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CKJ Review

CKJ REVIEW

The true cost of phosphate control in chronic kidney disease

Cristian Rodelo-Haad[1,2,3,4,*], María E. Rodríguez-Ortiz[1,2,3,4,*], Raquel Garcia-Sáez[1,2,3], Antonio Rivas-Domínguez[1,2,3], Daniel Jurado-Montoya[1,2,3], Alejandro Martín-Malo[1,2,3,4], Mariano Rodríguez[1,2,3,4,5,6], M. Victoria Pendón-Ruiz de Mier[1,2,3,4,†] and Juan Rafael Muñoz-Castañeda[1,2,3,4,†]

[1]GC13, Mineral Metabolism, Vascular Calcification, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Cordoba, Spain, [2]University of Cordoba, Cordoba, Spain, [3]Nephrology Service, Reina Sofia University Hospital, Cordoba, Spain, [4]Redes de Investigación Cooperativa Orientadas a Resultados en Salud, RICORS2040, Institute of Health Carlos III, Madrid, Spain, [5]European Uremic Toxins Group (EUTOx) and [6]COST Action CA21165 – Personalized medicine in chronic kidney disease: improved outcome based on Big Data (PerMediK)

*Share the first authorship.
†Share the last authorship.
Correspondence to: Mariano Rodríguez; E-mail: marianorodriguezportillo@gmail.com

ABSTRACT

The loss of kidney function entails the development of a positive phosphate balance. The burden of addressing elevated phosphate levels is high. Both parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) are increased to promote phosphaturia, thereby preventing the rise in serum phosphate. However, if the phosphate load is excessive, the corresponding phosphaturia is maximal, kidney function deteriorates and hyperphosphataemia becomes clinically evident in advanced stages of chronic kidney disease (CKD). In addition to its role in CKD progression, hyperphosphataemia has been linked to a multitude of adverse outcomes, including overt inflammation, vascular calcifications, endothelial dysfunction, cardiovascular disease, renal osteodystrophy and secondary hyperparathyroidism. Collectively, these factors contribute to the markedly elevated mortality rates observed among individuals with CKD. Furthermore, hyperphosphataemia has been identified as a significant contributor to the development of inflammatory processes, oxidative stress and fibrosis, which underlie the aetiology of numerous comorbidities. Additionally, elevated levels of PTH and FGF23 have been demonstrated to independently induce organ and tissue injury, which is associated with poor outcomes in CKD. This article provides a concise overview of the current understanding of phosphate handling by the kidney in the context of CKD. It outlines the detrimental effects of phosphate on various organs and the mechanisms through which it contributes to CKD progression. Additionally, we discuss the tools available for clinicians to identify patients at risk of an excessive phosphate load.

Keywords: CKD, FGF23, hyperphosphataemia, inflammation, mortality

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INTRODUCTION

Phosphate is a key element for life. In humans, phosphate plays a regulatory role in enzymatic reactions, energy production and mineral metabolism [1]. The mean daily phosphate intake for humans is 1000–1500 mg, with 40%–80% of this being absorbed through the intestine. The rate of absorption differs depending on whether phosphate is organic or inorganic, with the latter being more readily absorbed. Once absorbed, phosphate becomes incorporated into different tissues and reservoirs. The bone serves as the primary reservoir for phosphate and calcium. Therefore, there are mechanisms to mobilize phosphate when required. In instances where the phosphate load is elevated, fibroblast growth factor 23 (FGF23) is increased in order to facilitate urinary phosphate excretion [2]. Furthermore, the secretion of parathyroid hormone (PTH) is increased due to the reduction of 1,25(OH)2D3 caused by high FGF23, reducing circulating calcium. However, this adaptive mechanism may become ineffective over time when kidney function is markedly decreased [3]. In this state, we must also add the negative effects associated with elevated levels of FGF23 and PTH, in addition to those caused by hyperphosphataemia.

Hyperphosphataemia is a defining feature of advanced CKD and secondary hyperparathyroidism (SHPT). The trade-off hypothesis states that the decline in kidney function results in an increment in PTH to enhance the urinary excretion of phosphate. Later, investigations showed that phosphate stimulated the production and release of PTH [4, 5]. More recently, evidence has emerged indicating that elevated serum phosphate levels can antagonize the calcium-sensing receptor (CaSR) on parathyroid glands, thereby promoting the secretion of PTH even in the presence of normal or elevated serum calcium concentrations [6]. In fact, the decrease in serum phosphate reduces serum PTH. Additionally, hyperphosphataemia prevents the calcium-mediated suppression of parathyroid CaSR [6]. Yet, the earliest hormone secreted to prevent the rise in serum phosphate is FGF23 [7]. It is crucial to recognize that the rise in phosphate load [8] and the increase in FGF23 are accompanied by a decline in Klotho [8]. Together, hyperphosphataemia, PTH elevation and supraphysiological serum levels of FGF23 are linked to a range of different comorbidities, overt inflammation, kidney fibrosis, vascular calcifications and CKD progression [2, 9, 10]. Furthermore, there is a consistent association between the phosphate–PTH–FGF23–Klotho axis and an increased risk of mortality [11, 12].

The 24-h urinary phosphate excretion does not correlate with daily intake, making it challenging to evaluate phosphate load with high reliability [13]. The different absorption rates of organic and inorganic phosphate may be the underlying cause of this lack of correlation between phosphate intake and excretion. The urinary phosphate-to-creatinine ratio is indicative of the quantity of phosphate that has been absorbed [14]. Furthermore, the urinary phosphate-to-urea ratio (P/UUN) provides insight into phosphate excretion relative to protein intake, which is metabolized to urea. An increment in the numerator would suggest phosphate from inorganic sources, while a disbalance in favour of the denominator would suggest the intake of phosphate from organic sources, thereby reducing the P/UUN ratio. Consequently, the P/UUN ratio enables clinicians to distinguish between phosphate derived from organic sources (proteins) and inorganic sources (additives) [15].

The current guidelines recommend the initiation of dietary phosphate restriction as a means of reducing hyperphosphataemia. However, this non-selective approach may increase the risk of nutritional imbalances. Furthermore, physicians prescribe phosphate binders to reduce the intestinal absorption of phosphate when serum phosphate levels exceed recommended thresholds. Nevertheless, this approach may prove inadequate, given that only 41% of patients achieve the targets [16]. Consequently, addressing hyperphosphataemia solely when it becomes ‘clinically relevant’ may be suboptimal, as adaptive mechanisms have already failed, and complications are likely to have emerged by this stage.

In this review, we will first summarize the renal management of phosphate across the different stages of kidney disease. We will also examine the recently identified adverse effects of hyperphosphataemia on the parathyroid glands, bone, kidney, vasculature and heart. Finally, special emphasis will be placed on the diagnostic tools available to assess phosphate burden and on implementing early interventions to mitigate phosphate-induced tissue damage.

