A Systematic Review on Hyperphosphatemia in Chronic Kidney Disease

Nikunj Rohit, Yukti Patel, Prajwal Waman Ghatol, S P Srinivas Nayak, G.S Chakraborty

ABSTRACT
Chronic Kidney Disease (CKD) is an important global public health problem, as kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. Progressive CKD is linked to several complications with higher prevalence and intensity at lower levels of kidney function, which interact with each other. These complications contribute to high morbidity and mortality and poor quality of life. Hyperphosphatemia is one of the important complications seen in CKD, in this review we are focusing on hyperphosphatemia. In this review describe pathology, clinical presentations and treatment available. Hyperphosphatemia in CKD patients is an important complication of reduced kidney function. It is associated with severe clinical consequences including cardiovascular tissues calcification, bone diseases, and secondary hyperparathyroidism leading to increased cardiovascular diseases and mortality rates. Therefore, dietary phosphate restrictions, adequate dialysis and phosphate binders are usually combined for effective management of hyperphosphatemia.

Keywords: Hyperphosphatemia, chronic kidney disease, complication, phosphate binders.

INTRODUCTION
Chronic Kidney Disease (CKD) is an important global public health problem. More than 2 million people worldwide are estimated to be receiving treatment with dialysis or transplantation for chronic kidney failure, and this population has been growing at an approximate rate of 7% per year. However, poor outcomes from CKD are not limited to kidney failure but also include a wide array of morbidity and mortality related to complications, particularly from decreased kidney function and Cardiovascular Diseases (CVD). The kidney plays a leading role in maintaining calcium and phosphorus homeostasis in association with other organs, i.e., the Parathyroid Gland (PTG), intestines and bones. It is not only the target organ for various hormones, such as Parathyroid Hormone (PTH), but also the principal site for the production of calcitriol (1, 25-dihydroxyvitamin D). Thus, along with the progression of CKD, various abnormalities of mineral and bone metabolism develop, which can result in altered serum minerals. In healthy individuals, mineralization of bone and appropriate blood concentrations of calcium and phosphate are maintained by a complex interplay between three feedback mechanisms. As kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. These include PTH, 25-hydroxyvitamin D (25(OH) D), 1, 25-dihydroxyvitamin D (1, 25(OH) 2D), and other vitamin D metabolites, FGF-23 and growth hormone. Beginning in CKD stage 3, the ability of the kidneys to appropriately excrete a phosphate load is diminished, leading to hyperphosphatemia, elevated PTH, and decreased 1,25(OH)2D with associated elevations in the levels of FGF-23. Therapy is generally focused on correcting biochemical and hormonal abnormalities in an effort to limit their consequences.

COMPLICATIONS OF CKD
Progressive CKD is linked to several complications with higher prevalence and intensity at lower levels of kidney function, which interact with each other. These complications contribute to high morbidity and mortality and poor quality of life. Some of these complications can be readily defined and quantified (cardiovascular disease, hypertension, anaemia, mineral bone disorder, volume overload, electrolytes, and acid-base abnormalities) and may require a specific management approach, for example, the prescription of erythropoiesis-stimulating agents to correct anaemia.

Hypertension
Hypertension remains one of the most damaging complications of CKD and is thought to contribute to the acceleration of progressive decline in kidney function, cardiovascular diseases (CVD), and related mortality. Both
detection and control of high blood pressure is frequently suboptimal and improvements could directly help patients.

**Cardiovascular complications**

CVD represents the leading cause of mortality in CKD patients, and the prevalence and burden of this complication increases with declining kidney function and For example, the risk of mortality from CVD is 8.1-fold greater in a patient with CKD stage G5 A3 (eGFR < 15 ml/min per 1.73 m² and urinary albumin-creatinine ratio > 300 mg/g) than in a reference population without kidney disease. While the risk of conventional atherosclerotic cardiovascular events increases with CKD, the majority of increased risk is attributable to non-atherosclerotic pathologies, such as left ventricular hypertrophy with diastolic and systolic dysfunction, valvular disease, and arterial calcification. These pathologies can manifest as atrial and ventricular dysrhythmias, heart failure, and sudden death.

**Anaemia**

Anaemia complications in CKD patients has been well characterized and treated in many parts of the world with iron and erythropoiesis-stimulating agents (ESAs). However, the optimal doses of ESAs and parenteral iron have not been established. While ESAs can provide symptomatic relief, the impact of these medications on survival remains unclear and may increase cardiovascular and cancer risks. The full spectrum of side effects of ESA is unknown, and the role of high hepcidin in CKD remains inadequately studied.

