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Managing Hyperphosphatemia in CKD: Current Insights into Pathophysiology and Therapeutic Approaches

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ABSTRACT:
Chronic Kidney Disease (CKD) is a progressive condition marked by a gradual loss of renal function and commonly associated with disturbances in mineral metabolism, particularly phosphate. As kidney function declines, phosphate homeostasis becomes impaired, leading to hyperphosphatemia, secondary hyperparathyroidism, and increased cardiovascular risks. This review explores the pathophysiological changes in phosphate metabolism in CKD, focusing on hormonal regulation involving parathyroid hormone (PTH), vitamin D, and fibroblast growth factor 23 (FGF23), as well as the roles of αKlotho and NaPi co-transporters.
The paper outlines the normal mechanisms of phosphate balance, factors contributing to dysregulation in CKD, and associated complications such as bone disease and vascular calcification. Additionally, the review provides an in-depth analysis of therapeutic strategies, including dietary phosphate restriction, dialysis modification, and phosphate binders like Sevelamer and calcium acetate. Advantages, limitations, side effects, and pharmacodynamic profiles of these agents are discussed in detail.
Special emphasis is given to patient education, lifestyle interventions, and pharmacologic treatment to manage hyperphosphatemia effectively. The importance of early diagnosis, screening of high-risk populations, and regular monitoring of phosphorus levels is also highlighted.
In conclusion, optimizing phosphate control is crucial in delaying CKD progression, minimizing systemic complications, and improving quality of life. A multidisciplinary approach involving nephrologists, dietitians, and patient participation is essential for effective CKD management.

I. INTRODUCTION

Chronic Kidney Disease

Chronic kidney disease (CKD) is characterized by the presence of kidney damage or an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m², persisting for 3 months or more, irrespective of the cause[1]. CKD is a state of progressive loss of kidney function, ultimately resulting in the need for renal replacement therapy, such as dialysis or transplantation. Kidney damage refers to pathologic abnormalities suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates.

The 6 CKD categories, known as stages 1 through 5, are described below (stage 3 is separated into 3a and 3b)[2]:

- G1:GFR90ml/min/1.73m^2 and above with evidence of kidney disease, such as hematuria or proteinuria
- G2:GFR60to 89ml/min/1.73m^2
- G3a:GFR45to59 ml/min/1.73m^2
- G3b:GFR30 to44ml/min/1.73m^2
- G4:GFR15to 29ml/min/1.73m^2
- G5: GFR less than 15 ml/min/1.73 m^2 or treatment by dialysis The 3 levels of album in uria include an album in: creatinine ratio (ACR):
- A1:ACRlessthan30mg/g(<3.4mg/mmol)
- A2:ACR30to299mg/g (3.4-34 mg/mmol)
- A3:ACRgreaterthan300mg/g(>34mg/mmol)

The improved classification of CKD has been beneficial in identifying prognostic indicators related to decreased kidney function and increased albuminuria. However, a downside of this classification system is the potential for over diagnosis of CKD, particularly in older individuals.

Etiology of CKD:

The causes of CKD vary globally, with the most common primary diseases leading to CKD and, ultimately, end-stage renal disease (ESRD) being[3]:

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- Type 2 diabetes (30%-50%)
- Type 1 diabetes(3.9%)
- Hypertension(27.2%)
- Primary glomerulonephr it is (8.2%)
- Chronic tubuleinterstitial nephritis (3.6%)
- Here ditary or cystic diseases (3.1%)
- Secondary glomerulone phritisorvasculitis(2.1%)
- Plasma cell dyscrasias or neoplasm(2.1%)
- Sickle cell nephropathy, which accounts for<1% of ESRD patients in United States.
- CKD may result from disease processes in any of the 3 categories, including prerenal (decreased renal perfusion pressure), intrinsic renal (pathology of the vessels, glomeruli, or tubules-interstitium), or postrenal (obstructive).

(A) Prerenal Disease: Chronic prerenal disease occurs in patients with chronic heart failure or cirrhosis, where persistently decreased renal perfusion increases the risk of intrinsic kidney injury, such as acute tubular necrosis. This can lead to a progressive loss of renal function.