PHOSPHATE HOMEOSTASIS

Dietary intake represents the primary source of phosphate (Fig. 1). Once absorbed through the intestinal wall, phosphate circulates in the blood. Approximately 10%–15% is distributed across soft tissues, including skeletal muscle, while only 1% is contained in extracellular fluids. The majority of absorbed phosphate (85%) is stored in the bones or teeth. The typical Western diet contains approximately 1500 mg of phosphate daily. However, the renal excretion of phosphate does not correlate directly with dietary phosphate intake [13] attributable to variations in absorption rates contingent upon the phosphate source. While organic phosphate, present in vegetables and animal proteins, is absorbed at rates of 30%–60%, respectively, the inorganic phosphate, primarily found in processed and ultra-processed foods and soft drinks, demonstrates an absorption efficiency reaching up to 80% [17–19]. Intestinal phosphate absorption occurs via passive paracellular pathways and through active transport mediated by sodium-dependent phosphate cotransporters NaPi2b, PiT1 and PiT2 [20]. These sodium-phosphate cotransporters, members of the SLC protein family (SLC20), are expressed almost ubiquitously in all tissues. In the context of hyperphosphataemia and CKD, studying the role of these cotransporters in renal and vascular smooth muscle cells (VSMC) is of particular interest because phosphate entry promotes the activation of several signalling pathways [21].

The utilization of low-phosphate diets, calcitriol, oestrogens and acidosis, among other factors, has been demonstrated to stimulate the expression of NaPi2b [22]. Indeed, the paracellular transport of phosphate in the intestine is tightly modulated by sodium-hydrogen exchangers (NHE3), which are themselves regulated by the acid–base status [23].

KIDNEY HANDLING OF PHOSPHATE

In addition to the intestine, the kidney is the other major organ that regulates phosphate homeostasis. Although high phosphate levels alter the activation of the calcium-sensing receptor, which is present in the kidney in addition to parathyroid cells and other cells, it remains unclear whether the renal CaSR directly influences phosphate handling within the kidney. However, the rate of phosphate absorption or excretion may change depending on different situations and the expression of cotransporters. In the kidney, phosphate is filtered and almost 80% is reabsorbed by the NaPi2a and NaPi2c

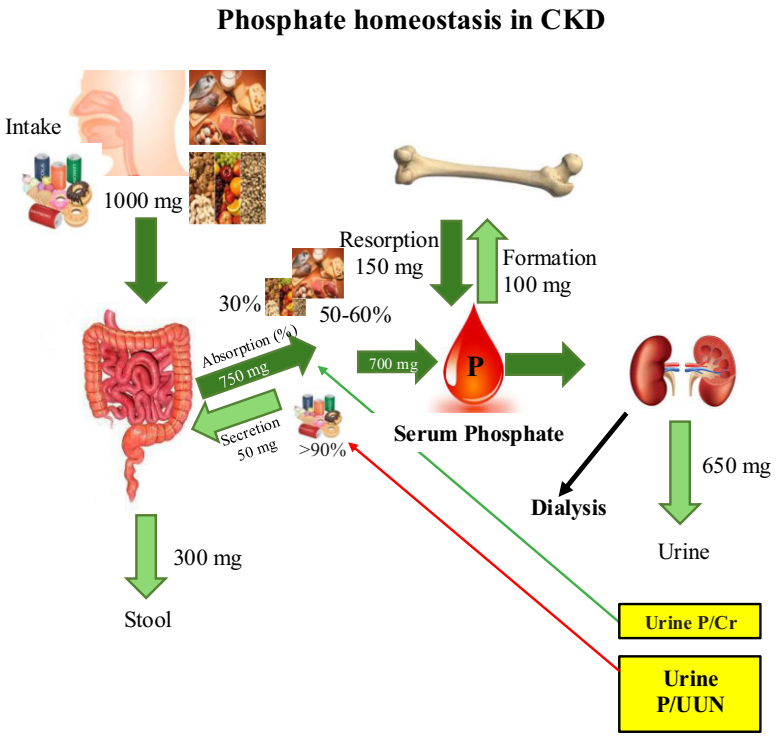

Figure 1: Phosphate homeostasis in CKD. The average intake of phosphate is 1000 mg per day, including organic and inorganic sources. The rate of phosphate absorption by the intestine may vary according to the source of phosphate: 30% vegetables, 50%–60% animal (therefore 30%–60% organic) and more than 90% inorganic. The urine P/Cr ratio reflects the total amount of phosphate being absorbed. The urine P/UUN ratio reflects the absorption of inorganic phosphate relative to organic phosphate contained in proteins. Inorganic phosphate should be restricted in CKD (red arrow). A small part of the absorbed phosphate is used in bone formation. The ingested phosphate that is not absorbed is eliminated in faeces (approximately 300 mg).

co-transporters, mainly located in the proximal renal tubules [1]. The increment in phosphate load increases the production of phosphaturic hormones such as PTH and FGF23, aiming to maintain normal serum phosphate concentration and prevent hyperphosphataemia [24] (Fig. 2). Other less significant mechanisms that facilitate phosphate excretion include calcitriol, dopamine, growth hormone, thyroid hormone and acid–base imbalances [1, 25]. PTH and FGF23 inhibit the reabsorption of phosphate in the renal proximal tubules by reducing the activity, suppressing the expression, and enhancing the degradation of NaPi2a and NaPi2c on the apical membrane of proximal renal tubules [26–29]. Phosphate handling may also be influenced by estimated glomerular filtration rate (eGFR), age and sex. In the CKD context, the maximum excretion rate of phosphate rounds 40 mg/mL/min of phosphate. This indicates that in advanced non-dialysis CKD patients, hyperphosphataemia becomes clinically relevant when phosphaturia adjusted for eGFR exceeds 40 mg/mL/min [30].

The mechanisms responsible for maintaining serum phosphate within the normal range are activated even when renal function is only minimally impaired [7]. In the early stages of CKD, serum FGF23 increases, resulting in phosphaturia, a decrease in circulating Klotho, and a halt in vitamin D hydroxylation, which reduces phosphate and calcium absorption in the intestine [31]. The resulting hypocalcaemia, together with the reduction in vitamin D metabolites promotes the increment in PTH. Subsequently, when the nephron mass is markedly reduced, the phosphate load per nephron increases significantly, and renal tubular reabsorption of phosphate declines due to an elevation in FGF23, resulting in increased phosphaturia [2]. The resulting phosphate overload not only produces worsening kidney function [10, 32] but also induces the downregulation of FGF receptor-1 (FGFR1) and Klotho expression [8]. Thereby, the resistance to the tubular action of FGF23 amplifies its secretion (Fig. 2). Finally, the progression of CKD overcomes the phosphaturic effects of FGF23-Klotho-, low vitamin D, and PTH, and hyperphosphataemia becomes evident (Fig. 2).

In parallel, hyperphosphataemia stimulates the proliferation of parathyroid cells, which in turn elevates PTH secretion and facilitates parathyroid nodular hyperplasia [4]. Under physiological conditions, FGF23 prevents the parathyroid gland from secreting PTH. However, in the context of CKD, FGF23 fails to inhibit PTH production due to a downregulation of the co-receptor Klotho [33].