**Gout and Uremic symptoms**

This is a type of arthritis caused by buildup of uric acid in your joints. Uric acid is filtered through the kidneys, linking the two conditions. The syndrome of uremia encompasses a variety of symptoms: anorexia, fatigue, cachexia, pruritus, nausea, restless leg syndrome, sleep disturbances, and sexual dysfunction.

**CKD-related mineral bone disorder**

The Kidney Disease: Improving Global Outcomes guidelines have defined the CKD-mineral and bone disorder syndrome, which includes traditional mineral biochemical abnormalities, various types of renal bone disease, and soft tissue calcification. It is possible that these abnormalities could be causing left ventricular hypertrophy. However, this group of disorders is not well understood, and although there is a lot of preclinical research on it, there have been very few clinical applications that have been developed. The reduced phosphate excretion which occurs due to impaired renal function leads to retention of phosphate. As a result of that, there is increased secretion of FGF-23 on one hand and impaired synthesis of calcitriol on the other. Decreased synthesis of calcitriol is the result of reduced renal mass, phosphate retention and the effect of increased FGF-23 level. A low level of calcitriol together with retention of phosphate leads to hypocalcaemia.

**Hyperkalemia**

Hyperkalemia is a frequent finding in patients with chronic kidney disease (CKD). This increase in serum potassium levels is associated with decreased renal ion excretion, as well as the use of medications to reduce the progression of CKD or to control associated diseases such as diabetes mellitus and heart failure. Hyperkalemia increases the risk of cardiac arrhythmia episodes and sudden death. Thus, the control of potassium elevation is essential for reducing the mortality rate in this population.

**HYPERPHOSPHATEMIA IN CKD**

**Importance of Hyperphosphatemia**

It is one of the important complication seen in CKD, in this review we are focussing on hyperphosphetemia. Phosphate is an abundant mineral found in the body. The body store of phosphate is 500 to 800g, with 85% of the total body phosphate present in crystals of hydroxyapatite in the bone about 10% found in muscles and bones in association with proteins, carbohydrates, and lipids. The rest gets distributed in various compounds in the extracellular fluid (ECF) and intracellular fluid (ICF). Phosphate is predominantly an intracellular anion. The normal plasma inorganic phosphate (Pi) concentration in an adult is 2.5 to 4.5 mg/dl, and men have a slightly higher concentration than women. In children, the normal range is 4 to 7 mg/dl. A plasma phosphate level higher than 4.5 mg/dL is hyperphosphatemia. Phosphate plays an essential role in many biological functions such as the formation of ATP, cyclic AMP, phosphorylation of proteins, etc. Phosphate is also present in nucleic acids and acts as an important intracellular buffer. Normal adult dietary phosphate intake is around 1000 mg/day. 90% of this is absorbed primarily in the jejunum. In the small intestine, phosphate is absorbed both actively and by passive paracellular diffusion. Active absorption is through sodium-dependent phosphate co-transporter type IIb (NPT2b). Kidneys excrete ninety percent of the daily phosphate load while the gastrointestinal tract excretes the remainder. As phosphorus is not significantly bound to albumin, most of it gets filtered at the glomerulus. Therefore, the number of functional nephrons plays a significant role in phosphorus homeostasis; 75% of filtered phosphorus is reabsorbed in the proximal tubule, approximately 10% in the distal tubule, and 15% is lost in the urine. In the luminal side of the proximal tubule, the primary phosphorus transporter is the Type II Na/Pi cotransporter (NPT-2a). The activity of this transporter is increased by low serum phosphorus and 1,25(OH)2 vitamin D, increasing reabsorption of phosphorus. Renal tubular phosphorus reabsorption also increases by volume depletion, chronic hypocalcemia, metabolic alkalosis, insulin, estrogen, thyroid hormone, and growth hormone. Tubular reabsorption of phosphorus decreases by parathyroid hormone, phosphatins, acidsis,
hyperphosphatemia, chronic hypercalcemia, and volume
expansion. Phosphorus is transported out of the renal cell
by a phosphate-anion exchanger located in the basolateral
membrane. Phosphate homeostasis is under direct
hormonal influence of calcitriol, PTH, and phosphatoninns,
including fibroblast growth factor 23 (FGF-23). Receptors
for vitamin D, FGF-23, PTH, and calcium-sensing receptor
(CaSR) also play an important role in phosphate
homeostasis. Serum phosphate level is maintained
through a complex interaction between intestinal
phosphate absorption, renal phosphate handling, and the
transcellular movement of phosphate that occurs between
intracellular fluid and bone storage pool. A transient shift
of phosphate into the cells is also stimulated by insulin and
respiratory alkalosis.

