The challenge of controlling phosphorus in chronic kidney disease

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ABSTRACT

The pathogenesis and management of chronic kidney disease-mineral bone disorders (CKD-MBD) has experienced major changes, but the control of serum phosphorus at all stages of CKD still seems to be a key factor to improve clinical outcomes. High serum phosphorus is the most important uremia-related, non-traditional risk factor associated with vascular calcification in CKD patients and in the general population. Phosphorus may also be one of the key elements linking vascular calcification with low bone turnover. The main hormones and factors that contribute to the kidney regulation of phosphorus and calcium include parathyroid hormone, FGF-23, klotho and 1,25-dihydroxyvitamin D (1,25(OH)2D). Serum phosphorus did not start rising until CKD 3b in contrast with the earlier changes observed with fibroblast growth factor-23 (FGF-23), Klotho, calcitriol and parathyroid hormone (PTH). Despite FGF-23 and PTH having synergic effects regarding phosphorus removal, they have opposite effects on 1,25(OH)2D3. At the same stages of CKD in which phosphorus retention appears to occur, calcium retention also occurs. As phosphorus accumulation is associated with poor outcomes, an important question without a clear answer is at which level-range should serum phosphorus be maintained at different stages of CKD to improve clinical outcomes. There are four main strategies to manage phosphate homeostasis; phosphorus dietary intake, phosphorus dietary intake, administration of phosphate binder agents, effective control of hyperparathyroidism and to ensure in the CKD 5D setting, an adequate scheme of dialysis. Despite all the available strategies, and the introduction of new phosphate binder agents in the market, controlling serum phosphorus remains challenging, and hyperphosphataemia continues to be extremely common in CKD 5 patients. Furthermore, despite phosphate binding agents having proved to be effective in reducing serum phosphorus, their ultimate effects on clinical outcomes remain controversial. Thus, we still need well-designed, large-scale, placebo-controlled studies to definitively prove that the reduction of serum phosphorus by phosphate binders improves clinical outcomes.

Keywords: chronic kidney disease, clinical management, hyperphosphatemia, phosphate control

WHY WE SHOULD CONTROL SERUM PHOSPHORUS IN CHRONIC KIDNEY DISEASE?

The knowledge on the pathogenesis and management of chronic kidney disease mineral bone disorders (CKD-MBD) has grown considerably, and the diagnosis, prognosis and management of these disorders have been recently addressed in several CKD-MBD guidelines [1, 2]. The control of serum phosphorus at all stages of CKD is considered one of the more important aspects to improve clinical outcomes in CKD-MBD [3–8]. In clinical and experimental studies, high phosphorus has been associated with several negative outcomes of CKD-MBD, such as parathyroid hyperplasia, progression of CKD, increased peripheral arterial stiffness, endothelial dysfunction, vascular calcification, cardiovascular disease, infections and decreased bone strength and bone mass with increased rate of fragility, bone fractures and a higher mortality risk [9–17]. The adverse effects of high serum phosphorus and/or phosphorus overload in human health seem not to be limited to advanced stages of CKD, as it has been found in earlier stages of CKD and also in the general population [14–16].

It is generally accepted that the accumulation of phosphorus appears to begin in CKD Stage 3b [18] and progresses...
accordingly as renal function worsens leading to a clear trend of positive phosphorus balance, which is the basis of the therapeutic strategies used to treat hyperphosphatemia. Cross-sectional studies have shown different profiles of changes in serum phosphorus, calcium, parathyroid hormone (PTH), 25-hydroxyvitamin D₃ (25(OH)D₃) and 1,25-dihydroxyvitamin D (1,25(OH)₂D), at different stages of CKD. Serum phosphorus values did not start rising until the glomerular filtration rate fell below 40 ml/min in contrast with the earlier changes observed with fibroblast growth factor-23 (FGF-23), klotho, calcitriol and PTH [18].

