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REVIEW ARTICLE

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Phosphorous metabolism and manipulation in chronic kidney disease

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Abstract

Chronic kidney disease-mineral bone disorder (CKD-MBD) is a syndrome commonly observed in subjects with impaired renal function. Phosphate metabolism has been implicated in the pathogenesis of CKD-MBD and according to the phosphorocentric hypothesis may be the key player in the pathogenesis of these abnormalities. As phosphorous is an essential component for life, absorption from the bowel, accumulation and release from the bones, and elimination through the kidneys are all homeostatic mechanisms that maintain phosphate balance through very sophisticated feedback mechanisms, which comprise as main actors: vitamin D (VD), parathyroid hormone (PTH), calciproteins particles (CPPs), fibroblast growth factor-23 (FGF-23) and other phosphatonins and klotho. Indeed, as the renal function declines, factors such as FGF-23 and PTH prevent phosphate accumulation and hyperphosphatemia. However, these factors per se may be responsible for the organ damages associated with CKD-MBD, such as bone osteodystrophy and vascular calcification. We herein review the current understanding of the CKD-MBD focusing on phosphorous metabolism and the impact of phosphate manipulation on surrogate and hard outcomes.

KEYWORDS
CKD, dialysis, outcome, phosphate binders, phosphorous

1 | INTRODUCTION

Although several lines of evidence suggest an association with poor outcomes, phosphorus is an anion element that plays a central role in life.[1] In humans, it exists as phosphate ($PO^{3}_{4}{}^{-}$) and is implicated in several biological systems. It is a critical component of nucleic acids (deoxyribonucleic acid and ribonucleic acid) carrying and storing genetic information, of adenosine triphosphate (ATP), having a pivotal role in energy production and storage, and has structural function both in cell membranes, as phospholipids, and in skeleton and teeth as hydroxyapatite. Moreover, phosphorus is involved in various phosphorylation reactions, hormones and cell-signalling molecules. Phosphorus in humans is estimated to represent 1%–1.4% of the fat-free mass.[2] To put these figures in perspective, about 22 moles (or 630 g) of phosphorus are present in a man of 70 kg of body weight. Of interest, about 85% can be found in bones and teeth, while about 15% is distributed in the soft tissues, and only a minimal portion (<1%) can be found in the blood. Hence, what we measure in the blood is only a

Marco Marando and Adriana Tamburello contributed equally to this work.

