The need for better control of secondary hyperparathyroidism

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Abstract
Secondary hyperparathyroidism (SHPT), a frequent complication of chronic kidney disease, develops in response to an imbalance in the serum levels of calcium, phosphorus and vitamin D as a result of altered metabolism. Elevated serum levels of PTH and calcium–phosphorus product (Ca\(\times\)P) have a major effect on morbidity and mortality in dialysis patients. The new Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, formulated by the National Kidney Foundation in the USA, propose strict targets for the control of serum levels of PTH, calcium and phosphorus. Meeting these targets will be a challenge for clinicians, because the traditional therapies for SHPT, such as vitamin D sterols and calcium-based phosphate binders, often exacerbate mineral imbalances. Results from a number of recent studies indicate that the majority of haemodialysis patients currently do not meet these new targets. Thus, there is a definite need to improve PTH, calcium and phosphate management of dialysis patients to reduce the incidence of uraemic bone disease and related disturbances of mineral metabolism as well as their unacceptably high cardiovascular morbidity and mortality.

Keywords: clinical trial; parathyroid hormone; secondary hyperparathyroidism; serum calcium; serum phosphorus

Introduction
Secondary hyperparathyroidism (SHPT) is a frequent complication of chronic kidney disease, which is characterized by hyperplasia of the parathyroid glands and increased serum levels of parathyroid hormone (PTH) [1]. It develops in response to an imbalance in serum levels of calcium, phosphorus and vitamin D as a result of altered metabolism. Elevated serum levels of PTH and calcium–phosphorus product (Ca\(\times\)P) have a major effect on morbidity and mortality in dialysis patients [2–5]. Both are risk factors for mortality in patients with end-stage renal disease (ESRD) [3,4]. A prolonged imbalance between serum calcium and phosphorus is associated with an increased risk of soft tissue and cardiovascular calcifications and an increased risk of cardiovascular morbidity and mortality [4,6,7], particularly deaths resulting from coronary artery disease and cases of sudden death [5]. In addition to the formation of soft tissue and vascular calcifications, uraemic bone disease (renal osteodystrophy) is another important clinical consequence of SHPT, and PTH is one of the main mediators of bone remodelling [8,9].

Conventional management of SHPT has focused on the suppression of PTH levels to prevent or treat renal bone disease. Over recent years, however, there has been an increasing realization that the regulation of PTH secretion, together with the maintenance of serum calcium, phosphorus and Ca\(\times\)P within target levels, may reduce morbidity and mortality in patients with SHPT [10]. The management of SHPT is complex, however, because of the inter-relationships between the serum levels of calcium, phosphorus and PTH. Thus, treatment to improve one of these factors may have an impact on the others. Reducing PTH levels possibly may lead to oversuppression of PTH and therefore the risk of adynamic bone disease. This is of utmost importance, considering the increasing age of patients, the higher percentage of diabetics and the frequent risk of PTH oversuppression.

The new Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines formulated by the National Kidney Foundation in the USA and forthcoming European guidelines include new guidance for the management of mineral homeostasis in patients with ESRD. The K/DOQI guidelines propose setting stricter targets for the control of serum levels of PTH, calcium and phosphorus: PTH 150–300 pg/ml (15.8–31.5 pmol/l), Ca\(\times\)P <55 mg\(^2\)/dl\(^2\) (<4.4 mmol\(^2\)/l\(^2\)), calcium 8.8–9.5 mg/dl (2.1–2.4 mmol/l) and phosphorus 3.5–5.5 mg/dl (1.1–1.8 mmol/l). Meeting these targets
will be a challenge for clinicians, as the traditional therapies for SHPT, such as vitamin D sterols and calcium-based phosphate binders, can often exacerbate mineral imbalances.

In this review, some of the recent studies of SHPT in haemodialysis (HD) patients will be discussed, including those that have assessed the relationship between serum calcium, phosphorus, Ca×P and PTH levels and morbidity and mortality.

