



A Systematic Review on Hyperphosphatemia in Chronic Kidney Disease

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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.

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INTRODUCTION

Chronic Kidney Disease (CKD) is an important global public health problem¹. 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 year² 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)³ 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 minerals⁴. In healthy individuals, mineralization of bone and appropriate blood concentrations of calcium and phosphate are maintained by a complex interplay between three feedback mechanisms⁵. 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 consequences⁶.

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 anemia⁷.

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 patients⁸.

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 death⁹.

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 studied¹⁰.

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 dysfunction¹¹.

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 hypocalcaemia¹².

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 population¹³.

HYPERPHOSPHATEMIA IN CKD

Importance of Hyperphosphatemia

It is one of the important complication seen in CKD, in this review we are focussing on hyperphosphatemia. 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 remainder¹⁴. 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 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. Tubular reabsorption of phosphorus decreases by parathyroid hormone, phosphatonins, acidosis,



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 phosphatonins, 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 alkalosis¹⁴.

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 reabsorption¹⁵. 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. Hyperphosphatemia 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 assay¹⁵.

Pathophysiology of Hyperphosphatemia in Chronic Kidney Disease-Mineral Bone Disorder

Serum phosphorus balance is dependent on the contribution of dietary phosphorus 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 phosphorus excretion (with associated increases in serum phosphorus 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 excretion¹⁶. FGF-23, secreted by cells in the bone in response to rising

phosphorus, acts to increase excretion of phosphorus 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 SHPT¹⁷. 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^{18,19}. Eventually, regardless of the levels of PTH and FGF-23, the kidney can no longer excrete sufficient phosphorus to maintain homeostasis, resulting in hyperphosphatemia²⁰ (Fig. 1)

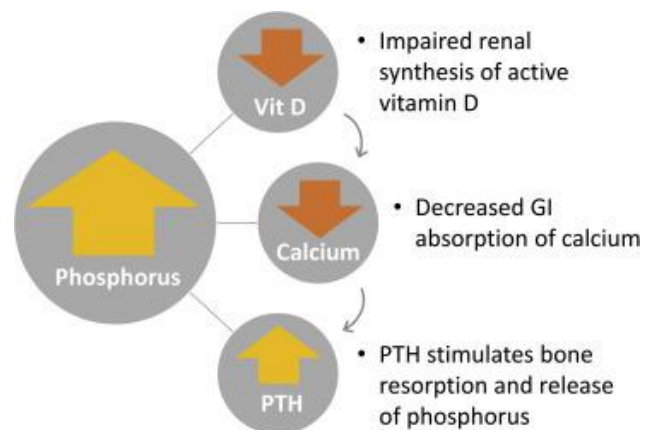


Figure 1: A simplified overview of disordered mineral metabolism in CKD-MBD.

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, over time, drives 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 death²¹. 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

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)²³. 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 \geq 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 1: Description of Drugs used in Hyperphosphatemia

Drugs	Information
Phosphate Binders	<p>In patients with persistently or progressively elevated phosphate despite dietary phosphate restriction, phosphate binders are the agent of choice. These are also used, concurrently with dietary restriction, when phosphate levels at presentation are very high (greater than 6 mg/dl).</p> <p>Phosphate binders reduce the absorption of dietary phosphate in the gastrointestinal tract, by exchanging the anion phosphate with an active cation (carbonate, acetate, oxyhydroxide, and citrate) to form a nonabsorbable compound that gets excreted in the feces.</p> <p>Aluminum-based agents are amongst the most effective and best tolerated. But doubts regarding their potential to cause aluminum toxicity, presenting with encephalopathy, osteomalacia, microcytic anemia, and premature death, have discouraged their prolonged use.</p>
Calcium-based binders	<p>Calcium-based binders (e.g., calcium carbonate and calcium acetate) are effective and do not have adverse effects associated with aluminum-based agents. However, they can lead to a positive calcium balance, which can aggravate the development of ectopic calcification in the media and intima of arterial vessels, a major contributing factor for the excess cardiovascular mortality observed in CKD patients.</p>
Magnesium carbonate	<p>Magnesium carbonate effectively reduces serum phosphate levels and shows good gastrointestinal tolerance. It also reduces vascular calcification by interfering with hydroxyapatite formation.</p>
Sevelamer	<p>Sevelamer is a crosslinked polymer that exchanges phosphate with HCl or carbonate in the gastrointestinal tract. The phosphate-laden polymer gets excreted in the feces. Both sevelamer hydrochloride (HCl) and sevelamer carbonate are options. Besides controlling hyperphosphatemia, sevelamer also improves endothelial function, binds bile salts, resulting in a significant reduction in serum total cholesterol and low-density lipoprotein cholesterol. However, this action may interfere with the absorption of fat and fat-soluble vitamins.</p>
Lanthanum Carbonate	<p>It is a chewable, calcium-free phosphate binder, which uses metal lanthanum for phosphate chelation. Lanthanum carbonate binds phosphate to form the nonabsorbable compound lanthanum phosphate.</p>
Ferric Citrate	<p>Ferric citrate exchanges citrate with phosphate in the gastrointestinal tract to form ferric phosphate, which is insoluble and excreted in the feces. An additional advantage of ferric citrate is that it increases</p>