HYPERPHOSPHATAEMIA AND INFLAMMATION

Chronic inflammation is a common feature of CKD. In this regard, CKD patients in the pre-dialysis stage exhibit significantly elevated levels of inflammatory markers, including C-reactive protein and interleukin (IL)-6 [34]. The Cardiovascular Health Study [35] suggested that renal dysfunction is independently associated with elevations in inflammatory cytokines. Similarly, the Chronic Renal Insufficiency Cohort (CRIC) study revealed that inflammation-associated molecules are linked to progressive decline in renal function [36]. It has been proposed that the presence of reactive oxygen species, advanced glycation

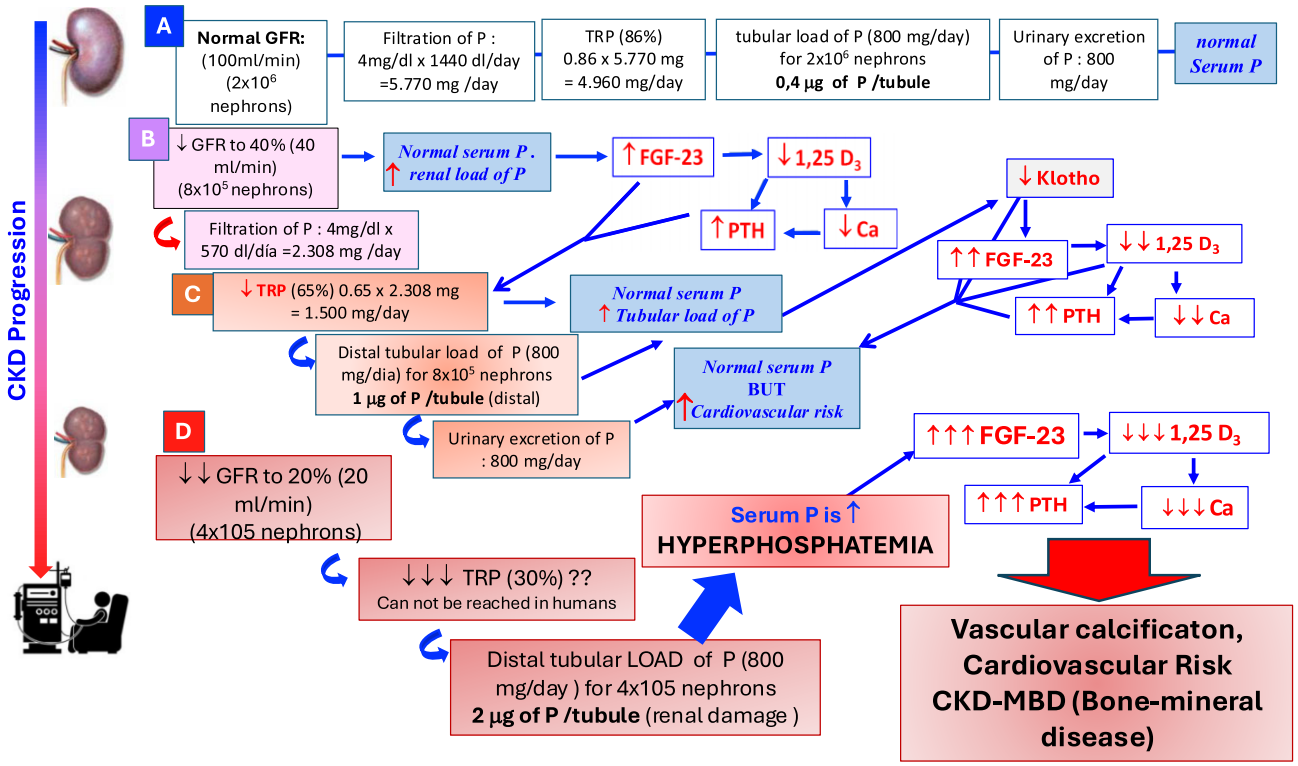

Figure 2: Renal phosphate handling according to different stages of CKD. Adapted from [131]. The illustration depicts the alterations that occur in the kidney in order to maintain serum phosphate (P) concentration in CKD. The reduction in GFR, that is to say, the decline in the number of functional nephrons, is accompanied by a reduction in proximal P reabsorption and an increase in the distal tubular phosphate load per nephron. Under normal kidney function (**A**), the majority of filtered phosphate (5770 mg per day) is reabsorbed, with a corresponding amount excreted to match the absorbed phosphate in the intestine. This process maintains phosphate balance. Based on these conditions, the estimated daily phosphate circulation through the distal tubules is approximately 0.4 μg. (**B**) When renal function declines to 40% (CKD stage 3), phosphate levels are typically within the normal range. This is because the reduction in filtered phosphate is compensated for by a decrease in renal tubular phosphate, which occurs due to the action of FGF23 and PTH. In essence, the phosphate level remains within the normal range. To achieve this, the phosphate load in the distal tubule must increase to 1 μg/day, to excrete the same amount of phosphate that has been absorbed in the intestine. This compensatory mechanism is gradually compromised as the augmented tubular phosphate load results in renal impairment and a reduction in tubular expression of Klotho, a co-receptor of FGFR and a prerequisite for FGF23 to exert its function. Resistance to the action of FGF23 emerges, necessitating an increased FGF23 dosage to sustain phosphaturia. Furthermore, elevated levels of FGF23 have been observed to diminish calcitriol production, thereby reducing intestinal calcium absorption and serum calcium levels and accelerating the progression of hyperparathyroidism. This surge in FGF23 and PTH, coupled with the decline in calcitriol, has been linked to an increased risk of developing cardiovascular disease, an elevated likelihood of vascular calcification and altered mineral metabolism. (**C**) As CKD progresses and there is a marked reduction in the number of functioning nephrons, the capacity of the tubular reabsorption of phosphate (TRP) is no longer sufficient to maintain phosphaturia, resulting in an increase in serum phosphate. (**D**) Compensatory mechanisms fail, and the tubular phosphate load approaches 2 μg of phosphate per tubule, leading to progressive renal damage, alterations in mineral metabolism, bone deterioration, vascular calcifications, cardiovascular disease and increased mortality.

end products, peripheral polymorphonuclear leukocyte priming, reduced clearance of inflammatory molecules and gut microbiome dysregulation may contribute to the exacerbated inflammatory state observed in CKD [37–39].

Furthermore, an elegant study by Navarro-González and colleagues demonstrated that elevated phosphate levels are independently associated with inflammatory markers in CKD. Specifically, in CKD stages 3–4, patients in the highest tertile of phosphate exhibited a significant increase in C-reactive protein and IL-6 levels, even after adjusting for age, gender and eGFR [40]. These findings were further validated in experimental studies, which demonstrated that phosphate plays a direct role in the induction of inflammation. Our research group demonstrated that the incubation of VSMC with high phosphate concentration significantly increased the expression of the IL-1β, -6 and -8, as well as tumour necrosis factor (TNF)-α. This effect was mediated by the activation of the nuclear factor (NF)-κB pathway [41, 42]. This work also highlighted the interplay between inflammation and oxidative stress, given that the pro-inflammatory effect of phosphate was attenuated in the presence of an antioxidant treatment. Such an inflammation-enhancing effect of phosphate has also been reported in other types of cells. Indeed, Ding and colleagues [43] reported that the expression of TNF-α and IL-6 in human monocytes was markedly increased after exposure to high phosphate levels.

