Hyperphosphataemia as a cardiovascular risk factor – how to manage the problem

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Abstract
Hyperphosphataemia is a frequent and important cardiovascular risk factor in patients with chronic kidney disease (CKD). High phosphate levels may influence vascular calcifications by two separate mechanisms: by worsening secondary hyperparathyroidism, which in turn facilitates calcification, and by promoting calcium phosphate deposition in pre-formed endothelial plaques and in the arterial wall. Recent studies have shown that hyperphosphataemia induces the proliferation and differentiation of endothelial vascular cells into osteoblast-like cells, promoting vascular calcification. High phosphate levels also increase the risk of mortality in patients with CKD. To reduce the negative impact of high phosphate, serum phosphate levels should be -5 mg/dl and serum calcium -10 mg/dl. This allows the calcium-phosphate product to be maintained at 50 mg2/dl2, reducing the risk of vascular, valvular, and extraskeletal calcification. A multiple-factor approach can be used to reduce serum phosphate: (i) decrease bone resorption by maintaining adequate serum parathyroid hormone levels; (ii) reduce phosphorous intake in the diet, (iii) use phosphate binders efficiently; and (iv) avoid under-dialysis. The patient’s diet should be high in nutrition but with the lowest possible phosphorous content. Doses of phosphate binders should be tailored to individual dietary habits and must be taken during meals in a dose proportional to the phosphorous content of the meal. Because of the risk of increased extraskeletal calcification, calcium-containing phosphate-binder intake should not exceed 2–3 g/day. Sevelamer hydrochloride, a non-calcium and non-aluminium phosphate binder with a potency similar to that of calcium salts has shown beneficial effects on lipid profiles. Better control of serum phosphate is achieved in patients on continuous ambulatory peritoneal dialysis than in those on haemodialysis. Removal of phosphate is directly correlated with duration and frequency of dialysis sessions. Thus, it is advisable not to reduce the duration of dialysis sessions to <4 h three times per week.

Keywords: cardiovascular; chronic kidney disease; hyperphosphataemia; secondary hyperparathyroidism; vascular calcification

Introduction
Hyperphosphataemia is an important risk factor for the development of calcification and cardiovascular (CV) alterations in patients with chronic kidney disease (CKD). This has great relevance from both the epidemiological and the clinical perspective. Between 40 and 60% of patients undergoing dialysis have high levels of serum phosphate [1,2]. The prevalence of vascular calcification and CV mortality is nearly 50% in this patient population. Hyperphosphataemia may influence vascular calcification and the CV mortality risk both directly, by facilitating endothelial and intra-wall vascular calcification, and indirectly, by worsening secondary hyperparathyroidism.

The best-known consequences of hyperphosphataemia are effects on the parathyroid gland [3,4], which in turn affect bone metabolism. High serum phosphate levels impair calcitriol synthesis, increase the skeletal resistance to parathyroid hormone (PTH) and also reduce PTH synthesis. In addition, recent studies have shown that hyperphosphataemia increases parathyroid cell proliferation and may reduce expression of the calcium-sensing receptor [5,6]. These combined effects of high serum phosphate levels make serum PTH levels the most relevant indicator of secondary hyperparathyroidism severity in patients on dialysis [2]. Furthermore, high serum PTH levels also have been shown to increase vascular calcification and the risk of mortality [7]. Because of the close relationship between high
serum phosphate and serum PTH, it may also be speculated that the relationship between PTH level and mortality may be indirectly reflecting the effect of hyperphosphataemia.

The predisposition of patients with CKD to vascular calcification was mentioned for the first time in the 19th century, since then, it has been the subject of many studies. A review of the papers published over the last three decades reveals that 40–92% of patients undergoing dialysis treatment, including young patients, have vascular calcifications [8–11]. In a recent study in a non-selected population without renal failure, 48.7% of vascular calcification was observed in people older than 65 years of age: 54.2% in men and 43.1% in women (Diaz Lopez et al. unpublished data). These percentages are only slightly lower than those observed in people undergoing dialysis. However, the great difference is that in patients with chronic renal failure (CRF), the process of vascular calcification occurs 10–20 years earlier than in the general population [12] and it has greater repercussions in terms of mortality [13].