(B) Intrinsic Renal Disease:

(a) Intrinsic renal vascular disease: The most common chronic renal vascular disease is nephrosclerosis, which causes ongoing damage to blood vessels, glomeruli, and the tubulointerstitium. Other renal vascular diseases include renal artery stenosis due to atherosclerosis or fibromuscular dysplasia, which over months or years, can lead to ischemic nephropathy. Intrinsic renal vascular disease condition is characterized by glomerulosclerosis and tubulointerstitial[4].

(b) Intrinsic glomerular disease (nephritic or nephrotic): A nephritic pattern is indicated by abnormal urine microscopy showing red blood cell (RBC) casts, dysmorphic red cells, and occasionally white blood cells (WBCs), along with a variable degree of proteinuria[5]. The most common causes are post-infectious glomerulonephritis, infective endocarditis, Ig A nephropathy, lupus nephritis, Good pasture syndrome, and vasculitis[6]. A nephrotic pattern is associated with proteinuria, usually in the nephrotic range (>3.5 g/24 h), and an inactive urine microscopic analysis with few cells or casts. Common causes include minimal change disease,focal segmental glomerulosclerosis, membranous glomerulonephritis, diabetic nephropathy, and amyloidosis.

(c) Intrinsic tubular and interstitial disease: The most common chronic tubulointerstitial disease is polycystic kidney disease (PKD). Other etiologies include nephrocalcinosis (often due to hypercalcemia and hypercalciuria), sarcoidosis, Sjögren syndrome, and reflux nephropathy in children and young adults[7].

(C) Postrenal (Obstructive Nephropathy): Chronic obstruction may result from prostatic disease, nephrolithiasis, or an abdominal/pelvic tumor exerting a mass effect on the ureter(s). Congenital abnormalities causing obstruction at the ureteropelvic or ureterovesical junctions are also common. Rare causes of chronic ureteral obstruction include retroperitoneal fibrosis or neurogenic bladder[8,9].

Epidemiology of CKD:

The true incidence and prevalence of CKD are challenging to determine due to the a symptomatic nature of early to mode rate stages. The prevalence of CKD in the general population is estimated to be around 10% to 14%. Specifically, albumin uria and an eGFR less than 60 mL/min/1.73 m² have prevalences of about 7%and 4%, respectively[10]. Worldwide, CKD accounted for2, 968,600 (1%) of disability-adjusted life-years and 2,546,700 (1%-3%) life-years lost in 2012. In the United States, CKD affected an estimated 26 million people in 2016[11]. The Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that for diagnosing chronicity and CKD, patients should be tested on 3 separate occasions over a 3-month period, with at least 2 of the 3 results being positive[12].

Progression of Chronic Kidney Disease:

CKD diagnosed in general population (community CKD) typically has a different natural history and progression compared to CKD in patients referred to nephrology practices (referred CKD). Community CKD primarily affects the older population who has had lifelong exposure to cardiovascular risk factors, hypertension, and diabetes, all of which can impact kidney function. The average rate of GFR decline in this population is approximately 0.75 to 1 ml/min/year after age 40to 50[13].Ina large study of community-based CKD by Kshirsagar et al, only1% and 20% of patients with CKD stages 3 and 4, respectively, required renal replacement therapy. However, 24% and 45% of patients with stages 3 and 4, respectively, died predominantly from cardiovascular disease (CVD),

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suggesting that cardiac events rather than ESRD are the predominant outcomes in community-based CKD[14]. In contrast to community CKD, patients with referred CKD often present at an earlier age due to hereditary conditions (eg, autosomal-dominant polycystic kidney disease or ADPKD) or acquired nephropathies (eg, glomerulonephritis, diabetic nephropathy, and tubulointerstitial disease) that cause progressive renal damage and loss of function. The rate of progression in referred CKD varies depending on the specific disease process. Diabetic nephropathy typically shows a rapid decline in GFR, averaging around 10 ml/min/year. In nondiabetic nephropathies, progression is generally faster in patients with chronic proteinuric glomerulonephritis compared to those with lower levels of proteinuria. Patients with ADPKD and CKD stage G3bor higher may experience a faster rateof progression than those with other nephropathies. In patients with hypertensive nephrosclerosis, well-controlled BP and minimal proteinuria are associated with very slow progression.