In addition, it is important to clarify that at the same stages of CKD in which phosphorus retention appears to occur, calcium retention also occurs [19]. Despite the fact that long-term calcium balance studies are needed to better clarify this aspect, it is known that the renal capacity of handling calcium is impaired as CKD progresses, mainly from Stage 3b and onward [20]. Therefore, we could assume that a positive calcium balance may arise, because the intestinal absorption of calcium overcomes the capacity of the diseased kidney for its excretion. Thus, in some circumstances the retention of calcium could be as important, or even more important, than the phosphorus accumulation [19], a matter that merits further research due to the relevant practical implications in the management of CKD patients Stages 2–5.

To support the concept of the importance of calcium excess, classical in vitro experiments clearly showed that cells treated with elevated calcium and normal phosphorus levels increased extracellular mineral deposition, indicating that the increases in calcium alone could promote the vascular smooth muscle cell (VSMC) transition to osteoblast phenotypes [21]. Furthermore, a recent clinical trial in patients with CKD Stages 3–4 demonstrated survival advantages of calcium-free compared with calcium-containing phosphate binders giving a further signal of the likely negative impact of calcium excess in the CKD setting [22].

Although we need more studies to address these issues, it seems reasonable to avoid any excessive calcium load in these groups of patients with CKD, in order to minimize its likely impact on their general health status and survival [20].

**FIGURE 1:** The pathogenesis of CKD-MBD. Reproduced with permission from Cannata-Andía et al., 2014 [23].
increases phosphorus removal reducing its kidney tubular re-  
sorption. The combination of some of the described adaptive  
changes aims to restore the calcium and phosphorus balance  
in the CKD setting (Figure 1) [23].

Despite FGF-23 and PTH having synergic effects regarding  
phosphorus removal, they have opposite effects on 1,25(OH)2D3,  
synthesis by inhibiting or stimulating 1-alpha-hydroxylase,  
respectively. FGF-23 exerts its renal effects by binding FGFR  
1 and 3 receptors and Klotho co-receptor, while PTH exerts  
its action through the PTH receptor. Both are able to increase  
phosphorus excretion by reducing the apical concentration  
of sodium-coupled co-transporters NaPi2a and NaPi2c via pro-  
tein kinase A (PKA)- and protein kinase C (PKC)-dependent  
pathways [23].

By late Stage 4 CKD and into end-stage renal disease  
(ESRD), all these mechanisms become insufficient and most  
patients show hyperphosphatemia, high PTH, marked eleva- 
tions of FGF-23 and reductions of klotho and 1,25(OH)2D3.  
All these adaptive changes are key triggers of the more relevant  
CKD-MBD outcomes, such as progression of renal failure,  
parathyroid hyperplasia, cardiovascular complications and in- 
creased vascular calcification [9–11, 13–17]. All of these are  
associated with higher risk of mortality [3–5, 7], but, in recent  
years the increased vascular calcification has awakened great  
interest due to its high prevalence and impact on CKD  
outcomes.

High serum phosphorus is the most important uremia-re-  
lated, non-traditional risk factor associated with vascular calci- 
fication in CKD patients and in the general population [25].  
In addition, it is well known that high serum phosphorus levels  
stimulate parathyroid activity, increasing cells proliferation  
and decreasing the levels of calcium-sensing receptor and vita- 

mamin D receptor; it also lowers the activity of 1-alpha-hydroxy- 
lase, consequently decreasing serum 1,25(OH)2D3 levels.

Phosphorus is also capable of acting as a secondary intracellu- 
lar messenger, activating several molecular pathways related  
to bone formation. It reaches the intracellular space via a specif- 
ic Na-dependent transporter called Pit-1 and exerts some impor- 
tant actions; in fact, the blockade of Pit-1 prevents  
vascular calcification [26, 27]. Elevated extracellular phospho- 

rus or increased intracellular phosphorus stimulate VSMCs  
to undergo transition to an osteoblastic phenotype, able to ex- 
press Runx2, Msx2 and osterix promoting the expression of the  
osteoblast transcriptome [27] and stimulating matrix vesicles.

