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In-Depth Review

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Management of hyperphosphataemia in chronic kidney disease—challenges and solutions

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Abstract

Hyperphosphataemia is a clinical consequence of the advanced stages of chronic kidney disease (CKD). Considerable evidence points to a role of hyperphosphataemia in the pathogenesis of CKD-associated cardiovascular (CV) complications, including vascular calcification, and with increased all-cause and CV mortality. These observations place management of hyperphosphataemia at the centre of CKD treatment. Although our increased understanding of the physiological role of FGF-23 may provide a long-term alternative biomarker of phosphate load and underlying disease progression, regular determination of serum phosphate is currently the most frequently used parameter to evaluate phosphate load in clinical practice. This review considers the challenges physicians and patients face in trying to control hyperphosphataemia. Amongst these are the limitations of dietary phosphate restriction, giving rise to the need for phosphate binder therapy to maintain serum phosphate control. Once the decision to use phosphate binders has been made, considerations include the relative efficacy, different potential side effects and pill burden associated with various phosphate binders. Although a number of phosphate binders are available, adherence poses a major obstacle to effective treatment. This emphasizes that further improvements to phosphate binder therapy can be made. Evaluation of novel agents and their potential role in the clinic should continue.

Keywords: chronic kidney disease; hyperphosphataemia; phosphate binder

Introduction

Currently, the global prevalence of chronic kidney disease (CKD) is estimated to be around 7% in people aged ≥30 years, with a higher prevalence (23–36%) in people aged ≥64 years [1]. CKD is a key determinant of poor health outcomes in patients with major noncommunicable diseases, contributing to their substantial worldwide burden [2]. Elevated serum phosphate levels (hyperphosphataemia) are an unavoidable clinical consequence of the advanced stages of CKD [3, 4]. Hyperphosphataemia is linked with a number of serious clinical complications, including vascular calcification [5] and left ventricular hypertrophy [6], as well as increased all-cause and cardiovascular (CV) mortality [7, 8]. Large observational studies have shown a graded association between levels of serum phosphate and all-cause mortality in patients undergoing dialysis [7–11]. Given these observations, one of the principal challenges in the management of patients in the advanced stages of CKD is control of hyperphosphataemia. This review focuses on selected questions surrounding the diagnosis and management of hyperphosphataemia in daily clinical practice.

What is the effect of hyperphosphataemia in patients?

Although an in-depth description of the pathophysiology of hyperphosphataemia has been provided elsewhere [6], a brief overview is helpful to provide a basis for discussion of therapeutic approaches. In healthy individuals, phosphate homeostasis is maintained by regulation of dietary absorption by the gastrointestinal (GI) tract, bone turnover and mineralization, and renal excretion [12]. Following renal filtration, most of the serum phosphate is reabsorbed across the epithelium of the kidney proximal tubule (Figure 1) [13]. The sodium-dependent phosphate co-transporter proteins play a role in this process, mediating phosphate reabsorption from the filtrate across the renal proximal tubules (NaPi-2a and 2c) and phosphate absorption across the intestinal apical brush border (NaPi-2b; Figure 1) [13, 14]. In patients with impaired renal function, this homeostasis is disrupted as renal excretion of phosphate generally declines with increasing severity of CKD [12]. Initial compensatory mechanisms, including elevated secretion of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) and temporarily elevated serum phosphate levels, reduce

