Phosphate, Chronic Kidney Disease and Cardiovasular Disease: Friends or Foe?

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Overview

Phosphorus is essential for life and exists in the body as phosphate. It is mainly intracellular (70%), about 29% resides in the bones and less than 1% circulates in the serum. Phosporous balance is regulated by kidneys (Figure 1A). It is filtered freely in the glomerulus and then it is reabsorbed in the proximal tubule under the effect of various hormones. The amount of reabsorbed phosphorus is the main regulator of the serum phosphorus levels in subjects with normal renal function, or moderately reduced glomerular filtration rate. Despite its importance, the accumulation of phosphate can produce deleterious effects. In Chronic Kidney Disease (CKD) the kidneys fail to excrete the phosphorus and the result is a positive phosphorus balance. However, the skeleton through the disorders of the bone that accompany CKD, contributes to this hyperphosphatemic state as it cannot handle the phosphorus excess. This leads to a need for new phosphorus reservoir and this is soft tissue organs including vasculature.[1] The final result is vascular calcification that is frequently observed in end stage renal disease. The vascular and valvular calcifications are predictors of cardiovascular diseases and mortality in patients with chronic renal failure.[2] To consider the pathogenesis of hyperphosphatemia in CKD, it is useful to understand the mechanisms of phosphate homeostasis in normal physiological conditions, along with the pathologic processes related to altered phosphate balance which conspire to result in more accentuated kidney damage and increased cardiovascular mortality and morbidity.