Also, serum phosphorus and calcium may promote VSMC  
apoptosis, contributing to the initiation of the calcification pro- 
duced by the fact that it facilitated the movement of phosphorus into the  
skeleton [29].

The effect of phosphorus as a stimulus of vascular calcification  
may be present before high serum phosphorus is detected  
[10, 30]. For example, vascular calcification has been observed  
in almost half of non-diabetic patients with Stage 4 CKD and  
in more than 90% of predialysis patients with diabetes [31],  
despite the fact that high serum phosphorus is only detected  
in late stages of CKD 4 and in CKD Stage 5. In addition,  
FGF-23 levels increase early in CKD and may reflect an in- 
creased phosphorus load; this elevation occurs ahead of the  
development of hyperphosphatemia [23]. Current evidence  
on the association of FGF-23 with vascular calcification is  
still controversial, but recent studies demonstrated in  
experimental models with mild reduction of renal function  
and in CKD patients, a likely positive and independent asso-

ciation between FGF-23 and aortic calcification [32]. In con- 
trast, another recent clinical trial failed to demonstrate an  
association between FGF-23 serum levels and vascular calcifi-
cation, a finding which leaves this aspect open for further con- 
clusive evidence [33].

Finally, of great interest for future research, in early CKD,  
the elevations in FGF-23 secreted mainly by the osteocyte  
may be indicative that the skeleton is able somehow to detect  
the renal damage, a matter of great importance as it may in-
volve the skeleton not just as a target of the mineral derange-
ments but also as a player in the early pathogenesis of the  
CKD-MBD.

In summary, the bulk of epidemiological, clinical and  
experimental evidence strongly suggest that phosphorus accu-
culation is associated with poor outcomes. Then, a question  
arises: at which level-range should serum phosphorus be  
maintained at different stages of CKD to improve clini- 
cal outcomes? There is no definitive answer for this query;  
the Kidney Disease Improving Global Outcomes (KDIGO)  
guidelines suggest that serum phosphorus should be main-
tained within the normal range at all stages of CKD [2].  
This target is easily achievable up to CKD Stage 4, but it is dif-
ficult from that stage onward, particularly in CKD 5d, when  
according to recent data [34], despite the use of phosphate-  
binding agents, serum phosphorus remains higher than the  
recommended upper normal serum values in a great percent-
age of patients (up to 70%). Recently, the COSMOS European  
study conducted in CKD 5 patients suggested 3.6–5.2 mg/dL  
as the safest serum phosphate range—values based on the  
serum phosphorus levels in which the lowest mortality risk  
was observed in the 3-year follow-up study [35].

Even though all of the phosphate-binding agents available  
have proved to be effective in reducing serum phosphorus,  
their ultimate effects on clinical outcomes remain unknown.

The need for large-scale trials based on clinical end points  
has been established; however, funding and organizing such  
large trials remain extremely difficult. In this scenario, obser-
vational prospective long-term studies testing the effectiveness  
of phosphate binding agents may provide useful information on  
their potential beneficial effect on survival of CKD patients  
[34].
HOW TO CONTROL HYPERPHOSPHATEMIA IN CKD

As outlined above, transient phosphate retention in early CKD, followed by phosphate accumulation and hyperphosphatemia in the later stages of CKD, are central to the development of CKD-MBD. Therefore, in an effort to control and treat CKD-MBD, interventions to affect phosphate homeostasis are clearly warranted.

There are four main strategies to manipulate phosphate homeostasis and the consequent compensatory changes in patients with CKD. These include (i) dietary phosphate restriction, (ii) administration of phosphate binders, (iii) effective control of hyperparathyroidism and (iv) in ESRD, ensuring adequacy of dialysis and the choice of dialysis regimen.