Risk Factors for Progression of Chronic Kidney Disease:

(a) Non-modifiable CKD risk factors: Older age, male gender, and non-White ethnicity, including Black Americans, Afro-Caribbean individuals, Hispanics, and Asians (South Asians and Pacific Asians), all adversely affect CKD progression. Genetic factors that affect CKD progression have been identified across various kidney diseases. A population-based cohort study found that single nucleotide polymorphisms in the genes TCF7L2 and MTHFS were associated with diabetic nephropathy and CKD progression. The same study also highlighted that polymorphisms in genes involved in renal scarring and the renin-angiotensin-aldosterone system (RAAS) affect CKD progression[15].

(b) Modifiable CKD risk factors: These include systemic hypertension, proteinuria, and metabolic factors[16]. Systemic hypertension is a major cause of ESRD worldwide and the second leading cause in the United States, following diabetes. Transmission of systemic hypertension into glomerular capillary beds and the resulting glomerular hypertensionis believed to contribute to the progressionofglomerulosclerosis[17]. Night-time and 24-hour blood pressure measurements (such as ambulatory blood pressure monitoring or ABPM) are more strongly correlated with CKD progression than standard measurements. Systolic blood pressure, inparticular, iscrucial predictor of CKD progression and is associated with complications in CKD. Multiple studies have demonstrated that significant proteinuria (albuminuria A3) is linked to a faster rateofCKD progression in both diabetic and nondiabetic kidney diseases. Reducing significant proteinuria through RAS blockade or dietary modifications is associated with better renal outcomes. However, large intervention studies, such as Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) and the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET), observed notable declines in GFR despite substantial reductions in albuminuria[18,19].Therefore, moderate-level albuminuria (A2) is not a reliable surrogate marker for CKD progression. Multiple studies have linked the RAAS system to the development of hypertension, proteinuria, and renal fibrosis throughout CKD. Consequently, interventions targeting the RAAS have been effective in slowing CKD progression, leading to wide spread use of RAAS blockers in managing proteinuric and diabetic kidney diseases. Obesity and smoking have been associated with the development and progression of CKD. Additionally, metabolic factors such as insulin resistance, dyslipidemia and hyperuricemia have also been implicated in CKD development and progression[20,21].

(c) Recommendations for Chronic Kidney Disease Screening: Screening, primarily targeting high-risk individuals, is being implemented worldwide. The KDOQI guidelines recommend screening high-risk populations, including those with hypertension, diabetes mellitus, and individuals older than 65. Screening should involve urinalysis, measurement of urine ACR, serum creatinine levels, and estimation of GFR, preferably using the CKD Epidemiology Collaboration (CKD-EPI) equation. Currently, evidence to support screening asymptomatic individuals from the general population for CKD does not exist.

Pathophysiology of CKD:

Unlike acute kidney injury (AKI), which often results in complete functional recovery,

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chronic and sustained insults from progressive nephropathies lead to ongoing kidney fibrosis and destruction of normal kidney architecture. This process affects all three compartments of the kidney: the glomeruli, tubules and interstitium, and vessels. Histologically, it manifests as glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. Following events leading to scarring and fibrosis are complex, overlapping and multistage phenomena:

- Infiltration of damaged kidneys with extrinsic inflammatory cells.
- Activation, proliferation, and loss of intrinsic renal cells (through apoptosis, necrosis, mesangiolysis, and podocytopenia).
- Activation and proliferation of extracellular matrix producing cells, including myofibroblasts and fibroblasts.
- Deposition of extracellular matrix, replacing the normal architecture.

Mechanisms of Accelerated Progression of Chronic Kidney Disease

- Systemic and intraglomerular hypertension
- Glomerular hypertrophy
- Intrarenal precipitation of calcium phosphate
- Altered prostanoid metabolism

All these mechanisms lead to a histological entity called glomerulosclerosis[22]. Clinical risk factors for the accelerated progression of CKD include proteinuria, hypertension, Blackrace, and hyperglycemia. Environmental exposures, such as lead, smoking, metabolic syndrome, certain analgesic agents, and obesity, have also been linked to the accelerated progression of CKD[23].