Given the pro-inflammatory effect of phosphate, therapeutic strategies aimed at controlling hyperphosphataemia may have a direct impact on the inflammatory profile of CKD patients. In this context, Yamada and colleagues demonstrated that the administration of a dietary phosphate overload resulted in systemic inflammation in a rodent experimental model of adenine-induced CKD. Notably, the reduction in phosphate loading through dietary restriction or the administration of the phosphate binder lanthanum carbonate attenuated the inflammatory status [44]. Chertow and colleagues observed a significant reduction in C-reactive protein levels among haemodialysis patients undergoing sevelamer therapy over 52 weeks [45]. Similarly, sevelamer regimes of 24 or 52 weeks also resulted in

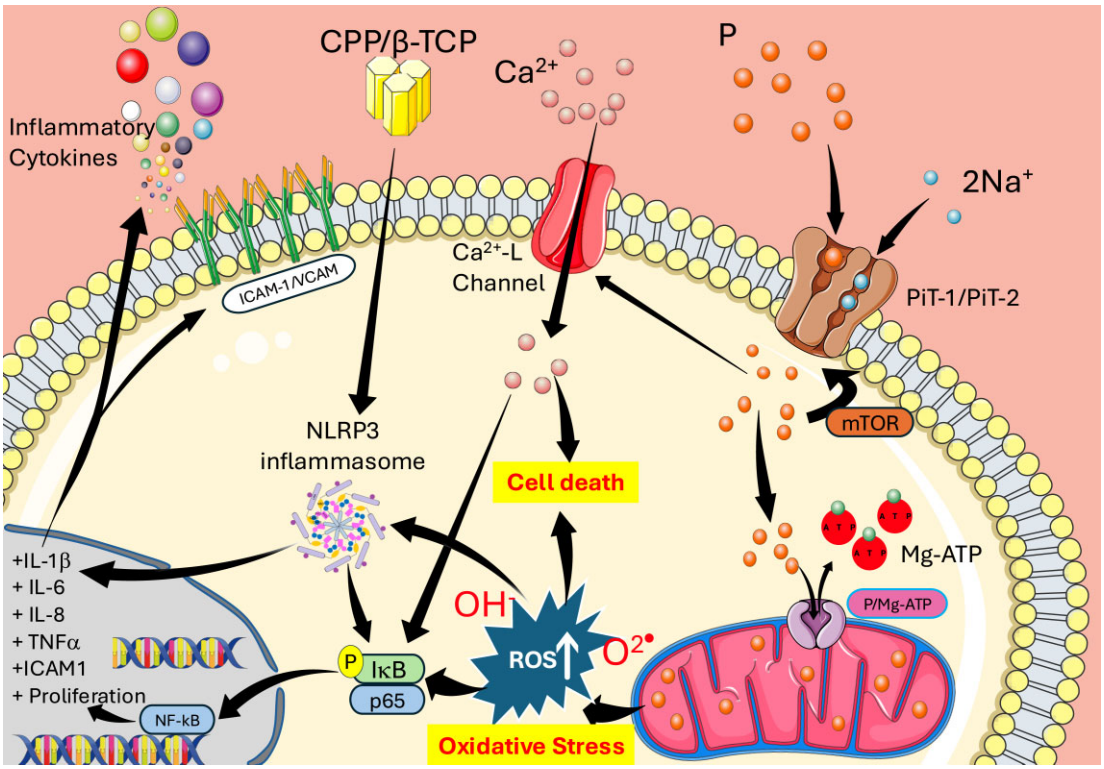

Figure 3: Hyperphosphataemia, oxidative stress and inflammation. It has been observed that phosphate overload in VSMCs upregulates the expression of the co-transporters PiT-1/PiT-2 through ERK/mTOR (mammalian target of rapamycin) pathway and stimulates their trafficking to the plasma membrane, increasing intracellular phosphate levels [132]. This involves the cotransport of 2 Na^+ ions for each phosphate, resulting in a net positive current flow that depolarizes the plasma membrane of VSMCs. This depolarization allows greater Ca^{2+} entry through L-type voltage-gated Ca^{2+} channels. Additionally, phosphate overload in the cell promotes phosphate internalization and Mg-ATP extrusion into the mitochondria via a Ca^{2+}-dependent P/Mg-ATP transporter, triggering an increase in mitochondrial ROS [133, 134]. Therefore, increased phosphate entry into the cell triggers changes in the influx and efflux of other ions such as Na^+, Mg^{2+} or Ca^{2+}, leading to ROS generation.

reductions in C-reactive protein levels [46, 47]. Further investigation is required to confirm this hypothesis, but the available evidence suggests that the clinical management of hyperphosphataemia may contribute to alleviating the inflammatory status in CKD patients.

In addition, phosphate has been demonstrated to act as an activator of the inflammasome. The inflammasome plays a pivotal role in the innate immune response, functioning as a signalling platform that detects danger signals and pathogens, thereby initiating inflammatory processes. Inorganic phosphate can activate the inflammasome. One of the primary sensors is NLRP3 (Nod-Like Receptor Protein 3). The activation of the NLRP3 inflammasome results in the production of IL-1β, a cytokine that is directly involved in the maintenance of inflammation [48]. Beta-tricalcium phosphate (β-TCP) has been demonstrated to activate NLRP3 inflammasomes and to increase IL-1β production in primary cultured mouse dendritic cells and macrophages, as well as in human THP-1 cells. This occurs in a caspase-1-dependent manner [49] (Fig. 3).

Calciprotein particles (CPPs) are nanoparticles composed of fetuin-A, matrix Gla protein and calcium-phosphate crystals. CPPs are also capable of activating the inflammasome and the production of pro-inflammatory cytokines, including IL-1β and IL-1α. The effects of CPP evoke an acute inflammatory response, indicating that a strategy targeting both IL-1β and IL-1α would be necessary to reduce the CPP-induced inflammatory response [50].

HYPERPHOSPHATAEMIA AND OXIDATIVE STRESS

Hyperphosphataemia induces oxidative stress, a key factor in systemic inflammation. Oxidative stress generates reactive oxygen species (ROS), which damage lipids, proteins and DNA, thereby activating inflammatory pathways such as NF-κB [51]. This, in turn, leads to the production of pro-inflammatory cytokines, creating a vicious cycle between oxidative stress, chronic inflammation and hyperphosphataemia (Fig. 3). Our group has demonstrated that high levels of phosphate significantly increased ROS production in HEK-293 renal cells. Similarly, we observed that in heminephrectomized rats, the administration of a high-phosphate diet modified the activity of the antioxidant enzyme glutathione peroxidase [10].