While efforts to control hyperphosphatemia are well established for the management of patients with ESRD, such efforts are not widespread in clinical practice in the early stages of CKD but perhaps should be considered. A note of caution has been raised, however, with the use of phosphate binders in early CKD. In these studies, Block et al. demonstrated that phosphate binders significantly lower serum and urinary phosphorus and attenuate progression of secondary hyperparathyroidism among patients with CKD who have normal or near-normal levels of serum phosphorus; however, they appeared to promote the progression of vascular calcification [36]. Accordingly, the safety and efficacy of phosphate binders in CKD remain uncertain and further study is required.

Dietary phosphate restriction

Effective dietary phosphate restriction is difficult in clinical practice because of the high phosphate content of the typical Western diet, which includes dairy products and various protein sources. Marked dietary phosphate restriction will also result in protein restriction, which may not be desirable. In addition, it has recently been brought to our attention that the protein sources of phosphate, whether meat/casein or vegetarian/grain in origin, may be quite different. It appears that the grain-based diet has a lower phosphate-to-protein ratio, and that phosphate in the form of phytate is not absorbed by mammals. The importance of this issue has been demonstrated by Moe et al., who conducted a crossover trial in nine patients with reduced GFR and compared vegetarian and meat diets with equivalent nutrients ingested [37]. These studies showed that one week of a vegetarian diet led to lower serum phosphorus and decreased the compensatory increase in FGF-23. Another recent short-term study has shown that FGF-23 is responsive to the phosphate content of the diet, both in CKD patients and controls [38]. These data demonstrate that the source of protein has a significant effect on phosphate homeostasis in patients with CKD and point out the difficulty in prescribing a phosphate-restricted diet, in that bioavailability of phosphate needs to be considered rather than simply the phosphate content [37]. An additional difficulty in achieving dietary phosphate restriction has recently been emphasized with the realization that many sources of processed foods contain additional phosphate salts, which have been added to preserve color and shelf life, and accordingly, this issue further complicates dietary counseling because the actual phosphate content, due to these added salts, may not be readily apparent [39]. Currently, there is no requirement to label processed foods with phosphate content, which makes efforts to decrease phosphorus intake quite difficult.

Use of phosphate binders

Because of these issues with dietary phosphate restriction, the use of phosphate binders has become the mainstay of efforts to decrease phosphate absorption from the intestine. A wide variety of phosphate binders have been used for this purpose, which are listed in Table 1.

The type of phosphate binders used has evolved over the years as a result of various limitations encountered with use. The aluminum-based binders, although quite effective, are rarely used in current clinical practice for long-term therapy due to the risk of aluminum toxicity. Calcium-containing phosphate binders are in widespread use either as calcium carbonate or calcium acetate. In recent years, however, there have been increasing concerns about markedly positive calcium loads, which result from the use of calcium-based phosphate binders; positive calcium loads have been associated with acceleration of progression of vascular calcification.

The non-calcium-containing phosphate binders, initially sevelamer hydrochloride and later sevelamer carbonate, are now widely used and were shown to be associated with decreased rate of progression of vascular calcification compared with calcium-based binders in the ‘Treat to Goal’ study [40]. An attempt to show whether this was associated with improved mortality was addressed in the DCOR study [41]. This was a multicenter, randomized, open label, parallel designed trial to compare sevelamer hydrochloride and calcium-based phosphate binders on all-cause and cause-specific mortality in a group of 2103 prevalent dialysis patients; 1068 patients completed the study. All-cause mortality rates and cause-specific mortality rates however were not found to be significantly different. In a subgroup of patients more than 65 years of age, there appeared to be a significant effect of sevelamer in lowering the mortality rate. Accordingly, this study did not definitively show that a mortality rate reduction could be achieved by the use of a non-calcium-containing phosphate binder. In contrast to these observations, a smaller study by Block et al. examined all-cause mortality in 127 patients new to dialysis, as part of a secondary