Sign and Symptoms:

Early CKD stages are a symptomatic, and symptoms manifest in stages4or5.Some common symptoms and signs at these stages of CKD include[24]:

- Nausea
- Vomiting
- Loss of appetite
- Fatigue and weakness
- Sleep disturbance
- Oliguria
- Decreased mental sharpness
- Muscle cramps
- Persistent pruritus
- Chest pain due to uremic pericarditis
- Shortness of breath due to pulmonary edema from fluid overload
- Hypertension

Physical examination is often not helpful, but patients may demonstrate the following symptoms:

- Skin pigmentation
- Scratch marks from pruritus
- Pericardial friction rub due to uremic pericarditis
- Uremic frost, where high levels of blood urea nitrogen(BUN)cause urea in sweat to crystallize into fine, white powder on the skin
- Hyper reflexia or muscle twitches
- Hyper tensive fundal changes suggesting chronicity

Evaluation of CKD[25,26]:

- Establishing Chronicity
- Assessment of Glomerular Filtration Rate
- Assessment of Proteinuria
- Imaging of Kidneys
- Establishing an Accurate Diagnosis

Differential Diagnosis:

When evaluating a patient for CKD, it is crucial to consider other potential diagnoses that may present with similar symptoms and clinical findings. The differential diagnoses include[27]:

- Acute kidney injury
- Al port syndrome
- Anti giomerular basement membrane disease
- Diabetic nephropathy
- Multiple myeloma
- Nephrolithiasis
- Rapidly progressive glomerulo nephritis

Systemic Complications of Chronic Kidney Disease:

(A) Salt/fluid balance: Salt and fluid balance abnormalities are common in CKD, becoming more apparent in stages 4 and 5. These patients often respond to sodium restriction and loop diuretics. The 2012 KDIGO guidelines recommend sodium intake be restricted to less than 2 g/d for all CKD patients[28].

(B) Hypertension: Hypertension in CKD can be a manifestation of volume expansion, although patients with CKD do not always have edema to suggest volume expansion. Many patients with CKD benefit from using a loop diuretic

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before escalating the doses of other antihypertensives. The KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD recommends aiming for a systolic blood pressure below 120mm Hg for patients not on dialysis[29].

(C) Hyperkalemia: Hyperkalemia in CKD can occur particularly in oliguric patients and those with distal renal tubular dysfunction. Contributing factors include dietary potassium intake, tissue breakdown and aldosterone resistance. Additionally, medications such as angiotensin- converting enzyme inhibitors and nonselective beta-blockers can also lead to hyperkalemia[30].

(D) Metabolic acidosis: Metabolic acidosis is a common complication of advanced CKD due to the retention of acidic compounds. Chronic metabolic acidosis can lead to osteopenia in these patients. Treatment typically involves bicarbonate supplementation to maintain a serum bicarbonate level of 23 mEq/l[31].

(E) Hyperphosphatemia: Hyperphosphatemia is a common complication of CKD due to a decreased filtered phosphorous load. This leads to increased secretion of PTH and causes secondary hyperparathyroidism. While hyperparathyroidism aims to normalize phosphorus and calcium levels, it often leads to hyperphosphatemia at the expense of bone health. Additionally, FGF23, a protein involved in calcium and phosphorus metabolism, is associated with cardiovascular mortality independently of its bone metabolic effects[28].

(F) Anemia: Anemia of CKD is typically normocytic normochromic and results from reduced erythropoietin production due to decreased functioning renal mass, abnormal iron metabolism, and reduced red blood cell survival. Hemoglobin levels should be checked annually in stage 3 CKD, every 6 months in stages 4 and 5, and monthly in dialysis patients. Erythropoiesis- stimulating agents should be considered when hemoglobin is below 10 g/dl, with iron saturation at least 20% to 30% and ferritin greater than 200ng/ml. For dialysis patients, the target hemoglobin concentration is 10 to 11.5 g/dl.

(G) Cardiovascular disease: The risk of CVD increases with these verity of CKD. Considerable evidence indicates a significant association between epicardial adipose tissue thickness and the incidence of CVD events in CKD patients. Therefore, assessing epicardial adipose tissue could be a reliable parameter for evaluating cardiovascular risk in CKD patients[32].