In VSMCs, a high phosphate concentration induces osteogenic differentiation through increased oxidative stress [52]. It is well-known that patients undergoing dialysis exhibit elevated levels of oxidative stress and a reduction in their antioxidant reserve [53]. Phosphate levels are associated with increased production of superoxide, an ROS species, which in turn induces damage to lipids, proteins and DNA, thereby promoting cellular ageing, chronic inflammation and vascular calcification [54]. Research on isolated mitochondria indicates that mitochondrial superoxide production steadily increases as the inorganic phosphate concentration in the medium is elevated

from normal to supraphysiological intracellular concentrations. This effect is dependent on the transport of inorganic phosphate within the mitochondria and results in an increase in membrane potential, which hinders the flow of electrons through the mitochondrial respiratory chain in coupled mitochondria, thereby enhancing superoxide production, particularly at complex III [55]. Mitochondrial superoxide generation induced by inorganic phosphate depends on the intracellular uptake of extracellular phosphate through electrogenic transporters of the SLC20 family. This process involves the co-transport of 2 moles of Na^+ for every 1 mole of monovalent phosphate, resulting in a net positive current that depolarizes the smooth muscle cell membrane and triggers Ca^{2+} influx through L-type voltage-sensitive calcium channels [21] (Fig. 3). Therefore, the influx of excessive phosphate into renal cells and VSMC initiates signalling pathways that enhance ROS production and activate NF-κB, leading to the release of inflammatory cytokines, apoptosis and inflammation.

HYPERPHOSPHATAEMIA AND CKD PROGRESSION

The prominent role of phosphate as a key factor in CKD progression was first established several decades ago. Ibels and colleagues demonstrated that phosphate restriction effectively mitigated the functional decline of the remaining kidney in nephrectomized animals by attenuating inflammatory and fibrotic processes [56]. These findings were corroborated by Neves *et al.*, who reported that the administration of a high phosphate diet exacerbated kidney dysfunction, in addition to the development of bone and heart alterations. It is noteworthy that this study employed a model of nephrectomy plus parathyroidectomy with the replacement of a fixed amount of PTH, enabling the attribution of these changes solely to the amount of phosphate ingested, excluding other mineral metabolism–related factors modified by dietary phosphate [57]. Thus, hyperphosphataemia is not only a result of advanced CKD but may also be an active driver of disease progression [58].

In humans, a study performed by Norris and colleagues aimed to identify baseline predictors of renal disease in patients with eGFR between 20 and 65 mL/min/1.73 m^2. They found that, among other factors, phosphate concentration was directly related to the occurrence of adverse clinical renal outcomes [59]. In CKD stages 1–5, both phosphate and calcium-phosphate product were associated with an accelerated progression of CKD. Specifically, a 1 mg/dL increase in phosphataemia was linked to a 1.29-fold increase in the risk of CKD progression [60]. This association was also reported in newly diagnosed pre-dialysis patients, even after adjusting for other factors such as proteinuria, baseline renal function or blood pressure [61]. More recently, Bellasi and colleagues proposed that the relationship between hyperphosphataemia and CKD progression may be influenced by various factors, including age, gender, CKD stage and the presence of diabetes [62].

Different studies have investigated the mechanisms by which high phosphate levels promote the accelerated progression of CKD. Experiments conducted in 5/6 nephrectomized rats evidenced that the administration of dietary phosphate was associated with severe glomerular sclerosis, interstitial inflammation, fibrosis and tubular atrophy with dilation [63]. More recently, it has been shown that elevated urinary concentrations of phosphate resulted in the formation of intraluminal calcium phosphate particles, which subsequently promoted tubulo-interstitial inflammation through the activation of toll-like receptor 4 (TLR4) [64]. Additionally, high phosphate levels directly increased inflammation through NF-κB activation [65] and the production of pro-inflammatory cytokines, not only at the renal level but also in the vasculature [66]. Both processes contribute to CKD progression and its complications (Fig. 4). It is noteworthy that this rise in inflammatory activity was accompanied by changes in mineral metabolism, including a decline in renal Klotho and an increase in FGF23. The inhibition of inflammation with SN50, a specific inhibitor of NF-κB, resulted in a reduction of FGF23 and an increase in renal Klotho. It is challenging to ascertain whether the activation of the Wnt pathway is a consequence of or a causal factor in the promotion of inflammation. Conversely, it is also possible that the increase in inflammation is the result of the activation of the Wnt pathway [67]. Nonetheless, in the kidney, high phosphate levels activate the Wnt/β-catenin pathway [8, 68].

Given the relevant role of hyperphosphataemia in the progression of CKD, it is reasonable to assume that appropriate management of phosphate levels could reduce the progression of kidney damage. Studies in patients have shown that better control of hyperphosphataemia is associated with slower progression of CKD [69].

Taken together, these findings highlight the direct and prominent role of phosphate as a key driver of CKD progression. In this context, dietary phosphate restriction, together with other strategies to control hyperphosphataemia, may help to prevent or slow the progression of kidney disease to more advanced stages.

PHOSPHATE, ENDOTHELIAL CELL ACTIVATION AND VASCULAR CALCIFICATION

Hyperphosphataemia has been demonstrated to induce endothelial damage, a pivotal factor in the pathogenesis of systemic inflammation and cardiovascular disease. Consequently, elevated phosphate levels have been shown to promote a pro-inflammatory phenotype of endothelial cells, characterized by the overexpression of adhesion molecules (ICAM-1, VCAM-1) and the production of pro-inflammatory cytokines such as IL-6 and TNF-α [41]. Nitric oxide (NO) is produced in the endothelium by the constitutive enzyme endothelial nitric oxide synthase (eNOS) [70]. Recent cell culture studies have shown that eNOS activity can be suppressed by hyperphosphataemia. Indeed, in dialysis patients, high phosphate levels reduce circulating levels of eNOS [71]. Additionally, Di Marco *et al.* [72], revealed a reduction in the phosphorylation of Akt and annexin II following the exposure of endothelial cells to elevated phosphate levels.