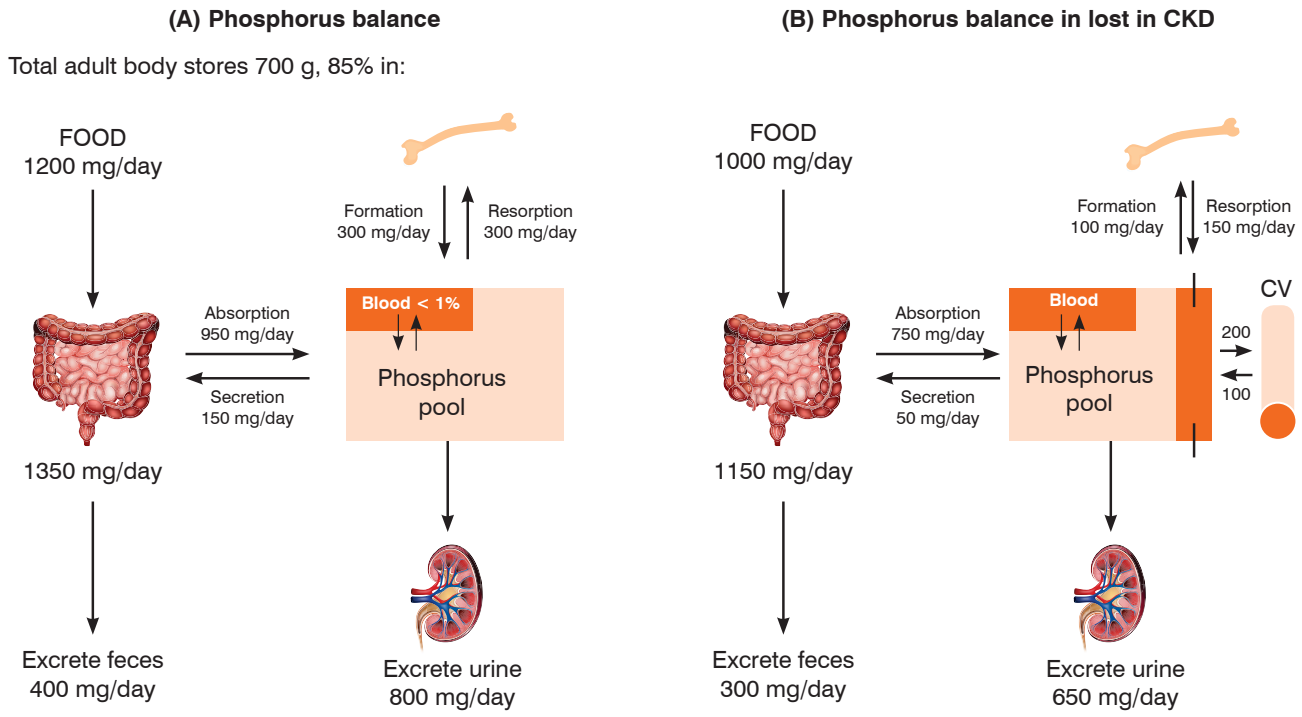
Phosphate Homeostasis in CKD

Serum phosphorus levels stay relatively constant through the influence of multiple factors such as parathyroid hormone, fibroblast growth factor 23, and vitamin D on the kidney, bone, and digestive system. Normal serum phosphorus ranges between 3 mg/dL to 4.5 mg/dL. However, evidence suggests that people with normal kidney function may sometimes have phosphate levels ranging between 1.6 mg/dL and 6.2 mg/dL.[3] Phosphate balance is maintained by regulation of its excretion by the kidney in normal day to day life. Kidney injury impairs the ability to maintain phosphorus balance, and in CKD, phosphorus homeostasis is lost and positive phosphate balance occurs in the later stages (4 and 5) of CKD. Loss of phosphorus homeostasis due to excretion failure in chronic kidney disease results in hyperphosphatemia (Figure 1B). Despite reductions in the fraction of filtered phosphorus that is reabsorbed, eventually the filtered load becomes insufficient to maintain homeostasis, and positive phosphorus balance ensues. Kidney disease decreases the exchangeable phosphorus pool size by inhibiting bone formation. The skeletal mineralization fronts at the sites of new bone formation are significant components of the exchangeable phosphorus pool. Positive phosphate balance is associated with establishment of heterotopic mineralization sites in soft tissue organs and the vasculature. Exit from the exchangeable phosphorus pool into the vasculature is portrayed as a bidirectional process because it has been demonstrated that stopping the exit into the vasculature results in diminishment of established vascular calcification levels.[4]

Phosphate and Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in CKD patients. Moreover, CVD often begins before end-stage renal disease (ESRD), and patients with reduced renal function are more likely to die of CVD than to develop ESRD. There are 3 pathological forms of CVD that should be considered in patients with CKD: alterations in cardiac geometry, including left ventricular hypertrophy, atherosclerosis, and arteriosclerosis. The clinical interventions on traditional and nontraditional risk factors for CVD were not as effective as in the general population; mainly because of the unique CKD setting.[5] Furthermore, hyperphosphatemia is a serious complication in late-stage

Figure 1: Potassium balance in normal physiology (A) and in chronic kidney disease (B)

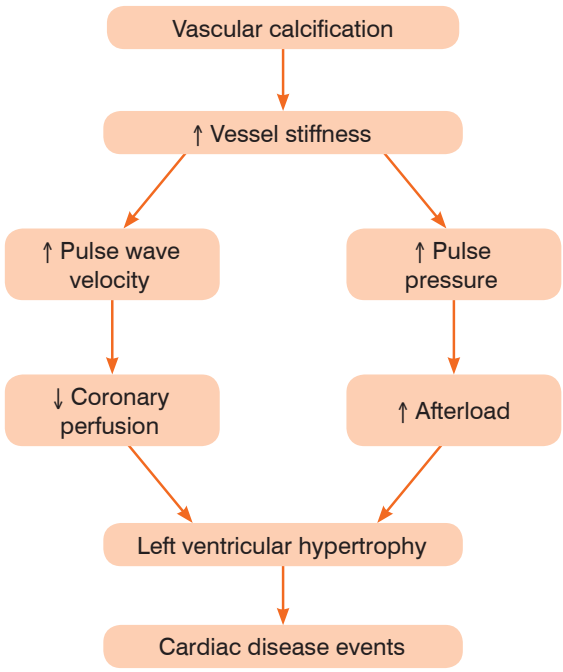


Adapted from: Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of Chronic Kidney Disease. *Kidney Int.* 2008;74(2):148-157.