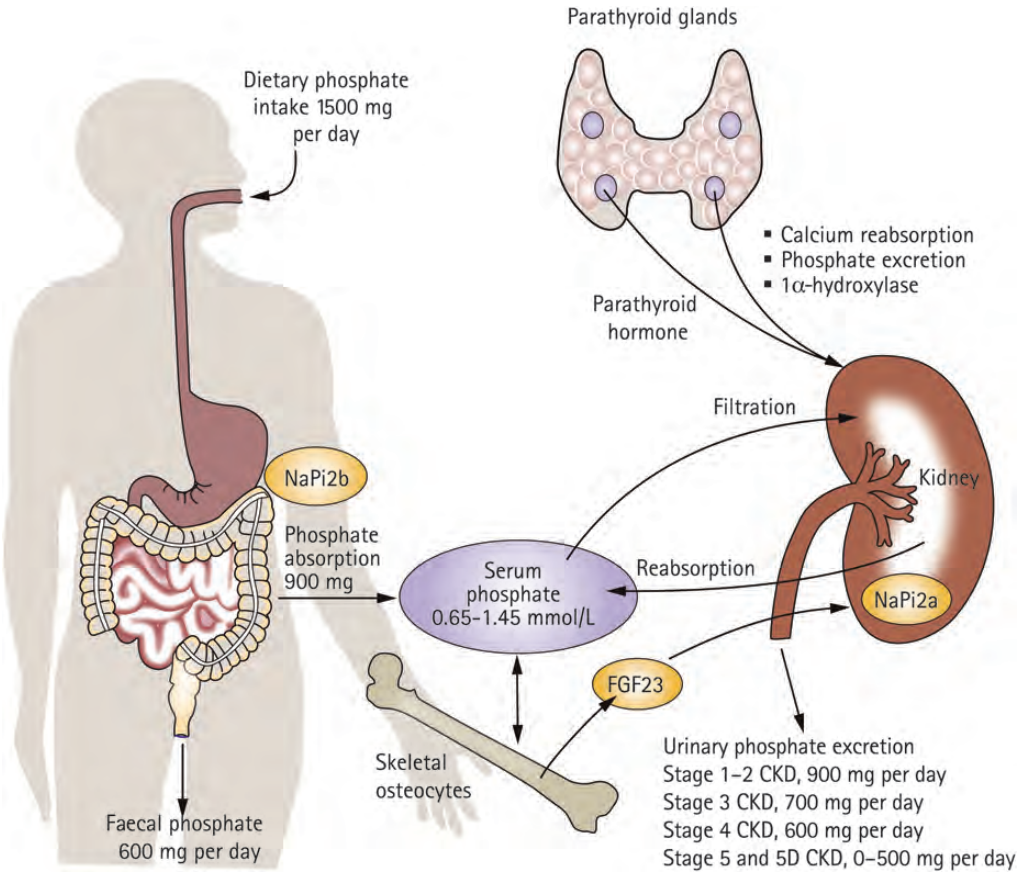

Fig. 1. Phosphate homeostasis is dysregulated in patients with late-stage CKD. Reprinted with permission from Macmillan Publishers Ltd [13].

phosphate reabsorption and thus maintain serum phosphate levels in normal to near-normal range. However, hyperphosphataemia occurs almost inevitably in the later stages of CKD, when dietary intake of phosphate exceeds the rate of renal excretion (Figure 1) [12, 13].

Multiple putative mechanisms link elevated serum phosphate levels with increased CV morbidity and mortality. These include the direct mechanisms of vascular injury by means of vascular calcification, oxidative stress or endothelial dysfunction [12]. Indirect mechanisms associated with CV damage include chronically increased levels of FGF-23 [15], inhibition of calcitriol synthesis and increased levels of PTH [12]. Strictly speaking, the effect of high phosphate levels on the progression of secondary hyperparathyroidism is also in part a direct one, by prolonging the half-life of PTH mRNA in the parathyroid gland and favouring PTH secretion [16].

Of these pathogenetic mechanisms, research in patients with CKD has largely focused on the role of elevated phosphate levels in vascular calcification. Hyperphosphataemia drives vascular calcification by regulating gene expression in vascular smooth muscle cells, causing them to undergo an osteochondrogenic phenotype change [5]. Vascular calcifications are associated with CV morbidity and are an independent predictor of all-cause and CV mortality in patients with CKD [17, 18]. Even in patients with CKD who were not receiving dialysis ($N = 181$), those with a coronary artery calcification score of >100 AU (Agatston unit) were found to have a significantly higher risk of cardiac death or myocardial infarction than those with a score of ≤100 AU [hazard ratio (HR) for the former group: 4.11, confidence interval (CI): 1.77–9.57, $P < 0.0006$] [19]. Together, these observations support the link between vascular calcification, CV events and increased mortality. Given the high rate of CV mortality in patients with CKD, the necessity of screening patients for vascular calcification, determining which patients are at high risk of CV events and which steps to take to attenuate further progression, is a matter of ongoing debate [20]. Regardless of the outcome of this debate, evidence points to a role of hyperphosphataemia in the pathogenesis of CKD-associated CV complications, making it a focus of clinical management of the disease. However, of note in this context is that definitive data from prospective interventional studies comparing the efficacy of phosphate binder treatment with that of no phosphate binder treatment in patients with CKD stages 3–4 not receiving dialysis are scarce. Whereas one short-term study ($N = 148$) reported no beneficial effect from various phosphate binders on the progression of arterial calcification [21], a longer study ($N = 90$) demonstrated that non-calcium-based binders halted the progression of vascular calcification [22]. As yet, no prospective study has evaluated the long-term effects of phosphate binder treatment versus no phosphate binder treatment in dialysis patients.