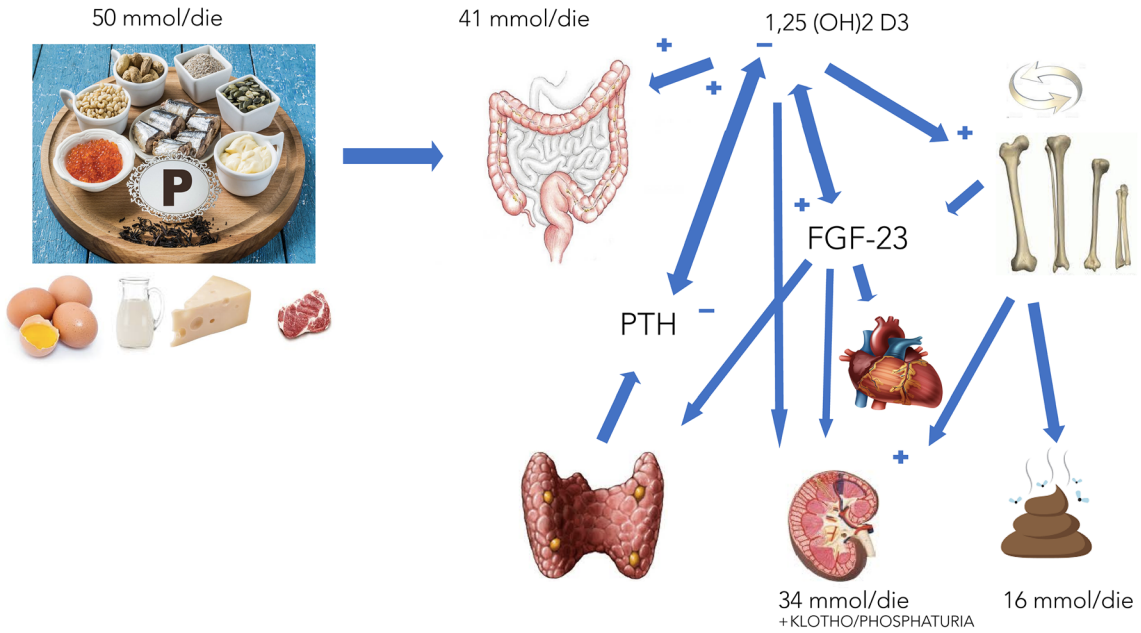

FIGURE 1 Phosphate homeostasis. Absorption from the bowel, accumulation and release from the bones, and elimination through the kidneys are all mechanisms involved in phosphate homeostasis maintenance through very sophisticated feedback mechanisms, which comprise as main actors: vitamin D (VD), parathyroid hormone (PTH), calciproteins particles (CPPs), fibroblast growth factor-23 (FGF-23) and other phosphatonins and klotho.

small part of the total body pool and likely does not represent the total amount of phosphate in the body, even if it is within what we consider the range for normal phosphorous (3.4–4.5 mg/dL or 1.12–1.45 mmol/L). Moreover, as with other substances, serum phosphorus concentration shows a circadian rhythm, with a nadir at 8 am, a first peak and a second peak at 4 pm and between 0 and 4 am,[3] which attenuates the association between serum phosphate values and total body pool and should be considered when interpreting phosphoremia. Since phosphorus has so many functions, its balance is strictly controlled. Absorption from the bowel, accumulation and release from the bones, and elimination through the kidneys are all mechanisms involved in phosphate homeostasis maintenance through very sophisticated feedback mechanisms, which comprise as main actors: vitamin D (VD), parathyroid hormone (PTH), calciproteins particles (CPPs), fibroblast growth factor-23 (FGF-23) and other phosphatonins and klotho (Figure 1). We herein briefly summarize the available evidence on phosphate handling in individuals with normal and impaired kidney function. A list of the abbreviations used in the text is provided in Table 1.

TABLE 1 Abbreviations used in the text.

ATP	Adenosine triphosphate
Calcitriol	1, 25 $(OH)_2$ VD
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease-mineral bone disorder
CPPs	Calciproteins particles
DD-CKD	Dialysis dependent chronic kidney disease
Fep	Fractional phosphate excretion
FGF-23	Fibroblast growth factor-23
GFR	Glomerula filtration rate
NDD-CKD	Non-dialysis dependent-chronic kidney disease
PTH	Parathyroid hormone
PTHrP	PTH receptor
VD	Vitamin D
VDR	Nuclear vitamin D receptor

2 | PHOSPHORUS METABOLISM IN PATIENTS WITH NORMAL KIDNEY FUNCTION

There are essentially three phases in phosphorus homeostasis: absorption, elimination and release from the storage (primarily bones).

Phosphorus can be found in various foods, such as dairy products, meat and vegetables.[4] Adults tend to introduce and eliminate about 50 mmol (about 1.5 g) of phosphorus daily to maintain a neutral balance on a regular Western diet. While the bones store most of the phosphate body pool, the kidneys are the most important organs responsible for the fine regulation of the phosphate excretion required to match the daily intake. Indeed, subtle changes in renal or bone function occurring with age or various medical conditions may impact phosphate balance. For example, phosphate balance tends to be slightly negative in the elderly due to the loss of bone mass and an increase in renal phosphate excretion.[5] The small bowel regularly absorbs about 41 mmol of the 50 mmol (about 80%) of phosphate

ingested daily, mainly in the duodenum and jejunum. Phosphate sources influence intestinal absorption since it is higher when phosphorus is in a soluble form, such as in meat, and lower when it is in an insoluble form, such as in vegetables. About one-third of the ingested phosphorus is eliminated through the faeces, including the amount unabsorbed and the amount actively secreted into the gut. Finally, two-thirds of the ingested phosphate is excreted through the urines. Intestinal absorption or renal excretion can be substantially modified to maintain phosphate homeostasis. In particular, in normal kidney function, phosphate excretion can be adjusted by increasing GFR and/or fractional phosphate excretion (FEp).[6]

3 | PHOSPHATE HANDLING IN THE KIDNEYS

Several calciotropic and phosphoric factors, such as vitamin D, PTH, FGF-23 and CCP, finely regulate these mechanisms. Herein, we briefly describe their effects and implications in phosphorus homeostasis.

