate is 3 per 1000 patient-years in patients who received renal replacement therapy (RRT) for < 5 years and 12–30 per 1000 patient-years in patients who are treated for 5–10 or > 10 years, respectively [2]. This rate has not significantly improved over the years [2,3].

As parathyroid hyperplasia and associated metabolic disturbances are not easily reversed, management is focused at preventing the development and progression of secondary hyperparathyroidism. Treatment with dietary measures, phosphate binding and active vitamin D should start in the pre-dialysis period [4]. Patients with established secondary hyperparathyroidism during RRT need intensified treatment using intravenous vitamin D. However, these therapeutic interventions are not always successful and their full potential is often attenuated by the development of treatment-related hypercalcaemia [5]. New therapies have been developed to overcome the latter problem, but their role in treatment and prevention of renal hyperparathyroidism is not clear yet [1,5].
More aggressive treatment at an early stage of RRT, when the tendency for hypercalcaemia is potentially less and hyperparathyroidism is not yet severe, might be helpful and more effective in the long run. In order for such an early and aggressive approach to be effective, early identification of high-risk patients is a prerequisite. The aim of our retrospective single centre study was to identify predictors at the start and during the first year of dialysis for the development of severe secondary hyperparathyroidism for which surgery is needed during long-term follow-up.

**Subjects and methods**

**Patients**

Consecutive patients were included in the study if the following criteria were met: first dialysis ever was performed at our institution between August 1988 and August 1996 and duration of RRT at our institution was >1 year. Exclusion criteria were previous renal transplantation, PTx before the start or during the first year of RRT and age <18 years.

**Treatment**

Haemodialysis (HD) treatment was performed three times weekly with, in most patients, cellulose triacetate-based dialysers and single-pass volume-controlled dialysis monitors. Dialysis duration was 3–5 h with a blood flow of 250–350 ml/min and adapted to maintain an equilibrated Kt/V >3.0 per week, including residual renal function [6]. Bicarbonate-based dialysate was used with a standard calcium concentration of 1.50 mmol/l. Continuous ambulatory peritoneal dialysis (PD) was done by four to five daily exchanges with 2000–3000 ml volume. A weekly Kt/V of >1.8 (including residual renal function) was aimed for. Standard (PD) solution contained 1.75 mmol/l calcium.

Calcium carbonate or calcium-acetate tablets taken with each meal were used as oral phosphate binders. A trained dietician adjusted the dose of phosphate binders to the estimated phosphate content of that meal. Dose adjustments were made to maintain pre-dialysis serum phosphate <2.0 mmol/l. If, due to hypercalcaemia, adequate serum phosphate levels could not be obtained, the calcium-based phosphate binders were partially replaced by aluminium hydroxide under frequent control of serum aluminium. Once adequate control of serum phosphate was obtained, all patients received oral daily alfacalcidol (0.25 μg once daily) or dihydrotestochesterol (0.2 mg once daily). If serum calcium was <2.5 mmol/l or if serum parathyroid hormone (PTH) was >20 pmol/l or radiographic signs of hyperparathyroidism were present, vitamin D dose was increased. If hypercalcaemia was encountered or control of PTH was insufficient, vitamin D therapy was switched to intravenous pulse therapy starting at 0.5 μg alfalcacidol three times weekly and, if necessary and possible, increased to 2–3 μg three times weekly (in use since 1991 at our institution). In case of persistent hypercalcaemia, dialysate concentrations were lowered to 1.25 mmol/l in HD and 1.00 mmol/l in PD. Sevelamer is in use at our institution since 2001, as combination therapy with calcium and vitamin D.

**Indications for parathyroidectomy**

PTx was considered necessary if, despite optimal medical and dietary treatment, a high serum PTH (110±50 pmol/l; range: 36–264 pmol/l) persisted in combination with either (i) radiological evidence of renal osteodystrophy; (ii) persistent hypercalcaemia not attributable to other causes; (iii) severe and intractable pruritus; (iv) serum calcium–phosphate product that consistently exceeds 5 mmol²/l² together with progressive extraskeletal calcification; (v) progressive skeletal and articular pain, fractures or deformities; or (vi) calciphylaxis [2].