(H) Insulin resistance: Insulin resistance and metabolic syndrome are strongly associated with CKD and contribute to the development of atherosclerotic disease. This association is thought to be mediated by increased inflammatory markers[11].

(I) Treatment of Complications of End-Stage Renal Disease: Malnutrition in ESRD is often caused by anorexia and inadequate protein intake. The diet for ESRD patients should provide at least 30 to 35 kcal/kg/d. Dietitians play a crucial role in improving the nutritional status and overall health of patients with CKD and ESRD. Uremic bleeding is a complication resulting from impaired platelet function, which leads to prolonged bleeding times. A symptomatic patients typically do not require treatment. However, correction of uremic platelet dysfunction is necessary during active bleeding or before surgical procedures. Interventions may include desmopressin (DDAVP), cryoprecipitate, estrogen, and initiation of dialysis.

(J) Complications of Renal Transplantation: Infectious complications are prevalent in post transplant patients, necessitating appropriate prophylaxis and vaccinations. Other common CKD complications include hypertension, dyslipidemia, coronary artery disease from new-onset diabetes mellitus, arrhythmias, and heart failure. Neurological complications include stroke and posterior reversible encephalopathy syndrome, central nervous system infections, neuromuscular andseizure disorders, and neoplastic disease. Gastrointestinal complications include infection, mucosal injury, mucosal ulceration, perforation, biliarytract disease, pancreatitis and diverticular disease. Due to immunosuppression, patients with kidney transplants have an increased risk of malignancy such as post transplant lympho proliferative disorder and skin cancer[33].

Patient education:

All high-risk patients, including those with diabetes or hypertension, should be screened for CKD and also receive counseling on the symptoms and signs of the condition. Patients with CKD can benefit from the following home interventions[34]:

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- About 85% of CKD patients have hypertension. They should be advised to measure their blood pressure daily and maintain a log of their blood pressure readings and daily weights.
- Patients with hemoglobin levels below 10.0 g/dL might benefit from home administration of subcutaneous erythropoietin-stimulating agents if this is more convenient than office visits.
- Consultation with a nutritionist is recommended for optimal dietary management and to avoid high-potassium foods.
- All patients with advanced CKD should be instructed to monitor their phosphorus levels and take phosphate binders with each meal.
- CKD patients who are pregnant or planning to become pregnant should be informed that pregnancy may exacerbate CKD and that impaired kidney function can negatively impact pregnancy. They should also be made aware that some medications used in CKD, such as ACE inhibitors, are teratogenic.

Facts to keep in mind regarding CKD:

Facts to keep in mind regarding CKD include[35]:

- CKD is defined as kidney damage or an eGFR less than 60 mL/min/1.73 m^2, persisting for 3 months or more, irrespective of the cause.
- CKD is usually a symptomatic until it reaches stages 4 and 5.
- The KDOQI guidelines recommend screening high-risk populations, which include individuals with hypertension, diabetes mellitus, and those aged 65 or older. This screening should involve urinalysis, measurement of urine ACR, serum creatinine, and estimation of GFR, preferably using the CKD Epidemiology Collaboration (CKD-EPI) equation.
- Calcium and phosphorus levels are not useful in distinguishing AKI from CKD. However, normal PTH levels suggest AKI rather than CKD.
- Systemic hypertension, proteinuria, hyperlipidemia, and metabolic acidosis cause the progression of CKD and need to be treated aggressively.
- Bicarbonate supplementation to reach a serum bicarbonate target equal to 23 mEq/L canhelp delay the progression of CKD.
- All CKD patients need to be evaluated for anemia, hypertension, metabolicacidosis, and bone and mineral disorders.