Vitamin D (VD) exists in two forms: vitamin D_2 and vitamin D_3. While vitamin D_2 or ergocalciferol is taken up with the diet, vitamin D_3 or cholecalciferol is ingested with food and synthesized in the skin in a non-enzymatic process from the photolyzing of 7-dehydrocholesterol by the action of UV-B photons.[7] To be biologically active, both vitamin D forms must undergo a double hydroxylation process by the liver and the proximal and distal tubule of kidneys, resulting in 1, 25 $(OH)_2$ VD or calcitriol.[8] Calcitriol affects the nuclear VD receptor (VDR), which can be found in nearly every tissue. VD effects on phosphorus metabolism are closely related to that of calcium, leading to an increase in the enteric and renal tubular absorption of phosphorus and calcium as well as calcium and phosphorus deposition in bones.

PTH is a peptide hormone secreted by the chief cells in parathyroid glands. Its effects are conducted by binding with the PTH/PTHrP type 1 receptor (PTH/PTHrP 1R), expressed primarily in bones and kidneys but also in vessels and other tissues. As VD, PTH regulates both calcium and phosphate balance. However, it induces renal tubular reabsorption of calcium in the distal convoluted tubule and tubular secretion of phosphorus in the proximal convolute tubule, calcium and phosphorus release from the bones, and indirect calcium and phosphorus absorption in the bowel by stimulating the renal hydroxylation of VD.

FGF-23 and phosphatonins are other protein hormones implicated in phosphate homeostasis. FGF-23, the most studied phosphatonin, is secreted by the osteoblasts and osteocytes following an increase in 1, 25 $(OH)_2$ VD or dietary phosphorus loading,[9–13] although, at present, a phosphate-sensing receptor has not been identified. FGF-23 production after phosphate loading seems to be magnified in diabetic patients[14] and possibly secondary to an increase in calciprotein particles.[15] FGF-23 acts on different target organs, such as kidneys, parathyroid glands and bones themselves, binding to the ubiquitous FGF-receptor due to the presence of an obligate co-receptor, klotho.[16,17] Its action reduces 1, 25 $(OH)_2$ VD activation, reduction of PTH secretion, and phosphaturia, resulting in a negative phosphorus balance. Of note, elevated levels of FGF-23 have been linked to left ventricular hypertrophy, heart failure, inflammation, immunosuppression, and renal function deterioration and mortality in CKD patients.[18]

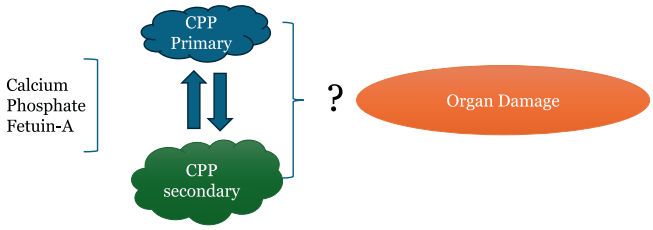

FIGURE 2 Calciprotein particles (CPPs) are compounds formed by calcium, phosphorus and serum protein fetuin-A. Being blood a supersaturated solution, increasing phosphorus or calcium would increase CPP formation. CPP can be primary, formed by calcium-phosphate in the amorphous phase, or secondary, constituted by calcium-phosphate in the crystalline phase. CPPs may mediate the organ damage and contribute to explain the CKD-MBD risk.