Etiology of Hyperphosphatemia
Renal failure is the most common cause of
hyperphosphatemia. A glomerular filtration rate of less
than 30 mL/min significantly reduces the filtration of
inorganic phosphate, increasing its serum level. Other less
common causes include a high intake of phosphorus or
increased renal reabsorption. High intake of phosphate can result due to excessive use of phosphate-containing laxatives or enemas, and vitamin D intoxication. Vitamin D increases intestinal phosphate absorption. Hypoparathyroidism, acromegaly, and thyrotoxicosis enhance renal phosphate reabsorption resulting in hyperphosphatemia. Hyperparathyroidism can also be due to genetic causes. Several genetic deficiencies can lead to hypoparathyroidism, pseudohypoparathyroidism, and decreased FGF-23 activity. Pseudohyperphosphatemia is a laboratory artifact sometimes seen in patients with hyperglobulinemia, hyperlipidemia, and hyperbilirubinemia. This artifact is due to interference in phosphate assay.

Pathophysiology of Hyperphosphatemia in Chronic
Kidney Disease-Mineral Bone Disorder
Serum phosphorus balance is dependent on the
contribution of dietary phosphate absorption in the
intestine, glomerular filtration, and tubular excretion and
reabsorption in the kidney, and a balance between bone
formation and resorption. As part of the normal
physiological process, these mechanisms work in tandem
to maintain serum phosphorus within a tight range (3.0–4.5 mg/dL in adults). Renal adaptation to changes in dietary phosphate intake is rapid, thus maintaining net phosphate balance. During the early stages of kidney failure, decreased renal phosphate excretion (with associated increases in serum phosphate levels) coupled with reductions in the renal synthesis of active vitamin D3 (with associated decreases in vitamin D-mediated calcium uptake from the intestine) results in elevated levels of serum phosphorus and lowered levels of serum calcium. Hypocalcemia is the main trigger of parathyroid gland PTH
synthesis and release, which in turn increases calcium
release from bone and renal phosphate excretion. FGF-
23, secreted by cells in the bone in response to rising
phosphorus, acts to increase excretion of phosphate by
the kidney, but has an inhibitory effect on active vitamin D
synthesis, further exacerbating disturbances in bone and
mineral metabolism. Together, these compensatory
actions are an adaptive response to maintain the
physiology of mineral homeostasis within normal levels.
With CKD progression, phosphorus handling by the
intestine, kidney, and bone becomes increasingly
dysregulated, and the adaptive response becomes
maladaptive. As the loss of renal function becomes more
severe, vitamin D levels become clinically deficient and
renal phosphorus excretion is increasingly impaired, with
exacerbation of the phosphorus and calcium imbalances
and elevations in PTH levels, leading eventually to SHPT.
Elevated PTH levels in SHPT increase bone turnover and
resorption, which releases phosphorus, reduces the
phosphorus reservoir capacity of the skeleton, and
contributes to fracture and bone pain in patients with CKD-
MBD. Eventually, regardless of the levels of PTH and
FGF-23, the kidney can no longer excrete sufficient
phosphorus to maintain homeostasis, resulting in
hyperphosphatemia.

Figure 1: A simplified overview of disordered mineral
metabolism in CKD-MBD.

The decline in kidney function with disease progression
leads to increased retention of phosphorus. Patients with
CKD-MBD have impaired renal synthesis of active vitamin
D, essential for GI calcium absorption. Decreased GI
absorption of calcium can lead to hypocalcaemia, which
signals the parathyroid glands to secrete PTH. High PTH
then triggers increased reabsorption of calcium (an
adaptive response to rebalance low calcium) and
phosphorus from bone. This maladaptive response
leads to greater progression of CKD-MBD. CKD-MBD, chronic
kidney disease-mineral bone disorder; GI, gastrointestinal;
PTH, parathyroid hormone; Vit D, active vitamin D.

Excessive retention of phosphate in the body can cause a
wide range of conditions, such as vascular calcification,
impaired bone mineralization, and dysregulated cell
signalling and cell death. Although less than 5% of people
with normal kidney function or those in CKD stages 1 and
2 exhibit hyperphosphatemia, the prevalence increases in
CKD stage 3b (estimated glomerular filtration rate [eGFR]
# 44 mL/minute/1.73 m2 ) and becomes incrementally