Does evidence support assessment of FGF-23 to guide treatment decisions?

A cornerstone of clinical monitoring in patients with impaired renal function involves assessing and managing serum phosphate levels. The Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines highlight the importance of regular determination of serum phosphate and provide recommendations for phosphate levels (Table 1) [3, 23]. It is also acknowledged that serum phosphate fluctuates more than, for example, serum calcium; as such, trends in serum phosphate, rather than single values, should drive treatment choices [3, 4]. In this context, the more recent KDIGO guidelines no longer recommend target levels of the calcium × phosphate product [3], because this is indeed mostly driven by the serum phosphate concentrations and because serum calcium levels are not predictive of overall calcium balance.

Serum phosphate does not increase until the estimated glomerular filtration rate falls below 0.5 mL/s/1.73m^2 (30 mL/min/1.73m^2), and as such it has been asserted that it may not be a sufficiently sensitive indicator of phosphate overload [6]. This has led to the investigation of possible alternative markers for future use in the clinical management of patients with CKD [24].

Emerging data highlight the potential of circulating FGF-23, a phosphatonin hormone that is released from osteocytes, most likely in response to phosphate overload [6], as a novel marker to identify patients with CKD who are at the highest risk of disease progression, CV disease and death [24–26]. In addition, it has been proposed that assessment of FGF-23 levels could help detect individuals who might benefit from early phosphate-lowering interventions before the onset of overt hyperphosphataemia [24–28]. Of particular interest is the proposal that elevated serum FGF-23 is independently associated with adverse outcomes in patients with CKD [6]. As such, it may be a biomarker of phosphate status, reflecting underlying disease progression.

The primary physiological roles of FGF-23 are two-fold: it inhibits the reabsorption of renal phosphate, thereby increasing the rate of urinary phosphate excretion, and it suppresses the production of 1,25-dihydroxyvitamin D and increases its catabolism by the kidney, thereby protecting the body from excessive vitamin D exposure (Figure 2) [29, 30]. As such, FGF-23 plays a central adaptive role in phosphate and 1,25-dihydroxyvitamin D homeostasis in healthy individuals, but may equally be involved in the pathogenesis of CKD [31]. In patients with CKD, circulating concentrations of FGF-23 increase progressively with declining renal capacity for phosphate excretion [27, 31]. Findings from animal studies and genetic research suggest that elevated FGF-23 may reflect pathogenetic changes in bone and/or kidney health [32, 33]. Other studies have shown an independent association of FGF-23 with early pathogenetic mechanisms, such as increased left ventricular mass [34–36]. Taken together, these studies suggest that features such as left ventricular hypertrophy, which are commonly observed in patients with CKD, may be an adverse consequence of adaptive mechanisms that involve FGF-23, triggered in response to phosphate overload [6].

