Editorial Review

Hyperphosphataemia and related mortality

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End-stage renal disease (ESRD) patients have a dramatically higher risk of death compared with the general population [1]. In 1998, Block et al. showed that hyperphosphataemia and a high calcium × phosphorus product are independently associated with mortality in dialysis patients [2]. More recently, based on a large cohort, the same authors have confirmed these findings adding hypercalcaemia and severe hyperparathyroidism (HPT) to risk factors for mortality. They have shown that the mortality risk associated with disorders of mineral metabolism is higher than that associated with a low urea reduction ratio (URR) and anaemia [3]. These risk factors for mortality were confirmed in the DOPPS study [4] and more recently in the USRDS waves study [5]. The excess mortality observed in dialysis patients is mainly of cardiovascular origin and it has been associated with cardiovascular calcifications in ESRD patients [6–8]. Non-modifiable risk factors (such as age, diabetes and dialysis vintage) and co-morbid factors (such as hypertension, tobacco use, hyperlipidaemia and chronic inflammation), which are prevalent among dialysis patients, are the main risk factors for increased mortality; disorders of bone mineral metabolism and related treatments are also contributory, as shown by Guerin and London [9,10]. Recently, these authors also pointed out that hyperphosphataemia per se, its associated treatments (calcium-based and aluminium-containing phosphate binders) and complications (parathyroidectomy and adynamic bone disease) are linked to a high prevalence of vascular calcification. However, the underlying relationship between calcium-phosphorus balance and vascular calcification is still unclear.

Based on earlier data, the DOQI guidelines for management of bone and mineral disease recommend targets for serum phosphorus level (3.5–5.5 mg/dl) and serum calcium × phosphorus product (55 mg²/dl²) for calcium corrected for albumin [11]. The general acceptance and wide dissemination of these guidelines enable us to estimate the proportion of patients meeting the guidelines in each country. In the USRDS Dialysis Morbidity and Mortality Study, a HD patient in 1993 had a 53.6% rate of hyperphosphataemia [5]. Bone mineral disorders were reported 10 years later by the DOPPS study (Table 1) [4] and the prevalence of hyperphosphataemia remained high in most countries, with 46.7% of patients having phosphate levels >5.5 mg/dl in spite of phosphate binders being used in ~80% of patients (DOPPS II). We can conclude from this that current dialysis schedules, dietary interventions and medications are not sufficient to meet the DOQI targets for phosphate.

Why? Are the treatments available inadequate or just not powerful enough? Can we improve their use?

Causes of, and therapy for, hyperphosphataemia

Phosphorus is an intracellular anion and its serum level may not represent the amount of body phosphate content. Phosphataemia displays a circadian variation (±30%) and is influenced by meals and carbohydrate intake. Phosphate balance in dialysis patients depends on phosphate intake and absorption (minus phosphate binding), and dialysis removal. Residual renal function may contribute to phosphate removal [12]. Serum phosphate levels depend on phosphate transfer from different body compartments, especially from bone (350 mg/day).

We have tried to identify the different mechanisms and optimum treatments of hyperphosphataemia based on our own results, as well as already published data and the K/DOQI guidelines.

Dietary phosphate intake

Bone mineral K/DOQI guidelines recommend restriction of dietary phosphorus to 800–1000 mg/day if the patient is hyperphosphataemic with kidney failure stage 5 [11], but this is not consistent with the nutrition
Table 1. Comparison of Tassin patients on 5–6 h (n=86) vs 7–8 h (n=113) schedules (age, sex ratio, dialysis vintage, BMI, nPCR and dialysate calcium are similar) and with the DOPPS report (E. Young, Berlin 2003, EDTA)

<table>
<thead>
<tr>
<th>% Patients exceeding DOQI guidelines</th>
<th>Europe</th>
<th>Japan</th>
<th>USA</th>
<th>Tassin (5–6 h)</th>
<th>Tassin (7–8 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH &lt;150 pg/ml</td>
<td>51</td>
<td>59</td>
<td>49</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>PTH &gt;300 pg/ml</td>
<td>26</td>
<td>19</td>
<td>29</td>
<td>35</td>
<td>9.6</td>
</tr>
<tr>
<td>PO₄ &gt;5.5 mg/dl</td>
<td>50</td>
<td>54</td>
<td>52</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Ca × PO₄ &gt;55 mg²/dl</td>
<td>43</td>
<td>43</td>
<td>44</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>

![Figure 1](image_url)  
**Fig. 1.** Frequency distribution of daily phosphate intake in all haemodialysis patients in Tassin (1 day analysis of 200 patients).