### Risk factors and mechanisms of extraskeletal calcification in CRF

Patients with CRF have multiple risk factors for the development of all types of calcification (Table 1). Some are modifiable, with the possibility of preventing calcification. Others are not. Hyperphosphataemia is an important modifiable risk factor for vascular calcification. Recent studies show that, following certain stimuli including phosphate, endothelial vascular cells can differentiate into cellular types similar to osteoblasts, which trigger signals ending in vascular mineralization [14]. The mechanisms by which this occurs are more complex than was first thought. It is not simple precipitation of calcium and phosphate. It is an active and modifiable process in which the end product is calcified tissue that has very similar characteristics to bone tissue and occurs in several conditions, such as atherosclerosis, cardiac valvular disease, and uraemic arteriolopathy. Experimental models and clinical studies [15–20] are investigating the specific roles of phosphate, extracellular matrix and bone matrix proteins, oestrogens, and vitamin D in this process. This area will not be covered by this review, although it is important to note that serum phosphate, alkaline phosphatase, bone morphogenic protein 2A, osteonectin, and osteocalcin may promote mineralization while matrix Glα protein, osteoprotegerin, and PTH-related peptides may inhibit mineralization [16,21,22].

### Strategies for the management of high phosphate and calcium levels

A recent Spanish study demonstrated that hyperphosphataemia (serum phosphate > 5.5 mg/dl) occurred five-times more frequently than hypercalcaemia in patients on dialysis, demonstrating that lack of control of serum phosphate, rather than hypercalcaemia, is the main contributor to increasing calcium×phosphate product (Ca×P) [2]. Target levels of Ca×P to avoid calcification have been the subject of much empiricism and little evidence over the last 30 years. Recent, objective data have allowed us to establish what Ca×P level can be considered ‘safe’, i.e. the level above which the risk of calcification begins to increase. A Ca×P > 72 mg²/dl² is associated with a significant increase in the relative risk (RR) of mortality (RR = 1.34) compared with Ca×P < 50 mg²/dl² [21]. In a study in patients on haemodialysis, those who did not experience valvular calcification had maintained Ca×P at an average of 51 mg²/dl² in the 6 months prior to the study, while those who did experience valvular calcification had an average Ca×P of 60 mg²/dl² [23]. This study also confirmed that hyperphosphataemia is a more frequent finding than hypercalcaemia in patients on dialysis and correlates strongly with calcification and mortality [1,14].

### Table 1. Risk of vascular calcification in CRF

<table>
<thead>
<tr>
<th>1. Non-modifiable risk factors</th>
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<tbody>
<tr>
<td>• Age</td>
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<tr>
<td>• Time on dialysis</td>
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<tr>
<td>• Other general factors: race, genetic, diabetes, local factors (transforming growth factor-β, osteopontin)</td>
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<th>2. Modifiable risk factors</th>
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<tr>
<td>• Increase of serum phosphorous and serum calcium</td>
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<tr>
<td>• Increase in calcium × phosphorous product</td>
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<tr>
<td>• Hyperparathyroidism</td>
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<tr>
<td>• Use of vitamin D metabolites</td>
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<tr>
<td>• Hypoparathyroidism (adynamic bone and aluminium intoxication)</td>
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<tr>
<td>• Hyperlipidaemia</td>
</tr>
<tr>
<td>• Hypertension</td>
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<td>• Habits (alcohol, smoking)</td>
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### How to avoid hyperphosphataemia and reduce CV risk

Diet, adequate use of phosphate-binding agents, and dialysis patterns can be used to modify the levels of serum phosphate in patients with CRF.

**The role of the diet**

It is important to stress the need to maintain a diet that is low in phosphorous [24], not exceeding 1 g/kg/day of protein. This level allows maintenance
of an adequate nutritional status. Nephrologists need to have a good knowledge of the dietary habits of their patients. They can then give individuals more detailed and precise advice on adapting diets to achieve an adequate nutritional content but with the lowest possible level of phosphorous. A diet rich in proteins is usually also rich in phosphorous. However, proteins with very different phosphorous contents can provide equivalent nutritional value, as can be seen from the difference in phosphorous content between meat, cheese, and eggs. Egg white is an excellent example of food with a high level of protein but low phosphorous content (Table 2). Thus, dietary advice, often considered to be of minor importance, is actually one of the major keys to success in the management of hyperphosphataemia. Unfortunately, effectiveness of this measure is limited due to the irregular distribution of dietitians among the dialysis units in Europe.