Although FGF-23 may have the potential to provide a better understanding of long-term phosphate status compared with the assessment of serum phosphate alone, the solution may not be entirely simple. The mechanism which regulates FGF-23 secretion from bone remains unclear, and the presence of modulators, or the down-regulation of co-factors such as klotho, may confound any signal from FGF-23 relating to underlying disease progression [33]. From a practical perspective, there is no validated standard assay for FGF-23 yet, and consequently, no reference range for interpretation of FGF-23 levels in clinical practice. Furthermore, in a recent study in a rat model of CKD, specific antagonism of FGF-23 increased mortality risk in the animals [37], calling into question the feasibility of developing therapies targeting FGF-23. In the meantime, assessment of FGF-23 may provide additional insights into the effect of different treatments on CKD progression to those provided by serum phosphate assessments. For example, an open-label randomized trial in 100 patients with stage 4 CKD showed that sevelamer was associated with a significant decrease in FGF-23 levels ($P = 0.002$) and increase in flow-mediated vasodilation ($P < 0.001$) from baseline compared with calcium acetate; both treatments were associated with a significant reduction in serum phosphate from baseline ($P < 0.01$), although this was more marked with the phosphate binder sevelamer [38]. Nonetheless, the measurement of serum phosphate and the fractional excretion of phosphate remain the primary tools for the physician, with regular determination of serum phosphate being the most frequently used parameter to evaluate phosphate load in clinical practice.

Can adequate phosphate control be achieved with dietary restriction?

Achieving recommended guideline serum phosphate levels can be challenging. In the Dialysis Outcomes and Practice Patterns Study (DOPPS) II, serum phosphate levels remained uncontrolled in 56% of patients with CKD receiving dialysis, with 9% and 47% of patients having serum phosphate levels <1.13 mmol/L (3.5 mg/dL) and >1.78 mmol/L (5.5 mg/dL), respectively [39]. While most of the phosphate burden is due to intestinal absorption, it remains to be considered that high or low turnover

Table 1. Recommended serum calcium, albumin-corrected calcium, phosphate and PTH levels in stage 5 CKD [3,23]

Organization (year)	Calcium	CA_{Alb}	Phosphate	PTH
KDOQI (2003)	Not reported	Stage 3–4: within the normal range; stage 5: 2.10–2.37 mmol/L (8.4–9.5 mg/dL)	Stage 3–4: 0.87–1.49 mmol/L (2.7–4.6 mg/dL), Stage 5: 1.13–1.78 mmol/L (3.5–5.5 mg/dL)	16.5–33.0 pmol/L (150–300 pg/mL)
KDIGO (2009)	Within the normal range	Not reported	Within the normal range; stage 5D: Toward the normal range	Stage 5D: 2–9× upper normal limit for the assay

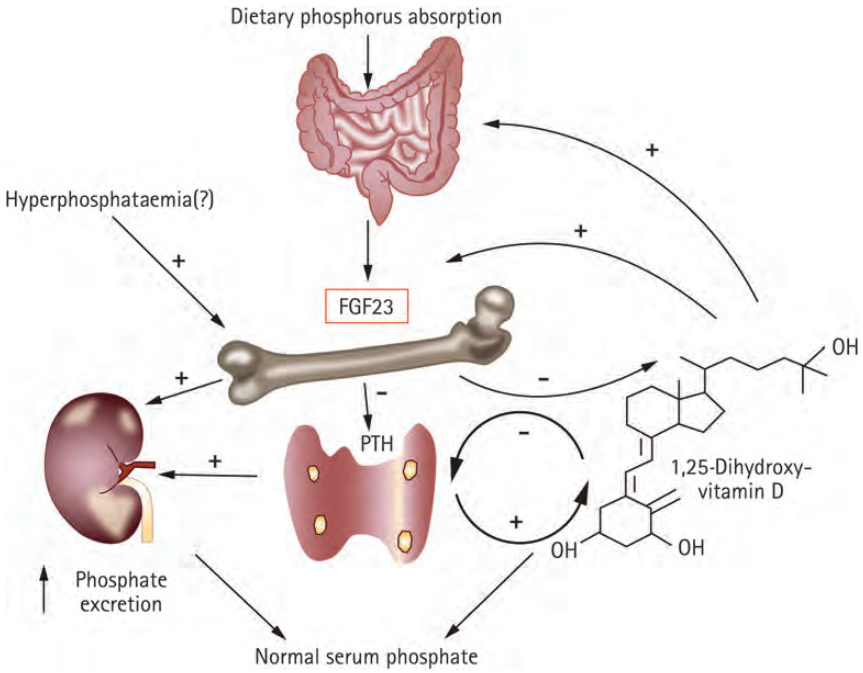

Fig. 2. FGF-23 regulatory systems in phosphate metabolism. Reprinted with permission from Macmillan Publishers Ltd [30].

bone disease may also contribute to intractable hyperphosphataemia.