Hyperphosphataemia represents the primary aetiological factor in the development of vascular calcifications. These calcifications are closely associated with an increased incidence of cardiovascular events and higher cardiovascular and all-cause mortality as a result of their impact on various organs and systems [73]. Vascular calcification is also an independent risk factor for myocardial infarction [74]. It predisposes to the rupture of atherosclerotic plaques and the formation of thrombi, which may result in an acute coronary event or stroke. The presence of calcifications in arteries in proximity to other organs, such as the kidneys, may result in reduced renal perfusion, thus contributing to the progression of CKD [75]. Recently, it has been observed that the ratio of calciprotein/serum phosphate is a useful biomarker for predicting the risk of cardiovascular events in

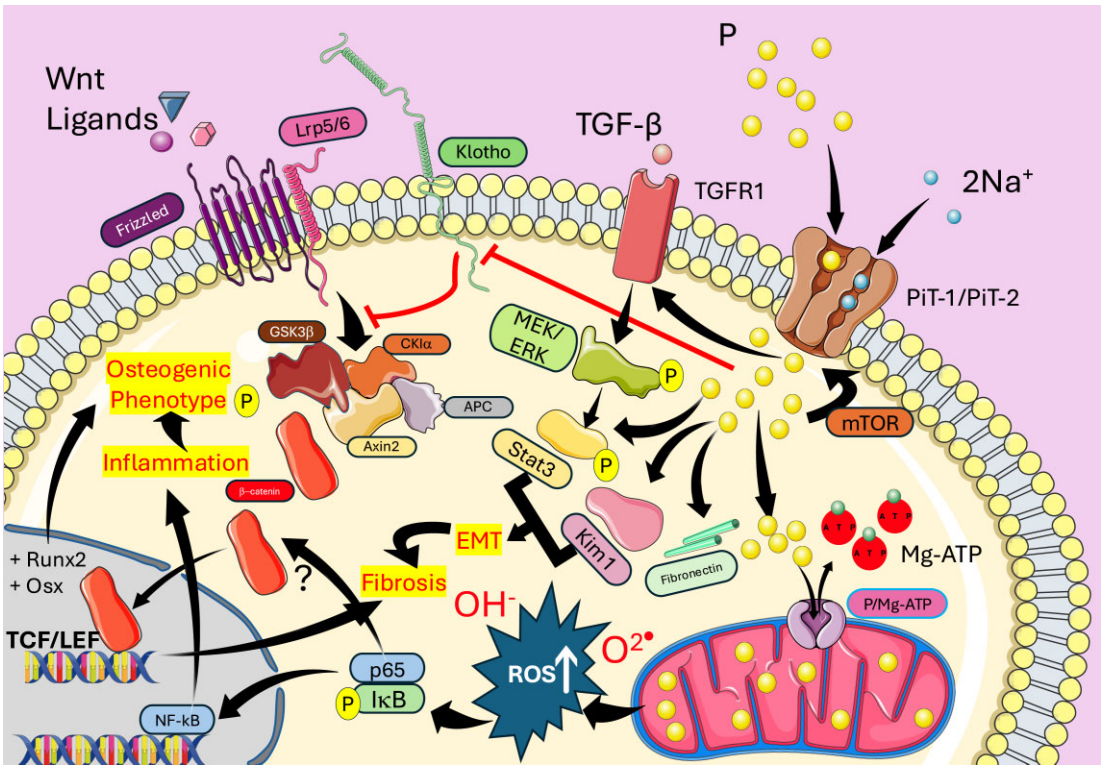

Figure 4: Hyperphosphataemia, vascular calcification and fibrosis. Both renal and VSMCs express PiT-1/PiT-2 cotransporters in their plasma membranes, allowing the exchange of sodium and phosphate into the cell. The excess of phosphate may cause mitochondrial stress through the excessive production of ROS, such as superoxide anion. This increase in ROS triggers the nuclear translocation of NF-κB, thereby stimulating inflammatory and pro-osteogenic responses in VSMCs. Phosphate overload contributes to the reduction of Klotho levels, which has been linked to the activation of the Wnt/β-catenin pathway, one of the main pro-osteogenic signalling pathways. The inhibition of GSK3β enables the nuclear translocation of β-catenin, leading to the transcription of pro-osteogenic and pro-fibrotic genes. Additionally, it has been shown that phosphate can activate the TGF-β receptor, promoting the expression of genes such as fibronectin, Stat3 and Kim1, which are associated with EMT and fibrosis.

patients undergoing incident haemodialysis [76]. The primary mechanism by which vascular calcifications occur is through the effect of high phosphate levels on the phenotype of VSMCs. Our group [77, 78] and others [79] have demonstrated that elevated phosphate levels activate the Wnt/β-catenin pathway in VSMCs, resulting in osteogenic transdifferentiation. The overexpression of Runx2, Osterix or Dmp1 and the downregulation of specific vascular smooth muscle proteins are responsible for orchestrating this change in phenotype (Fig. 3). In CKD, the development of vascular calcifications is also facilitated by the downregulation of anti-calcification proteins, including MGP, fetuin-A, osteoprotegerin and osteopontin [80]. In addition, other elements such as oxidative stress, miRNAs, microvesicles and other pathways are also involved in the process of calcification [81].

PHOSPHATE AND FIBROSIS

One of the consequences of high phosphate levels is the maintenance of a chronic inflammatory state that contributes to the development of fibrosis. The degree of renal fibrosis is rarely evaluated in patients with CKD, and there are no precise non-invasive techniques to assess it. It is challenging to establish correlations between phosphate levels and the degree of renal fibrosis. However, through experimental studies, we have shown that hyperphosphataemia produces renal fibrosis [42]. A high phosphate diet (2%) induced kidney injury in mice, characterized by progressive accumulation of collagen (Fig. 3). Furthermore, the elevated phosphate levels in the diet resulted in the activation of Stat3 and the expression of Kim-1 in proximal tubular epithelial cells. Additionally, renal production of chemokines that recruit monocytes and macrophages, as well as macrophage-related factors, was enhanced. Hyperphosphataemia reduced endothelium-dependent vascular relaxation and increased inflammation and vascular fibrosis through an impairment of the oxidant/antioxidant balance in the mesenteric arteries of aged mice. Conversely, a low-phosphate diet improved vascular function in aged mice [42].

Moyses RMA's research group showed that after only 6 days, nephrectomized rats on a high-phosphate diet (0.95%) compared with a low-phosphate diet (0.2%) had a greater degree of interstitial fibrosis, α-actin expression, proliferating cell nuclear antigen and renal macrophage infiltration, which contribute to the progression of kidney disease [82].

The pro-fibrotic effects of phosphate can be the result of either a direct action on fibroblasts and myoblasts or through the activation of epithelial–mesenchymal transition (EMT) [83] (Fig. 3). Tan and colleagues demonstrated that high inorganic phosphate directly induces fibrotic fibroblast activation, accompanied by increased expression of α-smooth muscle actin and increased synthesis of type I collagen. This effect was dependent on phosphate influx, aberrant phosphorylation of DNA methyltransferase (DNMT1) and abnormal CpG island promoter methylation [84]. In another study, it was shown in the kidney fibroblast cell line (NRK-49F) that high

phosphate increased fibronectin abundance and the total RNA in a dose-dependent manner. This effect was achieved through the activation of the ERK1/2 and AKT signalling pathways in kidney fibroblasts [85].

An additional mechanism that facilitates the development of fibrosis is the process of EMT. During EMT, cells undergo a transition from a structured, tightly connected epithelial phenotype to a more mobile, fibroblast-like mesenchymal phenotype. EMT plays a pivotal role in this process, contributing to the accumulation of myofibroblasts, which are instrumental in the excessive deposition of extracellular matrix and the subsequent development of tissue scarring and fibrosis. It has been demonstrated that high phosphate levels stimulate transforming growth factor-β (TGF-β) signalling and increased phosphorylated Smad2 and Snail via (ERK) pathways in HEK293 cells [83] (Fig. 3).