K/DOQI-recommended protein intake of 1.2 g/kg/day [13] that corresponds to a phosphate intake of 1000–1400 mg/day [14]. Normalized protein catabolic rate (nPCR) calculated from the urea generation rate might be considered a good measure of protein intake, but a formal dietary assessment is a much better guide to protein and/or phosphate intake. It is important to be aware that lowering protein intake may cause malnutrition [14,15] and the goal is to correct excessive intake (i.e. >1.2 g/kg/day recommended), and to reduce intake of high phosphate-containing foods recognizing that the phosphorus–protein ratio can vary between 12 and 16 mg/g [16].

Fractional phosphate intestinal absorption is ~65–80% depending on the serum phosphate and calcitriol level [17], resulting in daily absorption of 650–1100 mg for an optimal protein intake, i.e. 5600–7000 mg/week.

In dialysis patients, the distribution of daily phosphate intake is Gaussian and, for a recommended mean protein intake of 1.2 g/kg/day, 40% of patients are above 1000 mg/day (Figure 1). Therefore, the weekly phosphate absorbed can be >10000 mg and thus limiting dietary intake is the first step in a phosphate control strategy.

This is not expensive but it is time consuming. Not all renal units may have access to a dietician, and so nurses and doctors must take some responsibility for this measure. Most dialysis patients are not aware of phosphate-rich foods, and their compliance with dietary phosphate restriction would improve with better education [18–20].

**Phosphate binders**

K/DOQI recommends prescribing a phosphate binder when the serum phosphate level cannot be controlled by dietary restriction alone. Calcium-based phosphate binders can be used as initial therapy [11], but their use should be limited to 1500 mg of elemental calcium per day, and they should be avoided in patients with evidence of vascular calcification, which is present in over half of all ESRD patients [21–23], although this is only a K/DOQI opinion-based recommendation. Moreover, to prevent adynamic bone disease, they must be withdrawn when the intact parathyroid hormone (iPTH) level is low (<150 pg/ml), which, according to DOPPS, occurs in ~50% of dialysis patients [4] (Table 1) and in hypercalcaemia. Curiously, very few recommendations are given for dialysate calcium according to the overall calcium balance, but it should be adjusted. In large part, the recommendation to restrict calcium is based on retrospective analyses that suggest a relationship between coronary artery calcification [24] and excessive use of calcium-based phosphate binders [6,9].

Non-calcium- and non-aluminium-containing phosphate binders, such as sevelamer, may also be used as first line therapy. The Treat to Goal study has demonstrated that, when compared with sevelamer, calcium-based phosphate binders favour worsening cardiac calcification [25] that may have a deleterious effect on cardiovascular events [26]. In this study, with supposed optimal patient monitoring and compliance, phosphate control was good and similar, with a mean of eight sevelamer 800 mg tablets, seven calcium acetate 667 mg capsules and eight calcium carbonate 500 mg tablets. The calcium group displayed higher serum calcium levels, confirming that with sevelamer there is a less positive calcium balance. However, one may wonder if better dialysate calcium and vitamin D management in the calcium group might have modified these findings. Besides, the apparently beneficial effect of sevelamer on lipid levels is confusing. The CARE study, another comparative trial, reported better phosphate control with calcium acetate than with sevelamer, but with more frequent episodes of hypercalcaemia [27]. As for the Treat to Goal, no data are available on either dialysate performance or phosphate intake. Recently, a preliminary report of the Dialysis Clinical Outcomes Revisited had been reported by Genzyme (unpublished) showing that patients using Renagel for 2 years or more and being older than 65 years are less likely to die than those using a calcium-based
phosphate binder. This would be a strong argument for the prescription of non-calcium phosphate binders. However, sevelamer is 10 times more expensive than conventional binders. This will limit its prescription in underdeveloped and developing countries, and increase the costs of dialysis [28].

In uncontrolled hyperphosphataemia, K/DOQI recommend the use of aluminium-containing phosphate binders for short periods only (up to 4 weeks) to avoid aluminium absorption [29] and toxicity. Indeed, aluminium is associated with endemic bone disease, osteomalacia and cerebral toxicity [30,31], although the most severe complications are related to dialysate water aluminium content [32].