Therefore, multiple strategies can be implemented to control phosphate homeostasis in patients with CKD. These include dietary restriction and removal via dialysis or intensive (nocturnal or short daily) dialysis regimens. Pharmacologic interventions include reduction of intestinal phosphate absorption by administration of phosphate binders and suppression of PTH secretion and release by administration of calcimimetics, in order to normalize bone turnover in high turnover states. In addition, as overtreatment with active vitamin D analogues may favour both phosphate absorption and low bone turnover, dose reduction or cessation may have to be considered in individual patients.

Dietary restriction of phosphate is recommended in both the KDIGO and KDOQI guidelines [3, 23]. Support for this is provided by an observational study, which used questionnaires to assess dietary phosphorus and protein intake in 224 maintenance haemodialysis patients over 5 years of follow-up. The impact of phosphorus intake on patients was clear: higher levels of dietary phosphorus intake and a higher ratio of dietary phosphorus to protein were associated with an increased risk of death [40].

However, although dietary phosphate restriction can reduce serum phosphate levels, drawbacks to this approach include protein–energy wasting, which is itself an independent determinant of morbidity and mortality in dialysis patients [41]. Indeed, the risk associated with controlling serum phosphate by restricting dietary protein intake may outweigh the benefit of improved serum phosphate control [42]. This is supported by a *post-hoc* analysis of data from 1751 patients undergoing haemodialysis who were enrolled in the Haemodialysis Study, in which the prescribed recommendation for daily phosphate intake was recorded. The results showed that prescribed dietary phosphate restriction was not associated with a survival benefit [43].

A further complication of limiting dietary intake of phosphorus is that, whilst it may be relatively easy for patients to avoid foods which are naturally high in phosphate, it is more difficult to avoid consumption of processed food rich in phosphate-containing additives. These additives contain a form of phosphate that is more readily absorbed than that found in foods naturally high in phosphorus [44, 45]. The findings of the Chronic Renal Insufficiency Cohort study ($N = 2879$) showed higher serum phosphate levels in patients on the lowest income compared with those on the highest income, despite comparable phosphate intake. These observations were thought to reflect the different types of phosphates consumed in the different groups, with those on a low income consuming greater amounts of convenience food containing phosphate additives [46]. The widespread use of phosphate-containing additives has substantially increased our daily phosphate intake, and the frequent absence of phosphate levels on food labels makes it difficult to ascertain the phosphate content of food. These difficulties may even extend to the dieticians providing guidance to patients, as software programmes used to assess dietary composition have been shown to underestimate the phosphorus content of processed foods [47].

Poor knowledge of phosphate levels in food and phosphate management has been reported in haemodialysis patients, even in those patients taking phosphate binder medication [48]. In a randomized study, 145 dialysis patients received education on how to avoid foods containing phosphorus additives when purchasing food in shops or when eating out. These patients showed a 3-month decrease in serum phosphate levels of 0.19 mmol/L [0.6 mg/dL; 95% CI: −0.32 mmol/L to −0.032 mmol/L (−1.0 to −0.1 mg/dL)] greater than that observed in the control group ($n = 134$) which did not receive guidance [49]. This indicates that patient education can aid dietary phosphate restriction and contribute to clinically significant improvements in serum phosphate levels.

However, even with careful dietary modification, hidden sources of phosphate mean that dietary limitation of phosphate intake is difficult, and often remains an inadequate means of controlling hyperphosphataemia. Given these limitations, treatment with oral phosphate binders is an essential component of phosphate management for most patients undergoing dialysis. This may apply for those patients who are failing to achieve phosphate control through dietary restriction of phosphate intake, but also for those patients who are experiencing nutritional problems such as protein–energy wasting owing to following a strict dietary regimen.

What are the key considerations in phosphate binder treatment?