CPPs are compounds formed by calcium, phosphorus and serum protein fetuin-A.[19] Being blood a supersaturated solution, increasing phosphorus or calcium would increase CPP formation. CPP can be primary, formed by calcium-phosphate in the amorphous phase, or secondary, constituted by calcium-phosphate in the crystalline phase (Figure 2). CPPs can be dosed in the blood of CKD patients and animals[20–22] and increase as kidney function declines.[21] Although the role of CPPs some lines of evidence suggest that these compounds maybe implicated in mediating signalling among tissues and organ damage. In particular, evidence suggests that CPPs are linked with arterial stiffness, vascular calcification, and poor survival in CKD patients.[23]

4 | PHOSPHORUS METABOLISM IN CHRONIC KIDNEY DISEASE

In chronic kidney disease (CKD), phosphorus metabolism is deranged, and phosphorus tends to increase (Figure 3). Interestingly, non-dialysis dependent (NDD) CKD hyperphosphatemic patients are only 0.3% of total CKD patients.[24,25] The pathogenetic process of hyperphosphatemia is still debated.[26–28] As the nephron mass decreases, FGF-23 and PTH increase progressively, probably as early as stage 2–3a CKD.[29–31] Phosphorus increase would follow, classically, when GFR declines under 30 mL/min.[32] To complicate this scenario, some lines of evidence suggest that klotho is also reduced due to kidney function decline, thus inducing renal resistance to FGF-23 and a further increase in FGF-23 plasma levels.[33,34] Interestingly, a seminal study by Stremke and co-workers[35] demonstrates that fractional intestinal absorption of phosphorus in patients on high phosphate intake did not differ between those with and without chronic kidney disease (eGFR 29–55 mL/min per 1.73 m^2), despite of the fact that in the first group, there was an overall reduced plasma concentration of

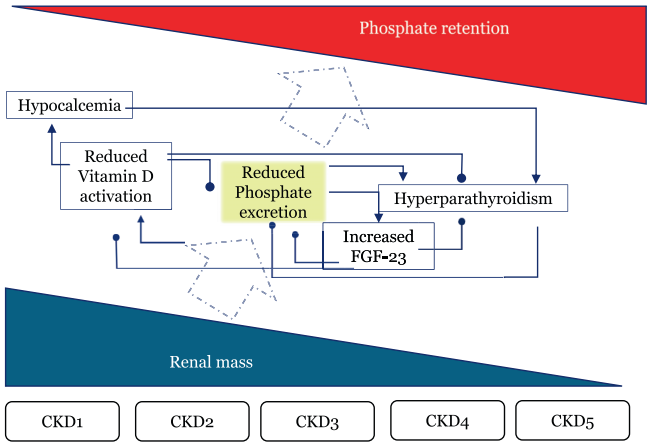

FIGURE 3 CKD-MBD pathogenesis. According to the "phosphorocentric view," phosphate excretion reduces as the GFR declines. In turn, phosphate triggers FGF-23 and PTH release to increase renal phosphate excretion. FGF-23 also reduces vitamin D activation, contributing to lower phosphate and calcium intestinal absorption. Lower levels of vitamin D, together with hypocalcemia, promote PTH secretion. Altogether, these mechanisms restore phosphate homeostasis by enhancing renal phosphate excretion and inhibiting intestinal absorption (adaptive mechanism). However, if renal function worsens, these compensatory mechanisms become ineffective in preventing phosphate retention, and the subject is exposed to phosphate, PTH, FGF-23, and low vitamin D levels may occur (maladaptive mechanism). Legend: The arrow suggests positive feedback, while the dot suggests negative feedback.

1, 25 $(OH)_2$ VD and an overall increase in PTH and FGF-23. It also shows that phosphorus urinary excretion is not associated with phosphorus intestinal absorption, as found in rats before[36] although classically, it was deemed a surrogate of phosphate intake.[37] These findings suggest reconsidering the role of 1, 25 $(OH)_2$ VD in intestinal phosphorus absorption, as phosphate transporters independent from VD activity have been described in patients with a phosphorus-restricted diet.[38] It should be nevertheless observed that circulating 1, 25 $(OH)_2$ VD could not be representative of tissue 1, 25 $(OH)_2$ VD, which could be finally responsible for 1, 25 $(OH)_2$ VD effects.[39,40]