Table 1. Phosphate binders with marketing approval in the USA

<table>
<thead>
<tr>
<th>Type of phosphate binder</th>
<th>Generic name</th>
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</thead>
<tbody>
<tr>
<td>Aluminum-based phosphate binders</td>
<td>Aluminum hydroxide</td>
</tr>
<tr>
<td>Calcium-containing phosphate binders</td>
<td>Calcium carbonate</td>
</tr>
<tr>
<td>Calcium/magnesium containing phosphate binders</td>
<td>Calcium acetate/magnesium</td>
</tr>
<tr>
<td>Non-calcium-containing phosphate binders</td>
<td>Sevelamer hydrochloride</td>
</tr>
<tr>
<td>Iron-containing phosphate binders</td>
<td>Lanthanum carbonate</td>
</tr>
<tr>
<td></td>
<td>Sucroferric oxyhydroxide</td>
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<td>Ferric citrate</td>
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end point of a randomized trial that examined coronary artery calcification [42]. These studies showed that mortality was significantly lower in subjects randomly assigned to sevelamer hydrochloride compared with those assigned to calcium-containing phosphate binders. This mortality benefit persisted after full multivariate adjustment. Accordingly, these results differ from the studies of Suki et al. [41] and the different results can conceivably result from a longer follow-up period or differences in the study population, namely incident versus prevalent. In this regard, recent studies by Di Iorio et al. also show that sevelamer therapy appeared to improve survival in a cohort of incident hemodialysis patients [43].

Additional non-calcium-containing phosphate binders such as lanthanum carbonate are also in widespread use. Recent studies by Torregrosa et al. in more than 500 patients confirmed that this therapy achieved effective control of hyperphosphatemia with an excellent safety profile [44]. In addition, there are some data to show that bone histology improves with use of lanthanum carbonate [45] and the use of this compound, alone or in combination, has been recently associated with good results, decreasing the relative risk of mortality [34].

A recent update in a meta-analysis of the use of calcium-based versus non-calcium-containing phosphate binders by Jamal et al. demonstrated that non-calcium-based binders appeared to be associated with a decreased risk of all-cause mortality compared with calcium-based binders [46]. An a priori subgroup analysis showed a statistically non-significant decrease in mortality in patients taking either sevelamer or lanthanum compared with those taking calcium-based phosphate binders [46].

Recently, two different types of phosphate-binding agents have been introduced to control hyperphosphatemia in CKD. On one hand, the combination of calcium acetate with magnesium carbonate (CaMg) is shown to be as effective as sevelamer hydrochloride to control serum phosphorus and reduce FGF-23 in hemodialysis patients [47, 48]. On the other hand, iron-containing phosphate binders such as sucroferric oxyhydroxide and ferric citrate have been introduced and appear to be effective for the control of hyperphosphatemia in ESRD. Unlike sucroferric oxyhydroxide, Phase-3 studies have shown that ferric citrate also significantly improves serum iron measures that allowed for reduction in intravenous iron and erythropoiesis-stimulating agent use [49–51]. In addition, as iron deficiency, a frequent finding in CKD patients, is associated with increased FGF-23 production but decreased FGF-23 cleavage, maintaining an adequate iron status seems to be a desirable goal in these patients [52].

All of these agents have been shown to be relatively effective phosphorus binders, and each class appears to have their advantages and disadvantages. The principle issues with all the current phosphate binders appear to be large pill burden and frequent dosing, and the necessity to try to take the phosphate binders at the time of ingestion of phosphate-containing foods. Although better adherence to lanthanum carbonate treatment has been claimed [44, 53], this issue is still a major problem which further limits the effectiveness of this therapy in the long term.

It is important to stress the fact that we still need well-designed, large-scale, placebo-controlled studies to definitively prove that the reduction of serum phosphorus by phosphate binders improves clinical outcomes [54].