**Data**

Pre-dialysis serum chemistry samples were drawn monthly. Measurements were performed using standard methodology. Serum PTH, aluminium and Kt/V were routinely measured every 6 months. In individual cases, for example following changes in therapy, more frequent measurements were sometimes performed at the discretion of the treating nephrologist. Intact PTH was measured with an IRMA (Nichols). The following data were analysed: serum calcium, phosphate, albumin, PTH, alkaline phosphatase and Kt/V. Serum calcium was corrected for serum albumin [7]. Means of all values during the first year of RRT per patient were used in order to define serum levels over time.

**Statistical analysis**

Data are presented as means±SD unless stated otherwise. For comparison between groups, a two-tailed Student’s t-test was used for continuous variables and chi-square analysis or Fisher’s exact test was used for discrete variables. Actuarial survival until need for PTx from the start of RRT was estimated with the Kaplan–Meier method. Patients were censored at the moment of renal transplantation, transfer to another centre, death or end of follow-up (August 2002), whichever occurred first without necessity for PTx at that point in time. Differences in survival time until PTx between groups were tested with the log-rank test. The following variables were tested: calcium, phosphate, calcium–phosphate product, alkaline phosphatase, intact PTH, Kt/V at the start and at 1 year of RRT and the difference between both; the mean value of these parameters during the first year of RRT; type of initial RRT; gender; age; renal disease; years of renal disease before the start of RRT; and use of vitamin D at the start and after 12 months of RRT. Multivariate analysis with time to PTx as the dependent variable was performed with the Cox proportional hazards analysis. Only variables with a P-value of <0.10 by univariate analysis were included. A two-sided P-value of <0.05 was considered to indicate statistical significance.

**Results**

**Patients**

Between August 1988 and August 1996, 391 patients started RRT at our institution. Excluded from the analysis were 50 patients who underwent renal transplantation during the first year, 69 patients who died...
The demographical, clinical and biochemical characteristics at the start of RRT are given in Table 1. As compared with the start of RRT, phosphate was not different after 1 year (1.93 ± 0.53 vs 1.88 ± 0.45 mmol/l; P = NS). Mean phosphate during the first year was 1.89 ± 0.31 mmol/l and was > 2.00 mmol/l in 31% of the patients. It exceeded 2.00 mol/l at some point during the first year in 37% of the patients. For HD-treated patients, a correlation between dialysis efficacy, measured as mean Kt/V during the first year, and mean serum phosphate was observed (r = −0.231, P = 0.007).

Calcium was higher at 1 year as compared with the start of RRT (2.67 ± 0.21 vs 2.47 ± 0.25 mmol/l; P < 0.0001). Mean serum calcium–phosphate product during the first year of RRT was 4.25 ± 0.81 mmol²/l² and was < 5.00 mmol²/l² in 54% of the patients. It increased over the first year (4.43 ± 1.23 vs 4.97 ± 1.21 mmol²/l²; P < 0.001). None of the parameters differed significantly between HD- and PD-treated patients.

PTH was > 20 pmol/l at the start of RRT in 37% of the patients. In the pre-dialysis period, the percentage of patients treated with vitamin D analogues was less in patients starting RRT with a PTH > 20 pmol/l (45% vs 61%; P = 0.037). They also had a lower calcium (2.37 ± 0.28 vs 2.53 ± 0.21 mmol/l; P < 0.001), higher phospho-skeletal product (2.30 ± 0.28 vs 2.53 ± 0.25 mmol/l; P = 0.022) and higher alkaline phosphatase (101 ± 60 vs 80 ± 29 U/l; P = 0.008) at the start of RRT as compared with patients who started with a PTH of < 20 pmol/l. Duration of renal disease before the start of RRT, as documented in 140/202 patients, was not different for both groups. Further information about pre-dialysis treatment was not available.

In 55% of the patients who started with a PTH > 20 pmol/l, the level decreased to < 20 after 1 year. In comparison with patients who maintained a PTH > 20 pmol, they showed a lower PTH (40 ± 21 vs 51 ± 23 pmol/l; P = 0.039) with a lower calcium (2.30 ± 0.28 vs 2.53 ± 0.25 mmol/l; P = 0.015) at the start of RRT. They also had a larger increase of calcium during the first year (0.38 ± 0.24 vs 0.05 ± 0.20 mmol/l; P < 0.001). There was no difference in the number of patients that used vitamin D. In 9% of the patients who started with a PTH < 20 pmol/l, the level increased to > 20 pmol/l after 1 year. In comparison with patients who maintained a PTH < 20 pmol/l, they showed a higher PTH at the start (12 ± 5 vs 8 ± 5 pmol/l; P = 0.005) and tended to have a higher phosphate after 1 year (2.09 ± 0.29 vs 1.84 ± 0.42 mmol/l; P = 0.057). Overall, the number of patients with a PTH > 20 pmol/l was reduced to 42 (21%) at 1 year. In these 42 patients, 19 could not be treated with vitamin D due to unacceptable high calcium and/or phosphate levels. A strong correlation was found between the PTH at the start and after the first year of RRT (r = 0.56, P < 0.001).