**Dialysis Outcomes and Practice Patterns Study (DOPPS)**

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a large, international, longitudinal, observational study. The goal of the study is to identify practice patterns and improve patient outcomes. The major outcomes of the study are mortality, hospitalization, vascular access and quality of life (QoL). The framework for the hypothesis included patient demographics, patient co-morbidities and practice patterns, in order to evaluate the patient outcomes. DOPPS consists of two phases: in phase I, the countries involved were France, Germany, Italy, Japan, Spain, the UK and the USA, while during phase II, Belgium, Norway, Sweden, Australia and New Zealand have also become involved.

DOPPS investigators recently analysed what proportion of patients in their respective countries were outside new K/DOQI targets for the levels of PTH, calcium and phosphorus [11]. Data were obtained from 8615 patients receiving HD treated in 309 facilities in the first seven countries: from the USA between 1996 and 1997, Europe in 1998 and Japan in 1999. The results indicate that significant improvements in therapy are required since many patients had suboptimal control of PTH and minerals (Table 1).

Within each country, ~50% of patients were below the low target for PTH (range 47.8–58.5%), thus underlining the risk of adynamic bone disease in the present patient population. In contrast, the upper PTH target was exceeded in 19–31% of patients. The proportion of patients who were above the Ca×P target was 35.1–56.5%, and there was also a wide variation in the percentage of patients within each country who exceeded the phosphorus target (range 37.8–69.6%). In all of the first seven countries, a large percentage of HD patients did not meet the proposed targets for PTH, phosphorus and Ca×P.

**Lack of control of SHPT in Italy**

Despite emerging data from DOPPS, information regarding the prevalence of hypercalcaemia, hyperphosphataemia and abnormal levels of PTH within Europe has been scarce. A recent study from Italy has, however, provided some insights.

Gallieni *et al.* investigated the calcium, phosphorus and PTH levels of an HD population in southern Italy (Sicily and Campania) by reviewing the records of 628 patients (mean age 61.2 years, 42% female) enrolled at 29 dialysis centres [3]. They observed the following PTH and mineral levels [mean±SD (95% confidence interval): calcium 9.06±0.98 (8.98–9.14) mg/dl; phosphorus 5.74±1.57 (5.62–5.86) mg/dl; PTH 318±413 (265–370) pg/ml and Ca×P 51.4±14.4 (50.3–52.5) mg²/dl². In a significant proportion of the population, however, these parameters were outside the normal range: 52% of patients had serum phosphorus concentrations >5.5 mg/dl, 36% had Ca×P levels >55 mg²/dl², 25% had hyperparathyroidism (defined as PTH >400 pg/ml) and only 20% of patients had PTH levels in the ideal range of 100–250 pg/ml. Nevertheless, these data appeared to indicate that the population of these regions in Italy was relatively better controlled than a recently evaluated group of patients from the USA. For example, the proportion of patients from the USA with phosphorus levels >5.5 mg/dl was >60% [2].

For patients with uncontrolled SHPT, parathyroidectomy is the treatment of last resort. Parathyroidectomy is therefore an interesting marker of the severity of SHPT and success, or failure, of pharmacological treatment. Malberti *et al.* also conducted a study in the Lombardy region of Italy on the epidemiology of parathyroidectomy in patients on renal replacement therapy (RRT) [12]. They evaluated the prevalence, incidence and risk factors for parathyroidectomy and investigated whether the incidence changed over time. The study included 14 180 patients from the Lombardy Registry of Dialysis and Transplantation who received RRT for ESRD between 1983 and 1996. Cox proportional hazards regression models were used to evaluate the relationship between parathyroidectomy and the possible risk factors for SHPT: age on admission to RRT, sex, underlying renal disease (diabetic or non-diabetic nephropathy) and initial type of dialysis (peritoneal dialysis or HD).