Adequacy of dialysis

Part of the therapy for hyperphosphatemia is to ensure adequacy of dialysis to adequately remove phosphorus. Dialysis on a three times per week regimen can only remove approximately one-day ingestion of phosphate at each treatment, leaving a relatively large amount to be handled by dietary phosphate binders. In contrast, the use of other dialysis modalities such as peritoneal dialysis, daily dialysis or nocturnal dialysis has been associated with improved management of hyperphosphatemia and even hypophosphatemia. In the context of ensuring adequacy of dialysis, such issues as adequate vascular access, exclusion of significant recirculation, adequate blood flow and dialysate flow and adequate duration of treatment should be considered.

The control of hyperparathyroidism

While one of the goals of the control of hyperphosphatemia is to facilitate the control of hyperparathyroidism, it is important to realize that severe hyperparathyroidism may also aggravate hyperphosphatemia by increasing the mobilization of phosphorus from bone. Accordingly, control of hyperparathyroidism is an important consideration for the treatment of hyperphosphatemia. This has been nicely shown in recent studies using a novel long-acting calcimimetic agent, velcalcetide. In these studies, following the administration of a large dose of this calcimimetic, PTH values are suppressed markedly in a dose–response fashion. These studies demonstrated that the rise in phosphate post dialysis was attenuated in a dose–response fashion according to the degree of suppression of PTH, implying that hyperparathyroidism was contributing to hyperphosphatemia by the mobilization of calcium from the skeleton [55]. These observations are also consistent with long-term studies of the oral calcimimetic agent, cinacalcet hydrochloride, where control of hyperparathyroidism has been associated with significant reductions in serum phosphorus. In contrast, efforts to control hyperparathyroidism with large doses of vitamin D sterols may not be as useful in this regard due to the intrinsic actions of vitamin D to increase phosphorus absorption from the intestine.

Other strategies

An additional approach to limit the intestinal absorption of phosphate might be to target the phosphate transport mechanism in the intestines. Recent studies have suggested that nicotinic acid and related compounds, such as nicotinamide, decrease intestinal absorption of phosphorus by decreasing phosphate transport [56]. These data suggest this strategy may be useful as an adjunct to current treatment and may point the way toward the discovery of more effective inhibitors of intestinal phosphate transport.

LOOKING TO THE FUTURE

Given the limitations of current strategies, controlling hyperphosphatemia remains challenging, and hyperphosphatemia...
continues to be extremely common in the majority of patients on dialysis. Our current efforts need to be refined, and increased focus is required on this major comorbidity of CKD. Efforts to limit phosphate intake might be facilitated by the wide-spread labeling of the phosphorus content of foods and improved knowledge of the bioavailability of ingested phosphorus in various foods. This needs to be coupled with a campaign to increase public awareness of the issues surrounding phosphate intake.

While phosphate binders have been the mainstay in clinical practice to limit phosphorus absorption in the intestine, additional approaches are beginning to emerge which directly target phosphate transporter mechanisms in the intestine. Additional studies will be required in this area with the goal of achieving effective inhibition of intestinal phosphate transport.

Efforts to maximize phosphate removal by dialysis should be encouraged, and consideration given to the use of additional treatments or longer treatments to facilitate phosphate removal. The development of methods to quantify phosphate removal with each dialysis treatment would also be helpful, as this may be a useful index of adequacy of dialysis.

Continued development of agents to achieve effective control of hyperparathyroidism will also help with controlling the release of phosphate from the skeleton because of high bone turnover and should also be another useful adjunctive approach.

While these considerations should be applied to patients on dialysis, at the same time, the adverse outcomes associated with phosphate retention and hyperphosphatemia raise the question of when, in the course of CKD, these strategies should be considered and implemented. Current agents are not widely used in the early stages of CKD, although experimentally, effective phosphate restriction has shown to be quite effective in minimizing the development of hyperparathyroidism. Further, outcome studies are required to assure that such strategies can be safety implemented in the early stages of CKD, coupled with studies to assess overall clinical outcomes of these strategies.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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Received for publication: 26.11.2014; Accepted in revised form: 30.1.2015