The importance of the early management of diet in the control of the hyperphosphataemia is demonstrated in a study of 157 patients with different levels of CRF not yet receiving dialysis. Moderate restriction of phosphorous in the diet, associated with the administration of calcium supplements, reduced the occurrence of secondary hyperparathyroidism in these patients [25]. If patients learn to manage their phosphorous and calcium intake in the predialysis phase, the benefit will increase when they start dialysis treatment. In addition, they will need less phosphate-binding agent, and will know when they need to take it and how to do so much more effectively [26–28].

The role of phosphate-binding agents

For the majority of patients, use of phosphate-binding agents is necessary in addition to monitoring diet. It is important to stress that prescription of these compounds should be individualized, adapting their use to the dietary habits of each patient. Phosphate binders should only be administered with foods with a phosphorous content high enough to justify their administration. They should be taken during meals (but before a meal is better than after). It is also very important that the patient understands why phosphate binders have been prescribed and what they do, so that he or she can use them properly. It must be borne in mind that the majority of phosphate binders are also used as antacids. The dose and time of taking the medication are very different depending on whether the compound is being used as an antacid or as a phosphate binder.

Aluminium hydroxide, which has been widely used for many years, is the most potent phosphate binder and also the most toxic [27–29]. It was the only phosphate binder used in the 1970s and the early 1980s, but during the last 15 years its use has become secondary to calcium salts. As the use of calcium salts became widespread, disadvantages started to become apparent. One drawback is that, compared with aluminium hydroxide, calcium salts are less potent, especially when administered in low doses. This lower potency led to use of higher doses of calcium, with three consequent disadvantages. First, less patients complied with treatment adequately (because they were asked to take too many tablets per day). Secondly, there was a very high incidence of hypercalcaemia in those who did comply. Thirdly, it has been recently demonstrated that the use of calcium salts increases the risk of vascular calcification, and also leads to greater rigidity of the arteries, such as the aorta [30]. These adverse effects seem to appear when the daily dose contains >3 g of calcium carbonate. The consequent greater risk of CV events is of crucial importance to patients undergoing dialysis [9,12,13].

These adverse events have limited the use of the calcium-containing phosphate binders and stimulated the development and production of new-generation phosphate binders, such as sevelamer, iron salts, and lanthanum carbonate. Sevelamer, the only one so far in commercial production and about which the most is known, seems to be capable of reducing the levels of total cholesterol and low-density lipoprotein cholesterol and of increasing high-density lipoprotein cholesterol without adding calcium nor aluminium, as well as reducing phosphate [31].

Management of hyperphosphataemia is also hampered by use of vitamin D metabolites, which promote absorption of calcium and phosphorous. Taken together, all these limitations on the control of hyperphosphataemia oblige us to return to the basics of a diet with a limited phosphorous content and individualization of phosphate-binder prescription, tailoring their use to the dietary habits of each patient.

The effect of dialysis modality

Dialysis modality can affect phosphate levels. It has been observed that better control of serum phosphate is possible in patients on continuous ambulatory peritoneal dialysis than in those on haemodialysis. For the latter, there are no important differences in the elimination of phosphate between high- and low-flow dialysis membranes [32]. Mobilization of phosphate in dialysis correlates with the duration and frequency of the sessions. If dialysis lasts <4 h, three times per week, there is insufficient phosphate removal. Therefore, long and frequent dialysis sessions are advisable to achieve greater phosphate removal. However, as this approach has many practical limitations in the daily management of hyperphosphataemia as currently practised, the main message is the need to avoid

<table>
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<th>Table 2. Difference in phosphorous content</th>
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<td>Material</td>
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</tr>
<tr>
<td>Meat</td>
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<td>Cheese</td>
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<td>Eggs</td>
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<td>Yolk</td>
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Reducing dialysis sessions below 4 h duration three times per week.

Conclusion

Hyperphosphataemia is a serious CV risk factor for patients with CKD. To reduce its effects, it is necessary to optimize the patient’s diet, the use of phosphate binders, and the dialysis procedure.

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