Two non-calcium- and non-aluminium-containing phosphate binders are absent from K/DOQI guidelines. The first is lanthanum carbonate [33,34], which will probably be available in most countries by 2006. More studies are needed to assess its effect on cardiac calcification, but it has been shown to be as efficient in controlling hyperphosphataemia as calcium carbonate with less hypercalcaemia [35]. However, the long-term consequences of its absorption and tissue deposition observed in rats must be explored in humans [36,37]. Its cost is similar to sevelamer in the USA. The major advantage may be the need for only one tablet per meal.

Second is nicotinamide, not really a phosphate binder, but an inhibitor of sodium-dependent phosphate co-transport in the small intestine. It has been found to be effective in reducing phosphataemia at a mean dose of 1000 mg (i.e. two tablets) compared with calcium carbonate [38]. It is a cheap medication that is non-reimbursable in most countries, but long-term experience is lacking.

Tolerance of, and compliance with, phosphate binders remain a challenge. Most of the available drugs have significant gastrointestinal side effects. Whatever type is used, its phosphate binding effect is dose related [39,40] and so are its adverse effects including poor compliance. Slatopolsky et al. reported that a mean dose of calcium carbonate of ~15 g is needed to bind phosphate adequately for a 1.2 g/kg/day protein intake [41], a daily dose requiring a large number of pills. Dialysis patients are also unaware of the potential toxicity of hyperphosphataemia compared with other risk factors such as hypertension [42], and this must be addressed to ensure compliance [43].

DOPPS reported that phosphate binders are prescribed to ~80% of patients whatever the serum phosphate level [4]. We must begin to individualize phosphate binder therapy according to bone mineral indices and the presence of vascular calcification to achieve the right choice and dose at the lowest cost. However, the best phosphate binder is still the one the patient will take.

**Bone-related hyperphosphataemia and vitamin D**

This is difficult to discuss because data are limited. Transfer of phosphate between bone and extracellular fluid occurs normally at a rate of 350 mg/day. The net balance must be neutral in normal bone turnover. In ESRD patients, two conditions can alter this balance: excess bone turnover leading to phosphate efflux from bone; or a low bone turnover reducing bone buffering of serum phosphate both related to calcium metabolism.

Advanced osteitis fibrosa is well known to impair phosphate control [44], which improves after surgical parathyroidectomy [45,46] or with use of calcimimetics [47]. The high doses of active vitamin D derivatives used in HPT lead to an increase in intestinal absorption of phosphate. Vitamin D derivatives must be reduced in cases of uncontrolled hyperphosphataemia, and K/DOQI recommends giving active vitamin D only if serum iPTH is >300 pg/ml and when serum phosphate and calcium are controlled. New vitamin D derivatives, such as Paricalcitol, seem to have a lower phosphaemic effect than calcitriol [48] but when vitamin D is contraindicated, calcimimetic therapy may be as, or more, effective in reducing bone turnover [49].

There is sometimes a direct relationship between PTH and serum phosphate levels over time, as illustrated in Figure 2. Lowering the dialysate calcium when PTH was <150 pg/ml caused HPT and hyperphosphataemia that reversed after crossover. However, the relationship between PTH and serum phosphate is bi-directional as hyperphosphataemia stimulates PTH secretion.

Hyperparathyroidism-related high bone turnover may be worsened by several K/DOQI recommendations such as a low target value for serum calcium, the restriction of daily total oral calcium and active vitamin D sterol intakes, and a standard use of 1.25 mmol/l for dialysate calcium concentration [50,51]. It must be remembered that HPT itself is an independent risk factor of mortality in dialysis patients [5].

In the case of endemic bone disease, mainly due to a positive calcium balance, an inadequate vitamin D prescription or a total parathyroidectomy, phosphorus cannot be used for bone synthesis and this may favour hyperphosphataemia. In this situation, there is a small amount of phosphate efflux from bone. Less active vitamin D should be prescribed, so it is less deleterious for phosphate control than high bone turnover.