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higher in stages 4 (eGFR 15–29 mL/minute/1.73 m²) (20%) and 5 (eGFR, 15 mL/minute/1.73 m²) (40%)20. By the time a patient receives dialysis, they are highly likely to be hyperphosphatemic. Several studies have demonstrated associations between disturbances in mineral metabolism and adverse CV and mortality outcomes in CKD patients, particularly in cases of elevated serum phosphorous levels22. In a meta-analysis of cohort studies (N 5 25,546 non-dialysis–dependent CKD patients), every 1 mg/dL increase in serum phosphorous was shown to be associated with increased risk of both kidney failure (hazard ratio 5 1.36) and mortality (hazard ratio 5 1.20)21. A systematic review of 47 cohort studies (N 5 327,644 CKD patients) linked higher serum phosphorous levels with mortality and observed that the risk of death increased by 18% for every 1 mg/dL increase in serum phosphorous24. Although there is some evidence linking elevated serum phosphorous with adverse outcomes in CKD patients, high-quality clinical evidence supporting an ideal target range is lacking. The ongoing pragmatic, multicenter Pragmatic Trial of Higher vs Lower Serum Phosphate Targets in Patients Undergoing Haemodialysis trial (NCT04095039) aims to assess the optimal serum phosphorous range and compares all-cause hospitalization and mortality rates between patients assigned to the experimental Hi arm (phosphorus $ 6.5 mg/dL) or standard of care Lo arm (phosphorus, 5.5 mg/dL)25.

Treatment / Management of Hyperphosphatemia

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the management of hyperphosphatemia suggest that, in dialysis patients, phosphate levels require lowering toward the normal range; however, there is no given specific target level. In chronic kidney disease patients not receiving dialysis, serum phosphate levels require maintenance in the normal range (i.e., under 4.5 mg/dL [1.45 mmol/L]). There are several strategies to control phosphate levels26.

**Acute hyperphosphatemia**

If renal function is good, renal phosphate excretion can increase through extracellular volume expansion by saline infusion and diuretics.

**Dietary Restriction**

Dietary restriction of phosphate is effective both in predialysis and in dialysis patients. KDIGO recommends a daily phosphate intake of 800 to 1000 mg/d with a daily protein intake of 1.2 g/kg body weight. Also, it is reasonable to consider phosphate sources (e.g., animal, vegetable, additives) in making dietary recommendations. Severe protein restriction can cause malnutrition and, eventually, poorer outcomes26. If renal function is impaired, it is an indication for hemodialysis. The drugs used in hyperphosphatemia are described in (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Description of Drugs used in Hyperphosphatemia</th>
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<td><strong>Drugs</strong></td>
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<tr>
<td><strong>Phosphate Binders</strong></td>
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<td><strong>Calcium-based binders</strong></td>
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<td><strong>Magnesium carbonate</strong></td>
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<td><strong>Sevelamer</strong></td>
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<td><strong>Lanthanum Carbonate</strong></td>
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<td><strong>Ferric Citrate</strong></td>
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Drugs targeting intestinal phosphate transporters:

Phosphate is absorbed in the small intestine by at least two distinct mechanisms: paracellular phosphate transport which is dependent on passive diffusion and active transport which occurs through the sodium-dependent phosphate co-transporters. The drugs are described in (table.2).

Table 2: Drugs targeting intestinal phosphate transporters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
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<td>Nicotinic Acid and Nicotinamide</td>
<td>These drugs lower sodium-dependent intestinal phosphate absorption via a reduction in NaPi2b expression. The degree of reduction is modest. Adverse effects included flushing, nausea, diarrhea, thrombocytopenia, and accumulation of potentially toxic metabolites.</td>
</tr>
<tr>
<td>Tenapanor</td>
<td>Tenapanor inhibits sodium/hydrogen ion-exchanger isoform 3 (NHE3), which plays a role in secondary active phosphate absorption. It thus reduces intestinal sodium and phosphate absorption.</td>
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Renal replacement Therapies:

Both peritoneal and hemodialysis remove phosphate, but the amount of phosphate absorbed from a normal diet is for more than that removed by any of these dialysis methods. Recommendations are for more intensive dialysis to improve phosphate removal.

Management of Secondary Hyperparathyroidism:

For better control of hyperphosphatemia, control of secondary hyperparathyroidism is essential, using vitamin D metabolites and the calcium-sensing receptor agonists. Calcitriol or synthetic vitamin D analogs should not be given unless the serum phosphate concentration is < 5.5 mg/dL and the serum calcium is less than 9.5 mg/dL, as these agents can increase the serum calcium and phosphate, leading to metastatic and vascular calcification in patients with hyperphosphatemia before treatment. For all dialysis patients, the target serum levels of phosphate should be between 3.5 and 5.5 mg/dL (1.13 to 1.78 mmol/L). Serum levels of corrected total calcium should be maintained lower than 9.5 mg/dL (less than 2.37 mmol/L). The values of the parathyroid hormone (PTH) should remain less than two to nine times the upper limit for the PTH assay.