### Analysis of predictive factors associated with need for PTx during follow-up

Thirty-three patients required PTx after 52 ± 23 months of RRT. Survival without need for PTx was not different for patients with HD or PD as initial treatment modality. By univariate analysis, several parameters were found to be associated with the risk for PTx during follow-up (Table 2). Most of these parameters reflected...
Table 2. Variables associated with a P-value of < 0.10 by univariate analysis with time to need for PTx

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group definition</th>
<th>P-value</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/female</td>
<td>0.008</td>
<td>2.50 (1.28–5.26)</td>
</tr>
<tr>
<td>Ca (Alb) (mmol/l) t0</td>
<td>≤2.46, &gt; 2.46</td>
<td>0.020</td>
<td>3.23 (1.19–8.33)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l) t0</td>
<td>≤80, &gt; 80</td>
<td>0.072</td>
<td>1.85 (0.94–4.00)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l) t1</td>
<td>≤76, &gt; 76</td>
<td>0.056</td>
<td>2.00 (0.98–3.85)</td>
</tr>
<tr>
<td>Phosphate t1 (mmol/l)</td>
<td>≤1.85, &gt; 1.85</td>
<td>0.006</td>
<td>2.63 (1.22–5.52)</td>
</tr>
<tr>
<td>Calcium–phosphate product t1 (mmol²/l²)</td>
<td>≤4.97, &gt; 4.97</td>
<td>0.015</td>
<td>2.33 (1.19–4.76)</td>
</tr>
<tr>
<td>PTH t0 (pmol/l)</td>
<td>≤20, &gt; 20</td>
<td>0.001</td>
<td>3.23 (1.79–7.69)</td>
</tr>
<tr>
<td>PTH t1 (pmol/l)</td>
<td>≤20, &gt; 20</td>
<td>&lt; 0.0001</td>
<td>5.56 (5.00–33.3)</td>
</tr>
</tbody>
</table>

Relative risks are given for: *females compared with males; †the group with values above the median for the whole group compared with values below or equal to the median; ‡increased (>20 pmol/l) compared with normal (≤20 pmol/l) levels of PTH. CI, confidence interval; Ca (Alb), calcium corrected for albumin; t0, start of RRT; t1, at 1 year of RRT.

calcium–phosphate metabolism and levels of phosphate, calcium–phosphate product and PTH differed between patients with and without need for PTx (Figure 1). Especially, phosphate > 1.85 mmol/l at 1 year of RRT (median value) was strongly associated with the need for PTx (Figure 2). Multivariate analysis revealed that PTH, phosphate and alkaline phosphatase after 12 months of dialysis were independently associated with need for PTx during follow-up (Table 3).

Discussion

Serum PTH, phosphate and alkaline phosphatase at 1 year of RRT were identified as independent variables associated with severe hyperparathyroidism leading to PTx during long-term follow-up. Although PTH decreased between start and 1 year of RRT and the fraction of patients with a PTH > 20 pmol/l declined in this period, a substantial number (21%) of patients had persistent elevated PTH at 1 year of RRT. A failure to adequately control phosphate might have contributed to this.

A few studies have identified predictive variables associated with severe hyperparathyroidism, but never specifically during the first year of dialysis in an unselected cohort. Mizumoto et al. [8] found that initial PTH was a predictor of severe hyperparathyroidism, but PTH at 1 year was not analysed as a potential risk factor. We observed that initial PTH was significantly associated with need for PTx by univariate analysis, but became statistically insignificant in the multivariate analysis due to the greater impact of PTH at 1 year. One year after the start of RRT seems to be a better time point, as in a substantial number of patients initially elevated PTH levels are corrected by correcting hypocalcaemia. Likewise, a strong association was found between phosphate level at 1 year and need for PTx, but not at the start of RRT.