Abnormal bone turnover may partially explain the failure to maintain serum phosphate levels adequately in some patients treated with conventional dialysis and phosphate binders. Abnormal bone turnover must be diagnosed and corrected, and reliable serum markers of bone turnover are needed, since iPTH levels are unreliable within the normal K/DOQI range [52]. The 1–84/7–84 PTH ratio may be more reliable than iPTH [53], but a closer relationship to bone histomorphometry has not been demonstrated up to now [54]. Bone alkaline phosphatase is also a useful marker of bone osteoblast activity and bone turnover [55]. Osteocalcin can be measured, but it is less specific [56,57]. For bone osteoclast activity, CTXs (β cross-laps) are frequently used in the setting of osteoporosis and may also be helpful in renal bone disease [58], although normal values adjusted for renal function are lacking.
A biological bone marker of bone turnover is needed now that bone biopsy, the gold standard, is not routinely performed to adjust therapy.

**Dialysis prescription**

Dialysis treatment is also aimed at controlling hyperphosphataemia, but standard haemodialysis (SHD) may be inadequate. SHD removes 300–1100 mg/session (800 mg for the K/DOQI), i.e. 900–3300 mg per week [59–63], depending on dialysis efficiency and serum phosphate level; haemodiafiltration (HDF) a mean of 1100 mg, i.e. 3300 mg per week [64]; nocturnal daily haemodialysis (NDHD) a mean of 800 mg/session, i.e. 4800 mg per week [65]; short daily haemodialysis (SDHD) up to 3600 mg/week [63]; and long haemodialysis (LHD) 600–1500 mg/session, i.e. 1800–4500 mg/week [62].

Man et al. have shown that phosphate mass transfer is maximal in the first hour (300 mg) from the extracellular fluid compartment and remains stable after the third hour (100 mg/h) with the mobilization of an intracellular pool [66]. Figure 3 shows the phosphate kinetics profiles in three different dialysis prescriptions. Increasing dialysis efficiency increases phosphate clearance, mainly in the first hour when serum phosphate levels are high. Therefore, the simplest manoeuvre to improve phosphate control in SHD is to optimize dialysis dose by increasing dialyser phosphates clearance and blood flow, and reducing vascular access recirculation. When available, HDF may improve phosphate removal [64,67] due to its greater convective effect [68].

K/DOQI guidelines recommend longer and more frequent dialysis in cases of persistently high phosphate levels (>7.0 mg/dl) with good evidence to support this [11]. We recently have reported good serum phosphate control using LHD with phosphate binder use in <35% of patients [69]. Hyperphosphataemia is present in 12 and 25% of our patients treated with the 7–8 and 5–6h dialysis, respectively, whereas the DOPPS data show hyperphosphataemia in 46.7% of patients in the different participating countries [70] (Table 1). Better phosphate control has also been
reported by Alloatti et al. using LHD [71]. One may question the patient’s compliance with more dialysis time. The Tassin experience clearly showed that, when doctors are convinced, patients frequently trust them and very few ask for an SHD. This can be explained by the less restrictive diet and the lower medication prescription [72], and the better dialysis tolerance [69].

According to recent data comparing standard 3 × 4 h with 6 × 2 h schedules, increasing the frequency only, but with a constant weekly total time, is probably not sufficient for phosphate control [63,73]. For Gotch et al., the improvement in phosphate removal in high efficiency SDHD is largely offset by an increase in protein intake [61], as also observed by Traeger et al. [74]. Increasing the time and frequency in a 6 × 3 h schedule, Achinger et al. reported better phosphate control than in SHD [75]. Musci et al. reported better results in NDHD [65], mainly at home or in self-care units, as did Pierratos et al. [76,77] and Lindsay et al. [73], stopping phosphate binders and in some cases needing to add phosphate to the dialysate. Direct dialysis quantification techniques have demonstrated that the most important determinant of phosphate removal during a single dialysis session is the dialysis time [78,79]. Therefore, increasing dialysis time is a very efficient measure in dialysis session is the dialysis time [78,79]. Therefore, increasing dialysis time is a very efficient measure in dialysis efficiency. The Tassin experience clearly showed that, when doctors are convinced, patients frequently trust them and very few ask for an SHD. This can be explained by the less restrictive diet and the lower medication prescription [72], and the better dialysis tolerance [69].