Phosphorus metabolism has gained so much attention in the recent past because most of the epidemiological and clinical observations have reported an association between the progressive increase of phosphorus in CKD with adverse outcomes in both predialysis[41–43] and dialysis-dependent (DD) patients.[44–50] The cardiovascular system seems particularly involved as the kidney function decreases.[51–53] Interestingly, even in patients with normal kidney function, there is an association between phosphate levels and all-cause mortality, cardiovascular mortality, and morbidity.[54–58]

Phosphorus seems also to be an independent marker of progressive renal failure, especially in younger patients with moderate-to-severe CKD.[59] It has been shown that phosphorus can induce CKD in animals[60] and humans[61] when assumed in large amounts relative to the available nephron mass. According to recent animal data, the filtered phosphate in the renal tubule form with calcium and fetuin-A urine calciproteins (CPP) that in turn can trigger a local inflammatory response through the Toll-Like Receptor 4 which activates the NFkB factor and reduce klotho, ultimately leading to tissue fibrosis and loss of renal function. Hence the increased amount of phosphorous filtered per single nephron in CKD may perpetrate a vicious cycle and promote CKD progression.[62]

Besides phosphorus, other biomarkers implicated in CKD-mineral bone disease (MBD), such as rising FGF-23,[63,64] elevated PTH,[65] high levels of CPPs,[20,21,66–71] and low fractional excretion of phosphorus (FEp),[72] have been associated with adverse outcomes. As for FGF-23, rising values have been associated with death in CKD patients, speculatively due to left ventricular hypertrophy, anaemia, inflammation and immune dysregulation,[73–78] whereas stably elevated values were not. On the opposite, FEp seems inversely associated with worse renal outcomes. This is because, as kidney function decreases, CKD patients cannot increase GFR and rely solely on FEp to maintain a neutral phosphorus balance.[30]

5 | PHOSPHORUS SERUM LEVELS OR PHOSPHORUS BALANCE: WHAT IS THE MOST CLINICALLY RELEVANT BIOMARKER?

Being less than 1% of total body phosphorus dissolved in plasma, phosphoremia is probably a poor marker of phosphorus balance. Nevertheless, clinical studies have primarily focused on phosphoremia as one of the most important biomarkers of CKD-MBD. While treating hyperphosphatemia in NDD-CKD patients has shown improvement in outcomes[79,80] in normophosphatemic NDD-CKD patients, controversial results have been obtained, mostly showing unaffected outcomes after treating normophosphatemic patients with phosphate-binders.[81–87] Overall, RCT evidence is scarce, and most studies did not include analysis of the biomarkers, such as FGF-23, CPPs, and urinary FEp, or a comparison versus placebo. Therefore, it could be inferred that for decades, we have dosed the wrong analytic, being hyperphosphatemia possibly the epiphenomenon of metabolic derangement and not the cause of organ damage. This would lead to a focus on any of the biomarkers of CKD-MD as possible culprits.

As proposed by Isakova and co-workers in their seminal work,[22] phosphorus balance in CKD patients could be simplified in two phases. In phase 1, as kidney function decreases, there is a gradual increase in FGF-23 and PTH, with the preservation of normophosphatemia at the cost of increased phosphorus excretory capacity. In phase 2, which roughly starts when eGFR falls below 30 mL/min, renal dysfunction no longer guarantees proper phosphorus excretion despite increasing values of FGF-23 and PTH, thus leading to hyperphosphatemia. Interestingly, after phosphate loading, FEp is reduced in normal renal function and cardiopathic patients with respect to non-cardiopathic subjects[88] and acts as an independent risk factor, modulating the association between FGF-23 and cardiovascular outcomes in normal renal function, cardiopathic patients.[89] Reduced FEp could, therefore, represent a principal and an independent cardiovascular risk factor and could concur to reconsider the roles of biomarkers in

CKD-MBD. Moreover, in animal models, reduced FEp per nephron has been shown to correlate with tubule-interstitial lesions.[36]