Data from three observational studies have shown a survival benefit associated with the early administration of phosphate binders [50–52]. In the DOPPS study mentioned above, which included 23 894 haemodialysis patients, 6283 deaths were observed during follow-up (median time at risk: 1.92 years). Patients receiving phosphate binder treatment had a 25% reduction in the risk of death compared with those who did not receive phosphate binders (HR: 0.75; 95% CI: 0.68–0.83); in models adjusted for nutritional factors, a 12% lower risk of death was reported (HR: 0.88; 95% CI: 0.80–0.97) [52]. A study of 8610 incident haemodialysis patients found that 1-year all-cause mortality of patients who received phosphate binders within 90 days of starting haemodialysis ($n = 3555$) was significantly lower than in those who did not ($n = 5055$; relative risk: 0.58; 95% CI: 0.52–0.66, $P < 0.0001$) [50]. Recently published data from 6321 patients on haemodialysis included in the COSMOS study also indicate that the use of phosphate binders, either alone or in combination regimens, was associated with a significantly lower risk of all-cause mortality [51].

With evidence suggesting that phosphate binder treatment should be considered a central component of the management of hyperphosphataemia, it is worth considering how to optimize this treatment approach. Ideally, a phosphate binder should effectively bind dietary phosphate regardless of pH, have minimal systemic absorption, few side effects, good palatability, a low pill burden and be available at a low cost [53].

In the 1970s, aluminium represented the mainstay of phosphate-binding therapy; this treatment was largely abandoned when cases of systemic aluminium toxicity arose [13]. However, it has since been established that systemic exposure to aluminium can also arise from high aluminium concentrations in haemodialysis water [54]. The next class of phosphate binders to be introduced, and still used extensively today, was the calcium-based binders, calcium carbonate or calcium acetate [13]. Calcium-based binders have been shown to be more effective in reducing serum phosphate levels than sevelamer hydrochloride (HCl) in dialysis patients in the randomized, double-blind CARE study ($N = 100$) [55] and in a retrospective chart review ($N = 55$) [56]. In addition, in a prospective 42-month study including 1347 haemodialysis patients, those prescribed sevelamer HCl had a higher mortality risk compared with those prescribed calcium carbonate (HR: 1.46; 95% CI: 1.1–1.9) [57]. However, after concerns about hypercalcaemia and the risk of vascular calcification [58, 59], the option of non-calcium-based agents was explored further.

One of these compounds is sevelamer, a non-calcium anion-exchange resin [13, 60]. Sevelamer was initially available as sevelamer HCl and most clinical studies have used this formulation. However, sevelamer HCl was associated with reduced serum bicarbonate concentration, prompting concerns about metabolic acidosis [61]. Subsequently, a different formulation, sevelamer carbonate, was developed [62, 63]. A Cochrane review and meta-analysis of studies including patients with CKD stages 3–5D according to KDOQI guidelines indicated that sevelamer significantly decreases end-of-treatment serum phosphate levels compared with placebo (based on one study only, including 36 patients), although comparisons of reduction in serum phosphate with calcium-based binders favoured the latter group [64]. In the key Dialysis Clinical Outcomes Revisited study ($N = 2103$), results of the primary analysis did not show any difference in overall mortality among patients on dialysis receiving sevelamer compared with those receiving a calcium-based binder [65]. A randomized, open-label study compared CV (primary endpoint), overall and non-CV mortality in incident dialysis patients who were treated with sevelamer ($n = 232$) with that in patients receiving calcium carbonate ($n = 234$). After a mean 28-month follow-up, CV mortality in the sevelamer group was ten times lower than that in the calcium carbonate group ($P < 0.001$). A significant reduction in all-cause mortality, though not in non-CV mortality, was also noted in the sevelamer group [66, 67]. Similar results were reported in an observational study in patients with stage 5D CKD, which found a significant reduction in all-cause and CV cumulative mortality in patients receiving sevelamer ($n = 172$) compared with a matched control group receiving calcium carbonate ($n = 264$) or no phosphate binder ($n = 36$) [68].