Excessive phosphate also activates the Wnt/β-catenin pathway, which is widely associated with the progression of fibrosis in both the kidney and heart. This contributes to the development of cardiorenal syndrome and cardiovascular events [86]. We [8] and others [87] have reported that high levels of phosphate decrease renal Klotho leading to the activation of the Wnt/β-catenin pathway.

HYPERPHOSPHATAEMIA AND FGF23

Phosphate is the main stimulus for the production of FGF23 [3, 88]. It is recognized that from the early stages of CKD, a reduced renal filtration of phosphate causes an increase in the load of phosphate proportional to the loss of renal function. To maintain normal serum phosphate levels, mineral metabolism is regulated through increased concentrations of FGF23 and PTH, alongside a reduction in calcitriol synthesis, which leads to decreased gastrointestinal absorption of phosphate and calcium. Ultimately, the emergence of hyperphosphataemia signifies the inability to further diminish the tubular reabsorption of phosphate per nephron, thereby failing to align with the elevated quantity of phosphate filtered per individual nephron. At this point, hyperphosphataemia manifests, precipitating vascular calcifications and heightened mortality rates.

It is of paramount importance to recognize that in patients with CKD stages 2–4, the disturbances in mineral metabolism that are required to prevent an increase in phosphate, such as increased PTH or FGF23, or decreased calcitriol, can become deleterious. It is therefore important to develop a management strategy to maintain appropriate phosphate levels. In the context of CKD, the cost of maintaining normal phosphate levels is an increase in FGF23 and PTH, and a decrease in calcitriol. These changes are not free of negative cardiovascular and bone effects that ultimately contribute to a reduction in kidney function. For this reason, controlling the phosphate load in the early stages of CKD may be an appropriate strategy.

FGF23 levels begin to increase from the early stages of CKD to facilitate urinary excretion and maintain phosphate levels within the normal range [7]. However, prolonged elevations of FGF23 have also been linked to adverse cardiovascular effects, including left ventricle hypertrophy [89], by vascular damage through the modulation of VSMC contractile phenotype and the promotion of arterial stiffness and vascular fibrosis [90] or by promoting vascular calcification [91–93]. Nevertheless, the relationship between elevated FGF23 levels and the onset of VC remains a topic of debate, as other research has indicated that FGF23 may not be a direct contributor to vascular calcification [94, 95].

HYPERPHOSPHATAEMIA AND OTHER COMPLICATIONS OF CKD

Secondary hyperparathyroidism

Overall, hyperphosphataemia is a key factor in the development of SHPT in CKD. Phosphate stimulates PTH secretion, as evidenced by *in vitro* [5, 96], *in vivo* [97] and clinical studies [98]. It has been shown recently that hyperphosphataemia affects parathyroid function by direct interaction with the CaSR. It was recently discovered that phosphate enhances PTH secretion by stabilizing the inactive conformation of the CaSR, thus preventing its activation by agonists such as calcium. The inhibitory effect of calcimimetics on PTH secretion is only partially impaired by hyperphosphataemia [6]. Therefore, it is necessary to maintain serum phosphate levels within a normal range to sensitize the parathyroid cells to the inhibitory action of CaSR agonists such as calcium or calcimimetics. In the clinical setting, hyperphosphataemia does not predict the efficacy of calcimimetics in controlling PTH secretion [99]. The reduction of calcitriol due to inhibition by the high levels of FGF23 contributes to the development of SHPT and also exacerbates bone resorption, leading to renal osteodystrophy in CKD patients [100].

Bone alterations

Rix and colleagues [101] examined the frequency and severity of skeletal demineralization in patients with mild to moderate renal disease. The findings revealed that both cortical and trabecular bone were affected. In haemodialysis patients, hyperphosphataemia is associated with an increased risk of bone fractures, particularly among those with serum phosphate over 6 mg/dL [102]. In animal models, an analysis of the bone damage induced by hyperphosphataemia demonstrated that the administration of a high phosphate diet accelerates bone loss, with notable alterations in bone microarchitecture, as evidenced by a reduction in trabecular bone volume, trabecular number and trabecular separation [103]. Similarly, mice fed a phosphate-enriched diet exhibited bone abnormalities, including decreased cortical thickness and density, along with increased cortical porosity. These findings align with the characteristics of high-turnover renal osteodystrophy [104]. However, as suggested by Neves *et al.* [56] using parathyroidectomized rats, these bone changes cannot be solely attributed to the effect of high PTH production induced by high phosphate. In these animals, the harmful bone effects induced by hyperphosphataemia were not corrected after PTH replacement [57]. Additionally, high serum phosphate levels may also impact bone health by modulating FGF23 secretion. In this regard, it has been shown that the exacerbated FGF23 production induced by hyperphosphataemia stimulates Dkk1 expression, which in turn inactivates Wnt/β-catening at the bone level, known to modulate bone formation [105].

In sum, these lines of evidence confirm the complexity of the mechanisms by which hyperphosphataemia contributes to CKD-related bone disease. They also highlight the importance of preventing the development of hyperphosphataemia, as these changes can occur even in the early stages of kidney disease.

Hyperphosphataemia and mortality

CKD is considered a major cause of global morbidity and mortality mainly due to its direct impact on cardiovascular health [106]. Mortality rates are particularly elevated in dialysis patients, with age, race, and the presence of other comorbidities

Table 1: Methods to assess urinary phosphate (P) excretion.

	Advantages	Disadvantages	Sensitivity and accuracy for measuring urine P
Urine P excretion (mg/day)	It should match daily intestinal absorption of P	24-h urine collection is required. It does not correlate with total P intake	↑
Fractional excretion of P (FeP) (%)	It is an approximation of the amount of P that is ingested and absorbed	It is necessary to use a formula to calculate it. Not obtained directly from analytics. It shows only the load of P	↑
Urine P excretion/eGFR ratio (mg/day/eGFR)	It reflects the urine P excretion relative to kidney function	24-h urine collection is required. It does not correlate with total P intake	↑
Urine P/creatinine ratio (P/Cr ratio) (mg/mg)	It reflects daily intestinal absorption of P relative to creatinine excretion. It is obtained with the results of routine analysis	It cannot discriminate the origin of P ingested	↑↑
P/UUN ratio (mg/g)	It reflects daily intestinal absorption of P relative to daily amount of absorbed and metabolized protein. It is obtained with the results of routine analysis	Not validated for advance CKD	↑↑↑

exerting a considerable influence [107]. Block and colleagues conducted a comprehensive analysis of the impact of mineral metabolism parameters on the mortality of dialysis patients, identifying evidence-based targets for phosphate, calcium and PTH [108]. The DOPPS (Dialysis Outcomes and Practice Patterns Study) identified a greater risk of mortality with phosphate levels above 7.0 mg/dL [109]. A notable elevation in the risk of mortality from all causes and cardiovascular disease was evident in individuals with serum phosphate levels exceeding 7.5 mg/dL. This study found a 2.24-fold increase in all-cause death and a 2.5-fold increase in the risk of death from cardiovascular causes [110].