In a new paradigm,[90] positive phosphate balance could be forecast by increased FGF-23 levels, irrespective of phosphoremia, which consecutively would warrant phosphate-lowering strategies, such as phosphate restriction and phosphate binders. High levels of FGF-23 would justify FEp measurement, which, if increased, would suggest an excessive phosphate intake and, if reduced, a worsening of the kidney function. Notably, reduced phosphate absorption, such as in a phosphate-restricted diet or during phosphate binder therapy, would reduce FEp. Positive phosphate balance would engender CPP formation, which then would be the ultimate responsible for phosphate-induced organ damage[19,90] To interpret CKD-MBD biomarkers, it is essential to consider their evolution prospectively, as recommended in the KDIGO 2017 clinical practice guidelines on CKD-MBD.[52]

6 | OVERVIEW OF EVIDENCE ON PHOSPHATE BINDER USE IN CKD PATIENTS

Strategies for controlling phosphorus in CKD-MBD have classically comprised dietary restriction of phosphate intake, phosphate binders, VD analogues and calcimimetics. Lately, tenapanor, a small-molecule inhibitor of the intestinal sodium/hydrogen exchanger (NHE3), has proven to reduce serum phosphate in patients on maintenance dialysis by reducing phosphate absorption, both alone[91,92] and in combination with phosphate binders.[93]

An ideal phosphorus chelator should avidly bind phosphorus in the gastrointestinal tract, not be absorbed, have few side effects, not require many tablets to facilitate compliance, and be inexpensive. Although numerous drugs are available today, the ideal phosphorus binder, which allows optimal chelation without side effects and with a positive cost-effectiveness ratio, does not exist. However, different formulations on the market enable the customization of therapy from case to case. Chelating agents based on calcium salts, sevelamer, lanthanum carbonate, ferric compounds and magnesium salts effectively reduce serum phosphate, although differences among compounds may exist. Phosphate binders, pre-dominantly based on calcium or aluminium, were commercialized in the early 1970s. Subsequently, other drugs with different formulations, characteristics, and side effects have been developed. Since the 1990s, aluminium-containing phosphate binders are no longer employed but for short periods of time, giving tissue accumulation of aluminium and toxicity such low turnover osteopathy (osteomalacia and adynamic disease), microcytic anaemia, encephalopathy and dementia, especially in DD patients.[94]

Phosphate binders have been studied clinically in DD and NDD CKD patients.

6.1 | Phosphate binders in DD-CKD patients

In DD-CKD patients, lanthanum carbonate-based[95–98] calcium-based,[99,100] sevelamer-based,[103,104] sucroferric oxyhydroxide-based[101] and ferric citrate-based,[102] phosphate binders have proven in RCTs to reduce serum phosphate successfully. However, as suggested before, hyperphosphatemia in CKD is possibly an epiphenomenon, while FGF-23-klotho axis derangement is the leading cause of subsequent organ damage. Furthermore, calcium supplementation could ultimately induce an increase in vascular calcifications, though the evidence is controversial,[103–111] and most, albeit not all, RCTs show an increase in vascular calcifications with calcium-based binders. However, accelerated vascular calcification progression was also noted in subjects starting haemodialysis[112,113] with calcium-based chelators. Interestingly, even in normal renal function subjects, calcium supplementation has been associated with increased coronary artery calcification,[114] while dietary calcium has not. Unlike dietary calcium, which is associated with higher serum calcium and lower FGF-23 concentrations, calcium supplementation is linked to increased serum calcium without influencing FGF-23 levels in DD-CKD patients.[115] While these pieces of evidence suggest that different sources of calcium may have other impacts on CKD-MBD parameters, it is also possible that various binders have different effects on the FGF23-Klotho axis. An RCT enrolling 1059 patients to take sucroferric oxyhydroxide or sevelamer proved to reduce FGF-23 over 1 year, with a beneficial adjunctive effect on bone metabolism.[116] Moreover, FGF-23 reduction has been demonstrated after treatment with sevelamer, magnesium carbonate,[117] and lanthanum carbonate, but not calcium carbonate.[118] In a small study, sevelamer was proven to reduce FGF-23 and increase klotho.[103] Unfortunately, in most of the studies, the effect of phosphate binders on FGF-23/Klotho levels has not been described, precluding any definitive conclusion on the effects of phosphate binders on the FGF23-klotho axis. Similarly, data on CPPs are scanty, and a small RCT including 50 haemodialysis patients showed no difference in serum fetuin-A decrement after 1-year treatment with calcium carbonate or sevelamer.[119]