The Importance of Phosphate Controlin Chronic Kidney Disease (CKD)

The series of changes that occur in renal dysfunction, including decreases in serum calcium levels due to impairment in vitamin D activation, hypersecretion of parathyroid hormone (PTH; i.e., secondary hyperparathyroidism), bone decalcification, and weak bones (osteomalacia), were collectively regarded as renal osteodystrophy. Following the introduction of the term “chronic kidney disease” (CKD), which expands the prior concept of renal dysfunction or renal failure, CKD-associated metabolic disorders of minerals (e.g.,calcium) are now defined asCKD-mineral bone disease (CKD-MBD). As if coinciding with these changes, αKlotho was first reported in 1997, a deficiency of which results in an aging phenotype[36], and fibroblast growth factor 23 (FGF23), which causes a form of rickets and hypophosphatemia in bone metastasis, was identified in the early 2000s[37]. Phenotypical similarities between αKlotho-deficient mice and FGF23-deficient mice indicated an association between these two molecules, and their considerable involvement in the regulation of phosphate metabolism was subsequently revealed[38]. Given the significance of phosphate metabolism in CKD, and that αKlotho and FGF23 are involved in the pathophysiology as well as the onset ofcomplications and survival in CKD, the importance of the αKlotho/FGF23 regulatory system in CKD-MBD is becoming clearer[39].

Phosphate homoeostasis in humans:

In healthy adults, most laboratories quote a normal phosphate reference concentration range of 0.80–1.45mmol/L. Overall intake and excretion is determined by the net balance of ingested and absorbed phosphate from food, and phosphate excretion through the bowels and the urinary tract. In addition, the plasma phosphate concentration is also influenced by the rate of bone formation and resorption, since phosphate moves in and out of the bone[40].

(A) Intestinal absorption: The average ingested phosphate content from dietary intake is in the orderof20 mg/kg/day and it is typically found in foods that are rich in protein such as dairy products, meats, eggs, and cereals as well as food additives that contain phosphate[41]. The bioavailability of phosphate from a vegetarian diet is relatively low compared to meat dietary protein[42]. Phosphorus from plant sources is mostly in the form of phytate, which is not

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hydrolysable by humans due the lack of phytase enzyme and hence, is not absorbable[42]. Vegetarians would therefore be expected to ingest less phosphate compared to non-vegetarians. Of the total amount of daily ingested phosphate, 16 mg/kg/day is usually absorbed by the intestine and approximately 3 mg/kg/day is secreted back into the intestine through pancreatic and intestinal secretions. The remaining 7 mg/kg/day of unabsorbed phosphate is excreted via the faecal route. The major sites for phosphate absorption are in the jejunum and ileum[43]. The absorption process is carried out both by diffusional, non-saturable influx and through an active uptake system influenced by sodium-phosphate co-transporters (NaPi co-transporters), that account for about 60% of "normal" dietary phosphate absorption[44]. This percentage can increase up to 80% under the influence of the active form of vitamin D (1α, 25(OH)2D3) and be reduced to 40% if a patient is taking phosphate binders[45]. Sodium-phosphate co-transporters (NaPi co-transporters) are carrier systems present in the brush border membranes of intestine and renal proximal tubular cells and are responsible for phosphate absorption from the intestine and reabsorption from proximal tubules of the kidney[46].

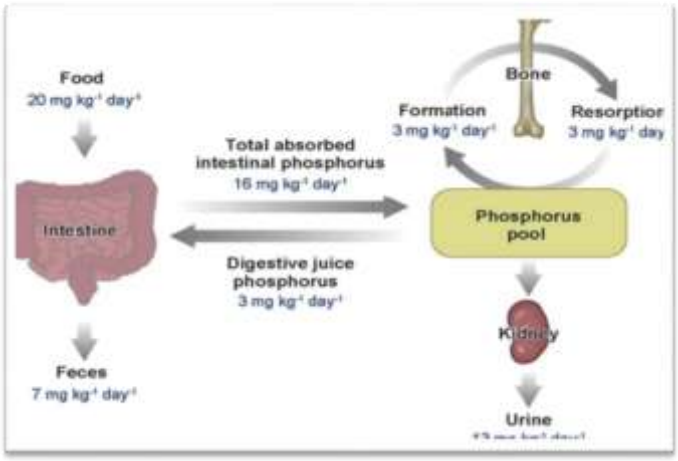

Figure 1: Phosphate homoeostasis in humans[46]

(B) Renal elimination: The kidney plays a major role in phosphate homoeostasis[47]. Kidneys excrete the total net amount of absorbed phosphate (13 mg/kg/day). Under normal physiological condition, in healthy individuals phosphate is freely filtered through the glomerulus. Majority (85–90%) of filtered phosphate undergoes tubular reabsorption primarily inproximaltubules[48,49].