Hyperphosphataemia has also been linked to mortality in the earlier stages of CKD. In a prospective study, Eddington *et al*. examined the risk of death in patients with CKD stages 3–4 according to quartiles of baseline serum phosphate. Their findings revealed that patients in the highest quartile exhibited an elevated risk of all-cause and cardiovascular mortality compared with those in the lowest quartile [111]. Likewise, Kestenbaum and colleagues identified a 23% elevated risk of mortality (95% confidence interval 1.12 to 1.36) for each 1 mg/dL increase in serum phosphate in a survival model adjusted for age, renal function, comorbidities, race, gender, haemoglobin and calcium in a large cohort of CKD patients. It is noteworthy that the authors observed a pronounced elevation in serum phosphate levels in the presence of creatinine clearance below 40 mL/min despite phosphate levels remaining within the normal range [112].

The impact of phosphate-lowering therapies on mortality has been the subject of several studies. In the COSMOS Study, the administration of phosphate binders was associated with improved survival outcomes, except for the use of aluminium-based salts [113]. In other studies, the use of non-calcium-based phosphate binders was found to be beneficial in terms of reducing mortality when compared with calcium-based molecules [114]. This beneficial effect has been also observed in CKD patients not yet on dialysis.

Therefore, it seems clear that derangements in phosphate metabolism have a significant impact on mortality in CKD patients, even in the early stages of the disease when serum phosphate levels are still within the normal range. It can thus be concluded that the prevention of hyperphosphataemia through the implementation of appropriate phosphate-lowering strategies may contribute to a reduction in mortality rates within the CKD population.

ASSESSMENT OF INCREASED PHOSPHATE LOAD

Early biomarkers to detect high phosphate intake

At present, there are multiple biomarkers of phosphate overload, which can be categorized as either clinical or non-clinical. The total urinary excretion of phosphorus should be reflective of intestinal absorption. One of the most employed clinical biomarkers is the urine phosphate/creatinine ratio (P/Cr), which is capable of capturing phosphate intake, but the source cannot be identified. A high phosphate intake in patients with CKD stages 2 and 3 maintains a normal serum phosphate level due to an increased tubular load [10]. The methods for the assessment of urinary phosphate excretion are presented in Table 1. Another early clinical biomarker is the phosphate/urinary urea nitrogen ratio (P/UUN), which is capable of detecting an excessive intake of inorganic phosphate relative to that of organic phosphate (Table 1) [17]. The significance of this marker for inorganic phosphate intake lies in the fact that it represents the primary source of highly absorbable phosphate [115, 116]. Even though the amount of phosphate contained in additives is relatively low, it is readily absorbed and excreted in urine. Phosphate-containing additives represent a significant and often overlooked source of phosphate in modern diets [117, 118].

An early non-clinical biomarker of phosphate overload could be FGF23, given that phosphate is its main regulator. MicroRNAs are novel, interesting markers. MiR-21 mediates high phosphate-induced endothelial cell apoptosis, which involves an ERK1/2/microRNA-21/PDCD4 pathway [119]. The miR-125b levels are associated with vascular calcification severity. Similarly, hyperphosphataemia induces a reduction in miR-145 levels and α-actin, both of which are linked to the development of vascular calcifications [120]. This microRNA

could even be considered a novel predictive marker for the risk of uraemia-associated calcification progression [121, 122].

On the other hand, there are clinical markers that have been proposed as a surrogate of phosphate overload. One such marker is the pulse wave velocity (PWV). The IMPROVE-CKD trial was a placebo-controlled, randomized study designed to assess the impact of phosphate reduction on vascular endpoints in patients with CKD stages 3b and 4. The trial investigated the effects of the phosphate binder lanthanum carbonate on intermediate cardiovascular markers of arterial stiffness and vascular calcification. The administration of phosphate binders for 96 weeks did not demonstrate beneficial effects in this endpoint compared with placebo [123]. However, analyses derived from a dietary sub-study of the IMPROVE-CKD trial reported that higher PWV levels were associated with higher intake of plant-based relative to animal-based phosphate intake in CKD patients [124].

Restrictive diets and nutritional risk

The latest KDIGO guidelines recommend a reduction in the consumption of ultra-processed foods and suggest that adults with CKD stages 3–5 maintain a protein intake of 0.8 g protein per kg body weight per day [125]. In patients with CKD, nutritional management should take into account the competing risks between renal disease progression and malnutrition. In patients with stable or slow CKD progression, maintaining a high protein intake may be beneficial, whereas in those with significant progression, protein restriction should be considered if their nutritional status is stable [126]. To avoid the increase in serum phosphate in the initial stages of CKD, our group has underlined the importance of using biomarkers for nutritional intervention [17]. Almost all food contains phosphate, the majority from proteins of animal origin [117]. Traditionally, it has been customary to advise patients with CKD to limit their phosphate intake and consume fewer protein-rich foods. This approach has been associated with a high prevalence of protein malnutrition. Therefore, overly restrictive diets pose a significant nutritional risk for patients with CKD. It is preferable to reduce the intake of inorganic phosphate rather than limiting the intake of phosphate contained in proteins, which are necessary to prevent poor nutrition and muscle wasting. Therefore, protein restriction should not be recommended in patients with an elevated P/UUN ratio; rather, in these patients, protein intake should be preserved, and the easily absorbable inorganic phosphate should be restricted. It is essential to make individualized dietary recommendations to reduce the risk of phosphate-related renal progression while maintaining good nutritional status.

Early initiation of phosphate binders

The prevention of hyperphosphataemia in CKD represents a key priority [127]. A reasonable strategy would be to reduce intestinal absorption of phosphate to decrease phosphaturia and also prevent the development of hyperphosphataemia [10]. It is therefore recommended that therapeutic measures be implemented at the earliest opportunity. Phosphate binders are employed in advanced CKD (stages 4–5) when serum phosphate concentration is already elevated [128]. In patients with non-dialysis CKD, it may be advisable to reduce the phosphate load, even in the presence of normal serum phosphate levels, in order to decrease the demand for PTH and FGF23. This is because both molecules have been demonstrated to have deleterious effects [108]. It has been demonstrated that the administration of the phosphate binder sevelamer in the early stages of CKD reduces phosphate overload, which is accompanied by a reduction in FGF23, PTH, leptin levels and sclerostin levels [129]. In these patients, a reduction in phosphate load may help preserve renal function and prevent the negative consequences of the increase in FGF23 [130].

CONCLUSIONS

A proactive approach to managing phosphate load is imperative to mitigate the risks associated with hyperphosphataemia, including inflammation, vascular calcification, fibrosis and mortality in CKD. Early intervention, before the clinical onset of hyperphosphataemia, may prevent the cascade of complications such as vascular calcifications and SHPT. Addressing elevated phosphate levels at an early stage could markedly reduce disease progression and improve patient outcomes.

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material. No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

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