CKD, and a well known association exists between hyperphosphatemia and cardiovascular disease in patients undergoing dialysis. The increased morbidity and mortality resulting from cardiovascular disease are associated with vascular calcification in these patients (Figure 2). There are two forms of vascular calcification prominent in CKD, calcification of atherosclerotic neointimal plaques and arterial medial calcification. CKD markedly stimulates both forms. The atherosclerotic calcification is especially appreciated in the coronary arteries as it is measured by the increasingly popular imaging techniques for determining coronary artery calcification. However, arterial medial calcification is as clinically important, as it is the likely the most important factor in vascular stiffness and increased pulse pressure in CKD.[4] Evidence suggests that phosphorous is an important component of the action of CKD to stimulate atherosclerotic calcification, and a signaling molecule serving to complete osteoblastic differentiation in the aorta. Thus, phosphorus is more than a stimulator of vascular calcification acting through an elevated calcium-phosphorus product in CKD and ESRD.[4]

It is incumbent upon the entire healthcare community to aim at therapeutic strategies which may help abate the catastrophic effects of hyperphosphatemia in patients with CKD.

Figure 2: Vascular calcification causes cardiac morbidity and mortality in chronic kidney disease



Adapted from: Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of Chronic Kidney Disease. *Kidney Int.* 2008;74(2):148-157.

Controlling Serum Phosphorus in CKD

The importance of controlling phosphate load remains the primary goal in treatment of CKD. Although treatment of phosphate retention is generally initiated after the development of hyperphosphatemia, it has been suggested that it may be important to treat phosphate retention at earlier stages of CKD to maintain near–normal phosphorus levels as long as possible as CKD advances.[6]

Controlling Serum Phosphorus in Predialysis CKD

Therapeutic approaches aiming at phosphate lowering (i.e., serum levels as well as phosphate load) include reducing oral intake of phosphate by dietary modifications as well as intestinal absorption using phosphate binders. Recommendations for the management of phosphate in predialysis patients by KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)[7] are as following:

- In patients with CKD stages 3–5, it was suggested to maintain serum phosphorus in the normal range
- In patients with CKD stages 3–5 and 5D, it was suggested to use phosphate binding agents in the treatment of hyperphosphatemia
- In patients with CKD stage 3–5D and hyperphosphatemia, it was recommended to restrict the dose of calcium-based phosphate binder and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia
- In patients with CKD stage 3–5D and hyperphosphatemia, it was suggested to restrict the dose of calcium-based phosphate binders in the presence of arterial calcification and/or adynamic bone disease and/or if serum PTH levels are persistently low
- In patients with CKD G3a–G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate
- In patients with CKD stages 3–5D, it was suggested to limit dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments.[7]

Controlling Serum Phosphate Levels in Dialysis Patients

Clinicians play a key role in diligent assessment of the altered phosphate levels and using a therapeutic strategy to alleviate the deleterious effects of hyperphosphatemia in dialysis patients. The clinical approach directed towards controlling serum phosphate levels in dialysis patients includes: (1) removal of ultrafilterable and diffusible phosphorus with dialysis, (2) restriction of dietary phosphate intake, and (3) use of orally administered phosphate binders to limit the absorption from the intestinal contents of ingested phosphate. Despite these efforts, serum phosphate levels in one-third to one-half of all patients on dialysis run higher than 5.5 mg/dL. While this is often attributed to patient nonadherence, there are a number of other factors contributing to persistent hyperphosphatemia in dialysis patients.[3]

However, novel approaches are being explored, such as inhibition of intestinal transport pathways, that may prove beneficial for improving serum phosphate control and hopefully reduce cardiovascular mortality.

Conclusion

Chronic kidney disease (CKD) is a global health burden and is independently associated with increased cardiovascular disease risk. Hyperphosphatemia is associated with mortality in patients with chronic kidney disease. In addition, phosphate overload and hyperphosphatemia have emerged as risk factors for vascular calcification, cardiovascular mortality, left ventricular hypertrophy and progression of chronic kidney disease. One of the unique features of hyperphosphatemia in CKD is the failure of the skeletal reservoir function. This feature 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. Management of hyperphosphatemia in patients with end-stage disease includes maintaining normal serum phosphorus requires dietary restrictions, phosphate-binding medications, and dialysis. However, normal serum phosphorus remains elusive in many patients with Stage 5 kidney disease. Thus, researchers are testing novel targets that may inhibit intestinal transport of phosphorus to achieve better phosphate control. Protecting and monitoring bone health should also aid in controlling serum phosphorus as kidney disease advances.