The results showed that the prevalence of parathyroidectomy increased in relation to the time spent on RRT. In the 7188 patients who were alive on 31 December 1996, the overall prevalence of parathyroidectomy was 5.5%, ranging from 0.9% in patients with <5 years on RRT, 3.8% in patients with 5–10 years on RRT, to 20.8% in patients with >15 years on RRT, while for transplantation patients the number was much lower (8.3%). Similarly, the incidence of

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**Table 1. Percentage of patients within each country in the DOPPS outside the new K/DOQI guideline targets [11]**

<table>
<thead>
<tr>
<th>Country</th>
<th>% PTH &lt;150 pg/ml</th>
<th>% PTH &gt;300 pg/ml</th>
<th>% Ca×P &gt;55 mg²/dl²</th>
<th>% Phosphorus &gt;5.5 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>55.6</td>
<td>21.4</td>
<td>38.0</td>
<td>45.1</td>
</tr>
<tr>
<td>Germany</td>
<td>50.5</td>
<td>25.5</td>
<td>56.5</td>
<td>69.6</td>
</tr>
<tr>
<td>Italy</td>
<td>52.6</td>
<td>25.5</td>
<td>35.1</td>
<td>37.8</td>
</tr>
<tr>
<td>Japan</td>
<td>58.5</td>
<td>19.1</td>
<td>43.1</td>
<td>53.6</td>
</tr>
<tr>
<td>Spain</td>
<td>50.8</td>
<td>27.5</td>
<td>43.2</td>
<td>46.4</td>
</tr>
<tr>
<td>UK</td>
<td>47.8</td>
<td>31.2</td>
<td>44.9</td>
<td>50.8</td>
</tr>
<tr>
<td>USA</td>
<td>48.8</td>
<td>29.3</td>
<td>43.8</td>
<td>52.0</td>
</tr>
</tbody>
</table>
parathyroidectomy also increased with increasing duration of RRT among the 10,591 patients who started RRT between 1993 and 1996. The incidence of parathyroidectomy in patients with >10 years on RRT was 30 per 1000 patient-years compared with 3.3 per 1000 patient-years in patients with <5 years on RRT. The overall incidence of parathyroidectomy was 5.28 per 1000 patient-years for patients on RRT.

The relative risk (RR) of parathyroidectomy was greater in women than in men (RR = 2.28, \( P < 0.001 \)), was very low in patients with diabetic nephropathy compared with non-diabetic nephropathy patients (RR = 0.09, \( P < 0.01 \)), and was lower in older (>64 years) than in younger (55–64 years) patients (RR = 0.23, \( P < 0.001 \)). In addition, patients receiving peritoneal dialysis had a higher RR than patients receiving HD (RR = 1.62, \( P < 0.003 \)), while transplantation patients had a much lower RR than patients on HD (RR = 0.15, \( P < 0.001 \)). The study showed that there was no difference in the incidence of parathyroidectomy in patients who started RRT between 1983 and 1985 and those who started between 1990 and 1992.

### Outcomes associated with poor control of SHPT

In order to avoid the serious consequences of SHPT, serum levels of calcium, phosphorus and PTH must all be controlled more effectively. Recent analyses from a large patient database in the USA illustrate the dangers of failing to achieve control of each of these different elements. In their analysis, Block et al. examined the relationship between serum levels of PTH and \( \text{Ca} \times \text{P} \) and hospitalizations, and the relationship between serum levels of calcium and mortality in patients on HD [13,14]. This was a 2 year observational study (from 1 July 1998 to 30 June 2000) of 44,550 incident and prevalent patients with ESRD. The eligibility criteria for the analysis were survival for at least 6 months after entry into the database (considered as the baseline period) and the availability of serum PTH \( (n = 36,266) \), \( \text{Ca} \times \text{P} \) \( (n = 37,167) \) or calcium \( (n = 37,169) \) levels.

Patients were followed-up for 6 months after the baseline period. Poisson regression was used to evaluate the relationship between serum levels of PTH and \( \text{Ca} \times \text{P} \) and hospitalization during the follow-up period. Cox proportional hazards methodology was used to evaluate the association between serum levels of calcium and mortality.