Although evidence is largely inconclusive, several other studies suggest the differential impacts of various binders on vascular calcification and cardiovascular outcomes. An RCT of 115 patients on maintenance dialysis showed delayed coronary artery calcification (CAC) progression over 1 year when a strict (targeting normal phosphate levels) versus a standard phosphate control using non-calcium-based phosphate binders were enforced.[120] If these data suggest that phosphate control may impact vascular calcification, some lines of evidence support the notion that using calcium-containing phosphate binders is associated with faster vascular calcification progression and worse prognosis than calcium-free phosphate binders.[79] Renal osteodystrophy, bone density is decreased by calcium-based phosphate binders in DD-CKD patients,[121–123] while sevelamer[124] and lanthanum carbonate[125] have been proven to prevent bone loss. A possible mechanism could be calcium supplementation's relative inhibition of PTH activity.[105] PTH levels and bone activity are inversely associated with CAC progression.[126]

However, not all trials confirmed the association of calcium-containing phosphate binders with vascular calcification progression. Interestingly, sevelamer showed similar CAC progression over 1 year

compared with calcium acetate when a concomitant intensive reduction of LDL-C was enforced,[127] questioning the impact of calcium-based binders on cardiovascular outcomes. In these regards, the recent LANDMARK study, enrolling over 2000 patients, showed no difference in cardiovascular outcomes over 3 years with lanthanum compared with calcium carbonate.[128]

6.2 | Phosphate binders in NDD-CKD patients

To interpret the effect of phosphate binders in NDD-CKD patients, for pathophysiological reasons, we refer to the two phases of the phosphorus balance in CKD,[22] differentiating normophosphatemic and hyperphosphatemic patients[129] due to the potential overlap of phosphate and FGF23/Klotho axis as the cause of CKD-MBD associated organ damages. Compared with the use of phosphate binders in DD-CKD patients, the evidence is scarce, and most of the RCTs focus on phosphate levels, very few considering important biomarkers, such as FGF-23, klotho levels, arterial calcifications and bone density.

Most of the trials included NDD-CKD normophosphatemic patients, the largest subgroup. At present, evidence is at least controversial. Most studies did not show any effect of phosphate binders (sevelamer, lanthanum carbonate, calcium-based and iron-based), as for phosphate levels,[130] vascular involvement progression,[83,84] FGF-23 levels,[131] klotho levels,[130] VD levels,[83] cardiovascular outcomes (such as arterial stiffness, left ventricular mass or function).[83,84,86]

An RCT including 148 stage 3b-4 CKD patients showed that phosphate binders altogether (calcium carbonate, sevelamer and lanthanum carbonate) reduce phosphate levels, FEp and PTH levels without influencing FGF-23 levels and promote vascular calcifications.[82] The increase in vascular calcifications could be driven by the effect of the calcium-based binders (34% of patients who received phosphate binders), which can induce positive calcium balance and tissue deposition, even if theoretically, phosphate chelation in the bowel by any phosphate binder could provoke an increase in calcium absorption and thus net calcium positive balance. However, it has been shown that calcium supplementation of up to 2000 mg/die in CKD patients can cause a substantial positive calcium balance. An RCT with 30 stages 3–4 CKD patients randomized to receive sevelamer carbonate or calcium acetate showed improvement in inflammatory biomarkers, HLD-c levels, CKD-MBD biomarkers (phosphate levels, FGF-23 levels), and vascular calcification biomarkers (such as P and E-selectins) in the sevelamer carbonate group.[87] An RCT including 39 patients showed that lanthanum carbonate and a phosphate-restricted diet successfully reduced FGF-23 levels in Stage 3 CKD patients.[132] As for iron-based binders, they proved to reduce PTH levels successfully.[131]