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A Case of Diuretic-Induced Hypokalemia Managed with Potassium Citrate

Case Presentation

A 56-year-old woman presented to the outpatient department with complaints of frequent muscle cramps, malaise and generalized weakness since past 2 months. She was a known case of hypertension for past 10 years for which she was taking chlorthalidone 25 mg/day. She also had history of diabetes since past 4 years for which she was taking metformin 500 mg/day. She worked as a professor and retired 2 years back. She was non-smoker and denied any history of alcohol intake. Her family history was positive for hypertension. Her father had hypertensive kidney disease.

Clinical examination

- Upon examination, she was well oriented to time, place and person
- Body mass index (BMI): 30 kg/m^2
- Vitals: Temperature–98.6°F; Pulse rate–80/minute; Normal rhythm and tone; Respiratory rate–15 breaths/minute
- General physical examination:
  - Blood pressure (BP)- 160/90 mmHg
  - Pallor negative, icterus negative, no edema, JVP not raised; no carotid bruit could be auscultated
- Systemic examination:
  - CVS examination: Normal
  - CNS examination: Normal
  - Chest examination: Normal
  - Abdominal examination: Normal

Laboratory Investigations

- HbA1c: 7%
- Lipid profile:
  - Total cholesterol: 180 mg/dL
  - High-density lipoprotein cholesterol: 60 mg/dL
  - Low-density lipoprotein cholesterol: 150 mg/dL
  - Triglycerides: 150 mg/dL
- Kidney function tests:
  - Serum creatinine: 0.8 mg/dl
  - Blood urea nitrogen: 14.31 mg/dl
  - Calcium: 9.96 mg/dl
  - Serum sodium: 140 mEq/L
  - Serum potassium: 3 mEq/L (Decreased)
- Electrocardiogram (ECG): No changes detected
- Chest X-ray: Normal

Diagnosis

Based on investigation findings, she was suspected to have chlorthalidone-induced hypokalemia.

Management

She was suggested to adopt lifestyle modifications in the form of regular exercise along with dietary modifications involving reduced salt intake and increased consumption of fruits and vegetables. Considering the fact that her BP was not controlled despite taking diuretics for 10 years, it was planned to discontinue chlorthalidone. The dose of chlorthalidone was tapered down to 12.5 mg/day and telmisartan 40 mg was started. In view of her low serum potassium levels, she was prescribed potassium supplements in the form of potassium citrate. Metformin 500 mg daily for diabetes was continued. A follow-up was planned following 1 week. At follow-up, there was mild improvement in her BP and hypokalemia symptoms. During this visit, chlorthalidone was discontinued and telmisartan dose was up-titrated to 80 mg. In addition, amlodipine 5 mg was added to ensure optimal BP control. Potassium supplements were continued as such. Following this, a second follow-up was planned after 2 weeks. At second follow-up, her BP was well-controlled and her repeat serum potassium evaluation demonstrated improvement ~3.5 mEq/L. Upon subsequent visits, she remained asymptomatic with optimum serum potassium levels. She was then lost to follow-up.

Discussion

Diuretic-induced Hypokalemia

Hypokalemia is a common electrolyte disorder resulting from changes in potassium intake, altered excretion, or transcellular shifts. Severe hyokalemia may lead to life-

Table 1: Severity, Levels, and Symptoms of Hypokalemia

Severity	Level	Symptoms
Mild	> 3.0–3.5 mEq/L	Asymptomatic
Moderate	2.5–3.0 mEq/L	Cramping Malaise Myalgia Weakness
Severe	< 2.5 mEq/L	Electrocardiogram changes (including ST-segment depression, U-wave elevation T-wave inversion) Arrhythmias Paralysis