DISCUSSION

Normal adult dietary phosphate intake is around 1000 mg/day. 90% of this is absorbed primarily in the jejunum. In the small intestine, phosphate is absorbed both actively and by passive paracellular diffusion. Active absorption is through sodium-dependent phosphate co-transporter type IIb (NPT2b). Reducing the daily phosphate intake in diet can be challenging as it is usually incompatible with the recommended daily protein intake of 1.0–1.2 g/kg/day. Dialysis is the cornerstone of homeostatic electrolyte management for end stage renal disease patients. However, the currently available dialysis techniques are usually ineffective in removing excess phosphate to the degree of normalising phosphate concentration since the rate of transfer of phosphate from the intracellular pool to the extracellular pool is relatively slow, dialysis treatments even when combined with dietary phosphate restriction are usually ineffective in managing hyperphosphatemia. Most dialysis patients require phosphate binders to control their hyperphosphatemia. Shama AM, Kowalski SR et al in their study entitled “Hyperphosphatemia Management in Patients with Chronic Kidney Disease” concluded that Hyperphosphatemia in CKD patients is an important complication of reduced kidney function. It is associated with severe clinical consequences including cardiovascular tissues calcification, bone diseases, and secondary hyperparathyroidism leading to increased cardiovascular diseases and mortality rates. Therefore, dietary phosphate restrictions, adequate dialysis and phosphate binders are usually combined for effective management of hyperphosphatemia Kidneys excrete ninety percent of the daily phosphate load while the gastrointestinal tract excretes the remainder. The kidney is a vulnerable organ as well as the most important target of microvascular damage in both type 1 (TIDM) and type 2 diabetes mellitus (T2DM) due to hyperphosphatemia.

As phosphorus is not significantly bound to albumin, most of it gets filtered at the glomerulus. Therefore, the number of functional nephrons plays a significant role in phosphorus homeostasis; 75% of filtered phosphorus is reabsorbed in the proximal tubule, approximately 10% in the distal tubule, and 15% is lost in the urine. In the luminal side of the proximal tubule, the primary phosphate transporter is the Type II Na/Pi co-transporter (NPT-2a). The activity of this transporter is increased by low serum phosphorus and 1,25(OH)2 vitamin D, increasing reabsorption of phosphorus. Renal tubular phosphorus reabsorption also increases by volume depletion, chronic hypocalcemia, metabolic alkalosis, insulin, estrogen, thyroid hormone, and growth hormone. Vitamins such as Vitamin D that are fat soluble, because of their potential to aggregate within the body, have a higher potential to cause toxicity than vitamins that are water soluble. Tubular reabsorption of phosphorus decreases by parathyroid hormone, phosphatidins, acids, hyperphosphatemia, chronic hypercalcemia, and volume expansion. Hruska KA, Mathew S et al has conducted a
study entitled “Hyperphosphatemia of chronic kidney disease” concluded that Hyperphosphatemia in CKD represents a signal that heterotropic sites of mineralization are being used to compensate for the failure of reservoir function of the skeleton in positive phosphate balance. In fact, hyperphosphatemia itself is one of the signals activating heterotropic deposition sites, and functions as a signaling molecule in stimulating atherosclerotic neointimal mineralization that is markedly increased in CKD. Unique features of hyperphosphatemia in CKD, especially the failure of the skeletal reservoir function, qualify it as a distinct syndrome characterized by phosphate excretion failure, contribution of the skeleton to hyperphosphatemia, heterotropic mineralization including the vasculature, and severe cardiovascular disease leading to morbid cardiac events and often to demise. Regular monitoring of health is necessary for healthy people as well as for those suffering from any medical condition—to keep tabs on their current condition and beware of any future health risk.

CONCLUSION

Hyperphosphatemia in CKD patients is an important complication of reduced kidney function. It is associated with severe clinical consequences including cardiovascular tissue calcification, bone diseases, and secondary hyperparathyroidism leading to increased cardiovascular diseases and mortality rates. Therefore, dietary phosphate restrictions, adequate dialysis and phosphate binders are usually combined for effective management of hyperphosphatemia. However, attainment of phosphate control targets is difficult and may not be achieved in many patients. The efficacy of phosphate binders, especially calcium carbonate, may be influenced by the co-administration of acid suppressant drugs and thus, clinicians should be aware of the potential of such interaction and review all CKD patients for inappropriate use of acid suppressive medications.

REFERENCES


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