Investigations into the effects of sevelamer on vascular calcification have shown variable results, with some reporting that sevelamer attenuated progression of vascular calcification but others reporting no effect [22, 69–74]. A recent meta-analysis ($N = 3271$) suggested that the effect of sevelamer on vascular calcification in haemodialysis patients was not significant compared with that of calcium-based phosphate binders [75]. However, data from three clinical trials, two of which were included in the meta-analysis, have shown slower progression of coronary artery calcification in haemodialysis patients treated with sevelamer compared with those treated with a calcium-based binder [69, 72, 76]. Given the discrepancies between study results on this matter, additional large, prospective studies would be welcome to ascertain the effect of sevelamer on vascular calcification. Of note, it has also been reported that sevelamer is associated with pleiotropic effects in haemodialysis patients which may be beneficial for vascular protection, including a prolonged significant rise in serum levels of the calcification inhibitor fetuin A [77] and lowering of total and low-density lipoprotein cholesterol [71, 74, 77].

An increased risk of GI side effects has been reported with sevelamer compared with calcium-based binders [64], which may contribute to poor adherence. In addition, a major limitation of both sevelamer and calcium acetate in terms of their effect on treatment adherence is their high pill burden (6–12 tablets per day) [12].

Lanthanum carbonate, another non-calcium, metal-based phosphate-binding agent, has been shown to have

similar efficacy to both calcium-based phosphate binders (78% of patients in the control arm were receiving calcium-based binders; $N = 1359$) [78] and sevelamer ($N = 181$) [79] in terms of reducing serum phosphate levels in haemodialysis patients. Similar to sevelamer, recent data suggest that lanthanum reduces FGF-23 levels in patients with stage 3 CKD [80]. Lanthanum carbonate is also associated with a lower pill burden than sevelamer or calcium-based binders [12]. In addition, in a Phase III, open-label study including 98 haemodialysis patients, more patients treated with lanthanum carbonate exhibited normalization of bone turnover than those treated with calcium carbonate, and fewer exhibited adynamic bone [81]. However, there are concerns about side effects associated with lanthanum carbonate, especially GI side effects [82, 83]. In addition, questions about the potential long-term accumulation of lanthanum in the liver have been raised, in part owing to the results from a rat model of chronic renal failure [84]. However, a *post-hoc* analysis of a subset of data from four Phase III trials of lanthanum, including data from some haemodialysis patients who were treated for up to 6 years, showed no detrimental changes in transaminase or bilirubin levels or significant increase in liver-associated adverse events compared with control groups [85].

Do patients take their phosphate binders?

One of the major potential drawbacks of treatment with currently available phosphate binders is that their effectiveness may be compromised by poor treatment adherence, possibly owing to side effects, high pill burden or a combination of these. Studies have shown that amongst haemodialysis patients, non-adherent patients are more likely to have elevated serum phosphate levels than their adherent counterparts [86, 87]. This is sobering, considering that the rates of non-adherence to phosphate binders are reported to range from 22 to 74%, with a mean in one systematic review of 51% [88]. The wide variation in reported rates of non-adherence can be attributed to differences in the way non-adherence was defined and assessed across studies [88].

Pill burden may be an important contributing factor to poor adherence in patients with CKD. A cross-sectional study conducted in 233 maintenance dialysis patients in the US showed that higher pill burden was associated with reduced adherence and lower health-related quality of life (HRQoL); almost two-thirds of patients (62%) were non-adherent [89]. Phosphate binders accounted for approximately one half of the daily pill burden, with the median daily pill number required for phosphate binder therapy being 9 (inter-quartile range: 6) [89]. Furthermore, this study showed that increasing the number of prescribed pills did not improve phosphate control [89].

These data suggest that the long-term maintenance of phosphate control using phosphate binders can be further improved for patients with CKD, in particular by considering ways of improving adherence, possibly by reducing pill burden.

Need for new therapies

A number of new therapeutic approaches to improve phosphate control in patients with CKD have been developed in recent years or are under clinical investigation; amongst these is intensive haemodialysis (more frequent or extended dialysis sessions). Analysis of data from the Frequent Haemodialysis Network Daily and Nocturnal Trials showed that daily and nocturnal dialysis regimens were associated with a reduction in mean serum phosphate of 0.15 mmol/L (0.46 mg/dL; 95% CI: 0.04–0.25 mmol/L [0.13–0.78 mg/dL]) and 0.40 mmol/L (1.24 mg/dL; 95% CI: 0.22–0.58 mmol/L [0.68–1.79 mg/dL]) compared with patients receiving conventional haemodialysis [90]. However, these intensive sessions may only be practicable for a relatively small proportion of patients [13].