Adapted from: Veltri KT, Mason C. Medication-Induced Hypokalemia. *Pharmacy and Therapeutics*. 2015; 40(3):185-190.

threatening complications such as cardiac conduction disturbances and neuromuscular dysfunction. Hypokalemia may be mild, moderate or severe depending on the potassium levels (Table 1). The symptoms of hypokalemia include malaise and generalized weakness. There might also be ECG changes in severe hypokalemia. Besides, there are several causes of hypokalemia, most common causes being gastrointestinal losses and diuretic use (Table 2). Diuretics are antihypertensive agents and are frequently associated with renally mediated hypokalemia. Among various diuretic agents, chlorthalidone is most often implicated in causing hypokalemia. Decrease in serum potassium due to diuretics may be mild. If accompanied by other causes, such as gastrointestinal losses, hypokalemia may be severe. More so, it is imperative to manage hypokalemia in order to prevent the occurrence of potentially fatal consequences as mentioned above.[1,2]

Management of Hypokalemia

Treatment for hypokalemia focuses on restoring a normal potassium balance, preventing serious complications, and removing or treating the underlying etiology.[2] Reduced serum potassium levels can be corrected by potassium maintenance therapy. Potassium maintenance therapy can be accomplished either with use of potassium-sparing anti-hypertensive agents or with use of potassium supplements.[3] Most cases of mild-to-moderate hypokalemia may be corrected with oral potassium supplements.[2]

Evidence suggests that potassium supplementation leads to improvement in reduced potassium levels in patients with hypokalemia. A study[4] showed that in patients with diuretic-induced hypokalemia, supplementation with potassium citrate resulted in increased serum potassium concentration from 3.45 mEq/L to 3.8 mEq/L.[4] Another study[5] showed that

Table 2: Causes of Hypokalemia

Abnormal losses

Medications

- Diuretics
- Laxatives and enemas
- Corticosteroids

Gastrointestinal losses

Renal losses

- Osmotic diuresis
- Mineralocorticoid excess
- Type I and II renal tubular acidosis
- Polydipsia
- Intrinsic renal transport defects

Hypomagnesemia

Dialysis/plasmapheresis

Transcellular shifts

Medications

- Insulin overdose
- Beta-2 sympathomimetics
- Decongestants
- Xanthines
- Amphotericin B
- Verapamil intoxication
- Chloroquine (Aralen) intoxication
- Barium intoxication
- Cesium intoxication

Alkalosis

Refeeding syndrome

Increased beta-2 adrenergic stimulation

- Delirium tremens
- Head injury
- Myocardial ischemia

Thyrotoxicosis

Familial hypokalemic periodic paralysis

Hypothermia

Inadequate intake

Anorexia

Dementia

Starvation

Total parenteral nutrition

Pseudohypokalemia

Delayed sample analysis

Significant leukocytosis
(> 75,000 cells per mm^3 [75.0 × 10^9 per L])

Adapted from: Viera AJ, Wouk N. Potassium Disorders: Hypokalemia and Hyperkalemia. *Am Fam Physician.* 2015; 92(6):487-495.

in patients with thiazide-induced hypokalemia, potassium supplement led to improvement in serum potassium levels.[5]

Besides, it is important to carefully monitor serum potassium in patients receiving potassium supplementation owing to risk of hyperkalemia, particularly in those who are hospitalized. There remains an increased risk for rebound hyperkalemia in the treatment of redistributive hypokalemia.[1] Thus, caution should be exercised in such cases. Apart from taking potassium supplements, it is necessary to increase the intake of potassium-rich food is diet. Various foods that are rich source of potassium include bran cereals, kiwis, avocados, dried fruits, spinach, potatoes, nuts and bananas.[2] Patients can be advised to include these foods in their diet.

Overall, in hypertensive patients taking diuretics such as chlorthalidone, hypokalemia can be a problem. Using potassium-sparing anti-hypertensive agents or including potassium supplementation can lead to improvement in hypokalemia; however, one should exercise prudence and carefully monitor serum potassium levels to obviate the risk of hyperkalemia.

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