Table 2. A comparison between patients with normal and high serum phosphate levels

<table>
<thead>
<tr>
<th>PO4 (&gt;5.5 mg/dl)</th>
<th>PO4 3.5–5.5 mg/dl</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 30)</td>
<td>(n = 120)</td>
<td></td>
</tr>
<tr>
<td>Session time (min)</td>
<td>348 ± 120</td>
<td>390 ± 78</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 19</td>
<td>66.4 ± 12</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Dialysate Ca (mmol/l)</td>
<td>1.5 ± 0.1</td>
<td>1.58 ± 0.1</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>346 ± 477</td>
<td>222 ± 195</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.44 ± 0.18</td>
<td>2.39 ± 0.15</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>106 ± 60</td>
<td>115 ± 50</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
<td>1.45 ± 0.2</td>
<td>1.26 ± 0.2</td>
</tr>
<tr>
<td>Blood flow (ml/min)</td>
<td>282 ± 33</td>
<td>256 ± 34</td>
</tr>
<tr>
<td>Dialyser area (m²)</td>
<td>2.0 ± 0.2</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Pi intake (mg/day)</td>
<td>1125 ± 262</td>
<td>975 ± 200</td>
</tr>
<tr>
<td>Phosphate binder (%)</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Sevelamer (tablets/day)</td>
<td>7.5 ± 2</td>
<td>5.4 ± 2</td>
</tr>
<tr>
<td>Compliance (%)</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>Alfacalcidol (%)</td>
<td>43</td>
<td>50</td>
</tr>
</tbody>
</table>

Compliance is defined as the percentage of treatment correctly taken in a week.

Table 3. A strategy to control hyperphosphataemia

| Dietary intervention | | | |
|----------------------|------------------|------------------|
| Consider haemodiafiltration | Increase blood flow and dialyser phosphate clearance, check for recirculation |
| Assess and correct protein intake to 1.2 g/kg/day | Consider calciimimetics or parathyroidectomy in the case of severe HPT |
| Restrict phosphate intake to < 1000 mg/day | Increase time and/or frequency |
| Restrict calcium-based phosphate binder prescription especially in the case of low bone turnover, vascular calcification and hypercalcaemia | |
| Consider calcimimetics or parathyroidectomy in the case of low bone turnover, vascular calcification and hypercalcaemia | |
| Diet | |
| Timing and quantity of phosphate intake | |
| Bone turnover | |
| Consider calcimimetics or parathyroidectomy in the case of severe HPT | |
| Dialysis prescription | |
| Hyperphosphataemia and related mortality | | | |

Characteristics of hyperphosphataemic patients in Tassin

Table 2 is a comparison between patients who are persistently hyperphosphataemic (15%) and those who are normophosphataemic (60%) in 200 patients dialysed thrice weekly in our centre. Hyperphosphataemic patients are younger (56 ± 19 vs 66.4 ± 12) with higher phosphate (1125 ± 262 vs 975 ± 200 mg/day) and protein (1.45 ± 0.2 vs 1.26 ± 0.2 g/kg/day) intakes and lower Kt/V (2.0 ± 0.3 vs 2.2 ± 0.5) due to shorter dialysis sessions (348 ± 120 vs 390 ± 78 min). All of them are on phosphate binders prescribed (mainly sevelamer) at high doses, but the majority admit to poor compliance. Vitamin D prescription is not different, although iPTH levels appear higher in the hyperphosphataemic group. Residual renal function was insignificant. So even with a longer dialysis schedule, hyperphosphataemia still occurs mostly in the 5–6 h schedule compared with the 7–8 h schedule (Table 1). Our strategy to control hyperphosphataemia is summarized in Table 3.

Finally, we agree with Schaefer who highlighted the problem of inadequate control of serum phosphate in dialysis patients 10 years ago. He concluded that protein restriction, increased use of phosphate binders and increasing dialysis efficacy (choosing large surface dialysers, prolonging dialysis time, increasing blood flow and eliminating access recirculation) are all necessary [44]. However, there is a need for long-term randomized studies to demonstrate the beneficial effect of all these measures on morbidity and mortality.
**Conclusion**

Hyperphosphataemia remains one of the major and modifiable risk factors for mortality in ESRD patients, and all measures at our disposal must be used to prevent it. An individualized approach is required to take account of diet, phosphate binders, bone turnover and dialysis itself. Dieticians, nurses and doctors must all be familiar with these measures, which will mean more time and perhaps more money, but the investment is worthwhile and will ultimately reduce morbidity and mortality in our patients.

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**References**

34. Al-Baaj F, Speake M, Hutchison AJ. Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis


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