	serum ferritin, reducing the need for intravenous iron and erythropoietin stimulating agents in chronic kidney disease.
Sucroferric Oxyhydroxide	Sucroferric oxyhydroxide is a chewable, iron-based phosphate binder. A lower dose helps in better compliance. As iron gets excreted as part of the phosphate complex, it does not cause iron overload.

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

Nicotinic Acid and Nicotinamide	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.
Tenapanor	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.

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 removal²⁷.

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 assay²⁸.

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/day²⁹. 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, [30] dialysis treatments even when combined with dietary phosphate restriction are usually ineffective in managing hyperphosphatemia. Most dialysis patients require phosphate binders to control their hyperphosphatemia³⁰. Shaman 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 (T1DM) and type 2 diabetes mellitus (T2DM) due to hyperphosphatemia³¹.

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 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 soluble³². Tubular reabsorption of phosphorus decreases by parathyroid hormone, phosphatonins, acidosis, 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 heterotopic 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 heterotopic 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, heterotopic 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 risk³³.

CONCLUSION

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. 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

1. Levey, A. S., Atkins, R., Coresh, J., et al. “Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes.” *Kidney International*, 2007;72:247–59.
2. Lysaght, M. J. “Maintenance dialysis population dynamics: current trends and long-term implications”, *Journal of the American Society of Nephrology*, 2002;1(3):S37– 40.
3. Ashish Upadhyay, Lesley A. Inker, and Andrew S. Levey “Oxford Textbook of Clinical Nephrology”, Fourth Edition, Published by: Oxford Publications, 2016:743, 755.
4. Hirota Komaba, Motoko Tanaka and Masafumi Fukagawa “Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)”, *Internal Medicine*, 2008;47:989-994.
5. Shigematsu T, Kazama JJ, Yamashita T, et al. “Possible involvement of circulating fibroblast growth factor 23 in the development of secondary hyperparathyroidism associated with renal insufficiency”, *American Journal of Kidney Diseases*, 2004;44:250–256.
6. Kristine S. Schonder “Pharmacotherapy Principles and Practice”, Published by: The McGraw-Hill Companies, 2008; 373,374 and 377.
7. Fox C.S., Matsushita K., Woodward M. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380:1662–1673.
8. Muntner P., Anderson A., Charleston J. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2010;55:441–451.
9. Wanner C., Amann K., Shoji T. The heart and vascular system in dialysis. *Lancet*. 2016;388:276–284.
10. Panwar B., Gutierrez O.M. Disorders of iron metabolism and anemia in chronic kidney disease. *Semin Nephrol*. 2016;36:252–261.
11. Urquhart-Secord R., Craig J.C., Hemmelgarn B. Patient and caregiver priorities for outcomes in hemodialysis: an international nominal group technique study. *Am J Kidney Dis*. 2016;68:444–454.
12. Syed Irfan Ali Ahmed, S.P.Srinivas Nayak, K.R.Madhuri, B.Jyothi, K.Umamaheshwar Rao, V.Kiranmayi, V.Siva Kumar a study on pharmacological management of mineral bone disease in chronic kidney disease patients in a tertiary care hospital, *ijsr*, 2018;9(11):201-206.
13. Watanabe R. Hyperkalemia in chronic kidney disease. *Rev Assoc Med Bras* (1992). 2020 Jan 13;66Suppl 1(Suppl 1):s31-s36. doi: 10.1590/1806-9282.66.S1.31.
14. Fukumoto S, Phosphate metabolism and vitamin D. *BoneKEY reports*. 2014.
15. Thongprayoon C, Cheungpasitporn W, Mao MA, Sakhuja A, Erickson SB. Admission hyperphosphatemia increases the risk of acute kidney injury in hospitalized patients. *J Nephrol*. 2018 Apr;31(2):241-247.
16. Beto J, Bhatt N, Gerbeling T, Patel C, Drayer D. Overview of the 2017 KDIGO CKD-MBD update: practice implications for adult hemodialysis patients. *J Ren Nutr*. 2019;29:2-15.
17. Goodman WG. The consequences of uncontrolled secondary hyperparathyroidism and its treatment in chronic kidney disease. *Semin Dial*. 2004;17:209-216.
18. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* (2011). 2017;7:1-59.
19. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2006;69:1945-1953.
20. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int*. 2007;71:31-38.
21. Razzaque MS. Phosphate toxicity: new insights into an old problem. *Clin Sci (Lond)*. 2011;120:91-97.