The results showed that the number of hospitalizations increased with increasing serum levels of PTH and \( \text{Ca} \times \text{P} \) (Figures 1 and 2, respectively). In addition, they showed that the RR of death in patients on HD was associated with serum calcium levels. The RR of death was increased in patients with serum levels of calcium of \( \geq 9.5 \text{mg/dl} \), but a serum calcium level of \(< 8.5 \text{mg/dl} \) was not associated with an increased mortality risk (Figure 3). Ganesh et al. analysed data from two special studies of the United States Renal Data System (USRDS) [1]. These investigators found that a 1 mg/dl increment in serum phosphate was associated with a 9% higher risk of death resulting from coronary artery disease (CAD) \( (P < 0.0005) \) and a 6% higher risk of death resulting from sudden death \( (P < 0.01) \), when adjusting for age at study start, duration of ESRD, race, gender, diabetes, smoking, AIDS and neoplasm.

Elevated serum phosphate was also significantly associated with deaths resulting from cerebrovascular disease (RR 1.08; \( P < 0.05 \)), infection (RR 1.05; \( P < 0.05 \)) and unknown causes of death (RR 1.07; \( P < 0.05 \)). Deaths resulting from CAD and cases of sudden deaths were also significantly related to elevated \( \text{Ca} \times \text{P} \), with an RR of 1.06 \( (P < 0.05) \) per 10 mg\(^2\)/dl\(^2\) higher \( \text{Ca} \times \text{P} \) for CAD and 1.07 \( (P < 0.005) \) for sudden death [1].

### Conclusions

These studies confirm a current lack of control in many patients with SHPT—whether in terms of the K/DOQI guideline targets not being achieved or in terms of parathyroidectomy being required. Furthermore, the studies also provided evidence of the serious consequences of inadequate control, with increased rates of...
morbidity and mortality occurring in suboptimally treated patients.

In the seven countries of phase I of the DOPPS, there was a large variation between the percentage of patients receiving HD who did not meet the new K/DOQI guideline targets for serum levels of PTH, phosphorus and Ca\times\text{P}. Overall, in each country, a large percentage of patients did not meet the new K/DOQI guideline targets. This lack of control was replicated in an Italian study by Gallieni et al. [3]. Eventually, data from the DOPPS and other observational studies will enable us to assess the impact of these new guidelines on improving the management and outcomes among HD patients.

The need for optimizing treatment in line with K/DOQI targets was demonstrated in the USA by Block et al. who showed that increased serum PTH and Ca\times\text{P} levels are associated with an increase in the number of hospitalizations, and that serum calcium levels of >9.5 mg/dl may be an independent risk factor for mortality in patients on HD [2]. Additional epidemiological research is needed, however, to determine the precise nature of these relationships.

In summary, SHPT should be treated more aggressively, with treatment starting at an earlier stage in the course of chronic kidney disease, in order to reduce the associated morbidity and mortality. Current therapies and medical care are inadequate for controlling PTH, calcium and phosphorus levels, and there is a clear need for a better medical approach and new therapeutic options to improve outcomes in these patients.

Conflict of interest statement. None declared.

References


5. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO_{4}, Ca\times\text{PO}_{4} product, and

![Fig. 2. Hospitalizations by Ca\times\text{P} category. Reproduced, with permission, from Block *et al.* [13]. The asterisks indicate that the number of hospitalizations is significantly different from hospitalizations in the next lowest Ca\times\text{P} category (P<0.05). CI = confidence interval.](image1)

![Fig. 3. Risk of death by serum calcium level. Patients with serum calcium concentrations of ≥9.5 mg/dl, when compared with patients with serum calcium concentrations of 8.5–9.5 mg/dl, displayed a significantly greater risk of death over the 6 month follow-up period. Patients with serum calcium levels <8.5 mg/dl displayed a reduced hazard risk of death that was not statistically significant. Reproduced, with permission, from Block *et al.* [14]. Bars represent 95% confidence intervals.](image2)
11. Young E, Satayathum S, Pisoni R et al. Prevalence of values on mineral metabolism being outside the targets from the proposed new draft NKF-K/DOQI and European Best Practice guidelines in countries of the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2003; 18 [Suppl 4]: 677