Novel pharmacologic approaches may widen options for patients with CKD (Table 2). For example, inhibition of the sodium-dependent phosphate co-transporters is an additional opportunity for therapeutic intervention to control hyperphosphataemia. Illustrating this principle, administration of niacin or nicotinamide–which inhibits the sodium-dependent phosphate co-transporter NaPi-2b–concomitantly with phosphate binders was associated with a significant reduction in serum

Table 2. New pharmacological approaches targeting phosphate overload [91, 93, 95–97, 98]

Compound	Class	Mechanism of action	Stage of clinical development	Company
Niacin/nicotinamide	Amide of vitamin B3	Inhibits the sodium-dependent phosphate co-transporter	Phase III ongoing	N/A
Calcium acetate/magnesium carbonate	Combination phosphate binder	Calcium acetate and magnesium carbonate bind phosphate, forming non-absorbable complexes	Approved (EU only)	Fresenius Medical Care
PA21	Iron-based phosphate binder	Iron(III)-oxyhydroxide binds phosphate by replacing hydroxide groups, forming non-absorbable complexes	Phase III ongoing	Vifor Pharma Ltd
Ferric citrate	Iron-based phosphate binder	Binds phosphate and forms non-absorbable complexes	Phase III ongoing	Numerous, including: Panion & BF Biotech Inc., Keryx Biopharmaceuticals, Torii Pharmaceutical Co., Ltd
Colestilan (MCI-196)	Non-calcium anion exchange resin	Binds phosphate and bile acid anions	Phase III ongoing	Mitsubishi Tanabe Pharma Corporation
HS219, a chitosan-loaded chewing gum	Natural polymer (dietary supplement)	Binds salivary phosphate	Phase II completed	KDL Inc.

phosphate from 2.1 mmol/L (6.45 mg/dL) to 1.71 mmol/L (5.28 mg/dL; P = 0.002) during an 8-week study in 33 dialysis patients [91]. There have, however, been reports of patients experiencing GI side effects (diarrhoea) when receiving this combination [91, 92]. In addition, existing approaches can still be refined. There is a need for new phosphate binders that address the limitations of current treatments and enable patients to achieve and maintain adequate control of serum phosphate levels. Potentially, improved clinical outcomes can be achieved by improving the side effect profile, reducing pill burden, increasing treatment adherence, and allowing patients greater nutritional freedom.

A combination calcium acetate/magnesium carbonate phosphate binder has shown a non-inferior reduction of serum phosphate levels compared with sevelamer in a 24-week randomized study in 255 haemodialysis patients, with no difference between groups in episodes of hypo- and hypercalcaemia [93]. In addition, a novel iron(III)-oxyhydroxide-based phosphate binder in clinical development may meet these criteria. Encouraging results have been reported in Phase I [94] and II studies [95]. In addition, the iron-based phosphate binder ferric citrate is also undergoing clinical evaluation [96]. The approach of binding salivary phosphate with a chitosan chewing gum during periods of fasting, to complement the use of phosphate binders, is also being investigated [97].

Conclusions

A strong evidence base places the diagnosis and management of hyperphosphataemia at the centre of patient care in CKD. Despite this, related diagnostic procedures and treatment decisions are far from straightforward and patients still suffer severe clinical complications and reduced QoL. Now that we have a greater understanding of the underlying pathophysiology of hyperphosphataemia, our focus can shift to identifying more reliable diagnostic markers of mineral- and bone-related disorders and more specific treatments to improve patients' clinical outcomes and their QoL. This requires us to assess the treatment of hyperphosphataemia in the context of the wider treatment that patients are receiving, consider pharmacologic interventions alongside available options for dialysis and dietary control, and continue to evaluate novel treatments and their potential place in the clinic.

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