Prevention of development or progression of secondary hyperparathyroidism should preferably start in the pre-dialytic period by dietary measures, phosphate binding and active vitamin D [4]. One of the factors associated with maintaining a PTH < 20 pmol/l or reducing it to < 20 pmol/l during the first year of RRT was a lower PTH at the start of RRT. Patients with a lower PTH at the start of RRT used significantly more vitamin D. Patients who started RRT with a PTH > 20 pmol/l combined with a low-normal calcium had a better chance to reduce their PTH to < 20 pmol/l compared with patients with a high-normal calcium. It should be noted that a dialysate with a standard calcium concentration of 1.50 mmol/l was used, which might have had an effect on the correction of calcium. Patients with a high-normal calcium and PTH > 20 pmol/l at the start may already have hyperplastic parathyroid glands with changes in setpoint and no longer respond adequately to vitamin D [1]. This stresses the importance of early pre-dialysis correction and treatment of calcium–phosphate metabolism [9].

The strong predictors found in this retrospective study do not necessarily imply causality. Elevated PTH and alkaline phosphatase are a consequence of hyperfunctional parathyroids and a statistical correlation was expected. Instead, the strong relationship found between phosphate > 1.85 mmol/l at 1 year of RRT and severe hyperparathyroidism might be causal. Hyperphosphataemia is associated with hyperplastic growth of the parathyroid glands, which may be related to the induction of parathyroid transforming growth factor-α expression [10]. Phosphate also regulates PTH in several ways. Hyperphosphataemia directly stimulates PTH synthesis and secretion by post-transcriptional mechanisms, induces skeletal resistance to PTH that decreases the release of calcium from bone, and inhibits the synthesis of active 1,25(OH)₂ vitamin D that is already low [10,11]. In addition, serum phosphate of patients with a calcium–phosphate product > 5 mmol²/l² during the first year of RRT, as seen in 46% of the patients, was 20% higher than in patients with a product < 5 mmol²/l², while calcium was only 4% higher. It seems, therefore, that phosphate is the major determinant of the calcium–phosphate product. An elevated calcium–phosphate product has been associated with increased mortality [12,13]. Also, it has been suggested that elevated phosphate is the main contributor to the higher mortality risk associated with a calcium–phosphate product > 72 mg²/dl² and is associated with the increased risk for cardiac valvular surgery [12,14]. Indeed, strict control of phosphate
Fig. 1. PTH at start, 1 year of RRT and end of follow-up (A) and phosphate (B), calcium (C) and calcium-phosphate product (D) at start, 1 year of RRT and the mean value beyond 1 year until the end of follow-up in patients who did (solid triangles) and did not (solid squares) need PTx. Horizontal error bars represent the mean±SD of duration of follow-up and vertical error bars represent the mean±SD of the level of the parameter. *Difference with $P<0.05$ between both groups.

Fig. 2. Actuarial survival without need for PTx in 202 patients according to phosphate <1.85 mmol/l (Ph <1.85; solid squares; $n=103$) or phosphate >1.85 mmol/l (Ph >1.85; solid triangles; $n=99$) at 1 year of RRT ($P=0.006$, log-rank test).
levels in the range 0.81–1.78 mmol/l (2.5–5.5 mg/dl) has recently been advocated to prevent cardiovascular disease in ESRD patients [15].

New therapies, such as calcimimetic drugs, sevelamer and new vitamin D analogues, have recently been introduced to avoid increase of calcium–phosphate product, as often is the case with current therapy [16–18]. Although these new therapies seem very promising in preventing severe hyperparathyroidism, long-term effects should be awaited. Chertow et al. [16] did not find an overall effect on the PTH level after treatment with sevelamer for almost 4 years in HD patients. Evaluating different dosage groups, they saw a reduced PTH, especially in the low dosage group representing patients with mild hyperphosphataemia. This means that, especially, patients at an early stage of disease might benefit more from treatment with sevelamer. The new vitamin D analogue paricalcitol was shown to be effective in lowering PTH without hypercalcaemia during 13 months of follow-up and recently was found to be associated with a better survival as compared with calcitriol [19,20]. Long-term effects of calcimimetic agents are not available yet. Experimental studies should evaluate whether these new therapies reduce severe hyperparathyroidism during long-term follow-up in high-risk patients at an early stage of disease.

In conclusion, serum PTH, phosphate and alkaline phosphatase after 1 year of RRT were found to be independent predictors of severe hyperparathyroidism needing PTx. Patients at high risk for PTx during long-term follow-up can be identified by these parameters at a relatively early stage. Pre-dialysis correction of the calcium–phosphate metabolism as well as early control of phosphate during RRT are of major interest in the prevention of severe hyperparathyroidism.

Conflict of interest statement. None declared.

References