22. Covic A, Kothawala P, Bernal M, Robbins S, Chalian A, Goldsmith D. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. *Nephrol Dial Transpl.* 2009;24:1506-1523.
23. Da J, Xie X, Wolf M, et al. Serum phosphorus and progression of CKD and mortality: a meta-analysis of cohort studies. *Am J Kidney Dis.* 2015;66:258-265.
24. Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA.* 2011;305:1119-1127.
25. HiLo: Pragmatic trial of higher vs lower serum phosphate targets in patients undergoing hemodialysis. <https://clinicaltrials.gov/ct2/show/NCT04095039>. Accessed December 24, 2019.
26. Beto J, Bhatt N, Gerbeling T, Patel C, Drayer D, Overview of the 2017 KDIGO CKD-MBD Update: Practice Implications for Adult Hemodialysis Patients. *Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation.* 2019 Jan [PubMed PMID: 30150095].
27. Barreto FC, Barreto DV, Massy ZA, Drüeke TB, Strategies for Phosphate Control in Patients With CKD. *Kidney international reports.* 2019 Aug [PubMed PMID: 31440695].
28. Monge M, Shahapuni I, Oprisiu R, El Esper N, Morinière P, Massy Z, Choukroun G, Fournier A, Reappraisal of 2003 NKF-K/DOQI guidelines for management of hyperparathyroidism in chronic kidney disease patients. *Nature clinical practice. Nephrology.* 2006 Jun [PubMed PMID: 29415048].
29. National Kidney Foundation 2000. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am. J. Kidney Dis.,* 35, S1–140.
30. Desoi C.A., Umans J.G. Phosphate kinetics during high-flux hemodialysis. *J. Am. Soc. Nephrol.* 1993;4:1214–1218.
31. Raj S. Baldha, S P SRINIVAS NAYAK, Maulik Kamleshbhai Pandya, Mohit Buddhadev, & Gunosindhu Chakraborty. (2021). Different Metabolic Pathways in Diabetic Kidney Disease and Recent Advances in Slowing Disease Progression. *European Journal of Pharmaceutical and Medical Research,* 2021;8(11): 269–276. <https://doi.org/10.5281/zenodo.5641313>
32. Jason Samuel Muthyala, Pharmd, Afreen Patan, Pharmd, S K Vandana, Pharmd, S.P.Srinivas Nayak 'a case report with ckd and hypervitaminosis d' in international journal dental and medical sciences, 2020;2(2):86-90. DOI: 10.35629/5252-02028690,
33. Twinkle Rathod, Vraj Patel, Mohit Buddhadev, S P Srinivas Nayak, Gunosindhu Chakraborty. "a case report on septic acute kidney injury with recently diagnosed hypothyroidism, hypertension, *Tinea corporis* and *Tinea cruris*." *IJCRT,* 2022; 10(1):b76-b82.

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