Concerning hyperphosphatemic NDD-CKD patients, trials have shown that most phosphate binders effectively reduce serum phosphorous levels, and some have investigated the impact of different binders on hard outcomes. Lanthanum carbonate demonstrated its efficacy in reducing phosphate load and FGF-23 levels, unlike calcium carbonate.[133,134] Ferric citrate hydrate reduced phosphoremia and FGF-23 levels.[135] Sevelamer proved effective in reducing all-cause mortality and CKD progression to dialysis when administered in conjunction with a phosphate-restricted diet[136] and in reducing all-cause mortality but not dialysis initiation when used as a single strategy.[80] Compared with calcium acetate, sevelamer proved more effective in reducing serum phosphate, and unlike calcium acetate, it reduced FGF-23 levels and increased flow-mediated vasodilatation.[137]

Two RCTs[138,139] have included both normophosphatemic and hyperphosphatemic patients. Ruggiero and co-workers[138] tested the hypothesis that sevelamer could act synergistically with RAS blockade to reduce proteinuria in CKD patients with residual proteinuria, knowing that phosphate levels have been associated with proteinuria in nondiabetics stage 5 CKD patients.[140] However, sevelamer did not reduce proteinuria, FGF-23 levels, PTH or klotho levels, while it reduced FEp, c-reactive protein, glycated haemoglobin and LDL-c. Lastly, Block et al.,[139] in an RCT involving stage 3–5 CKD patients, showed that ferric citrate repletes iron storages, increasing haemoglobin and reducing phosphoremia, FEp and FGF-23.[140]

7 | CONCLUSION

Phosphorus is a key element for the development of life. In humans, its levels are strictly regulated by feedback loops that are deranged in CKD due to the reduced nephron mass. Adaptive mechanisms are stimulated to enhance renal phosphate excretion. However, renal function deficit progression renders these mechanisms futile and exposes a subject with CKD to both phosphorus and adaptive mechanisms effectors toxicity. As the GFR drops below 30 mL/min/1.73 m^2 these mechanisms become maladaptive. Although the pathophysiology of phosphate toxicity needs elucidation, some evidence suggests that the FGF-23-klotho axis, vitamin D and PTH derangement provoke noxious effects and organ damage (especially cardiovascular morbidity), contributing to the dismal risk of unfavourable outcomes in CKD.[141]

To comprehensively assess the CKD-MBD associated risk biomarkers, such as FGF-23, klotho, FEp and PTH, should be evaluated prospectively together with serum levels of phosphate. Phosphate serum levels could be a mistarget, an epiphenomenon of FGF-23-klotho derangement, thus explaining the controversial results of the RCTs. In these regards, two large ongoing trials will provide us with evidence of the impact of phosphate-lowering strategies in CKD patients receiving hemo- and peritoneal dialysis.[142]

A general recommendation on what type of phosphate binder to use in any stage and patient with CKD is complicated and likely not sustained by current evidence. While there is a consensus on reducing the excessive amount of elemental calcium (i.e., above 1500 mg elemental calcium/day), it is still being determined whether we should not prescribe calcium-containing phosphate binders. Negative calcium balance should be avoided to reduce the risk of bone fracture. The CKD-MBD and European Renal Nutrition working groups of the European Renal Association (ERA), together with the CKD-MBD and Dialysis working groups of the European Society for Paediatric

Nephrology (ESPN), in a recent document, suggest a total calcium intake from diet and medications of 800–1000 mg/day and to not exceed 1500 mg/day to maintain a neutral calcium balance in adults with CKD.[143] However, if hyperphosphatemia must be treated, calcium-free binders may have a better risk–benefit profile in DD-CKD and NDD-CKD hyperphosphatemic patients. At the same time, the evidence is inconclusive in NDD-CKD normophosphatemic patients, and no phosphate binder is suggested for these subjects. Hence, the choice of binder should be individualized and encompass different aspects such as pill burden, cost and patient's preferences.

Several aspects of phosphate metabolism and CKD-MBD remain to be elucidated. Future studies should corroborate the use in the clinic of different biomarkers, such as FGF-23 and CPPs, to assess the risk of organ damage and provide us with solid evidence on how to manage CKD-MBD. Until then, available evidence suggests maintaining phosphate levels within the range of normality and avoiding excessive calcium loading (above 1500 mg/day, including dietary and phosphate binder sources).

CONFLICT OF INTEREST STATEMENT

AB has received speaking fees from Sanofi, Vifor, Sanifit and Amgen. All other authors have nothing to disclose.

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