Factors affecting phosphate homoeostasis:

Factors that regulate phosphate homoeostasis principally alter phosphate absorption from the intestine, reabsorption from kidney and mobilisation from and/or uptake by the bone.

(a) Parathyroid hormone (PTH): Parathyroid glands contain calcium-sensing receptors that sense the extracellular ionised calcium concentration and regulate PTH secretion. If ionised calcium is reduced with increased serum phosphate, PTH will be released and exert its phosphaturic effect directly on the kidney. In addition, PTH stimulates osteoc last activity in the bone to release calcium and phosphate into the extracellular pool, and also stimulate the activation of vitamin D to 1α,25(OH)2D3 via the 1α-hydroxylase enzyme[50].

(b) Vitamin D: Activated vitamin D (1α, 25(OH)2D3) acts on the intestine to increase the number of NaPico-transporters there by increasing the absorption of both phosphate and calcium. In contrast to PTH, 1α, 25(OH) 2D3 increases calcium and phosphate uptake by the bones by stimulating osteoblast and inhibiting osteoclast activities. In addition, 1α, 25(OH)2D3 directly inhibits PTH hormone action and stimulates renal NaPi co-transporters to inhibit phosphate excretion. As serum calcium and phosphate concentrations increase, the activity of αhydroxylase in renal

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tubules is reduced thus reducing the activation of vitamin D[51].

(c) Phosphatonins: Phosphatonins are a group of factors, originally identified in patients with tumour-induced osteomalacia. They are associated with inducing hypophosphatemia, lowering concentrations of vitamin D and increasing excretion of urinary phosphate. Several phosphatonins have been identified with fibroblast growth factor-23 (FGF-23), fibroblast growth factor-7, secreted frizzled-related protein and matrix extracellular phosphoglycoprotein being the most commonly cited[52].

(d) Dietary intake of phosphate: Low phosphate dietary intake stimulates intestinal and renal NaPi co-transporters expression leading to increased absorption of phosphate from the intestine and reabsorption from the proximal tubules. In addition, low phosphate induces an increase in circulating 1α, 25(OH)2D3. By contrast, high dietary phosphate intake stimulates a rapid release of PTHto increase renal phosphate excretion before any changes in serum calcium or phosphate concentrations occur[53]. Phosphate exchange from bone and intracellular compartment: changes in electro negativity gradients such as acid-base disorders can cause transcellular shifts of phosphate between intracellular and extracellular fluids. In metabolic acidosis, phosphate moves from inside the cell to extracellular space leading to increase phosphate concentration in the blood. In contrast, in case of alkalosis, phosphate moves intracellularly and serum phosphate concentration is reduced[54].

(e) Diurnal variations: Diurnal fluctuations in serum phosphate concentrations occur with phosphate concentration being lowest in the early morning but increasing by 16% by midday. During an evening sleep cycle, phosphate increases by approximately 40%, remains elevated, then drops rapidly after awakening. There are also seasonal variations with phosphate concentrations being higher in the summer than in the winter[55].

Management of Hyperphosphatemia in CKD Patients:

In clinical practice, the management of hyperphosphatemia is focused on controlling factors that are responsible for the intake and removal of phosphate from the body. There are three main strategies for correcting hyperphosphatemia:

- **Diet:** restricting dietary phosphate intake.
- **Enhancinge limination:** removing phosphate with adequate dialysis.
- **Minimising phosphate absorption:** reducing intestinal absorption using phosphate binders.

(A) Diet: restricting dietary phosphate intake: Reducing the daily phosphate in take in diet can be challenging as it is usually in compatible with the recommended daily protein in take of 1.0– 1.2 g/kg/day. In addition, the required intensive patient education, the complexity of dietary tables and booklets as well as the substantial variability of phosphate contents in food from the same category are added challenges for dietary phosphate control. This makes diet controlalone an insufficient and unreliable technique to keep phosphate concentrations within the recommended targets. However, when combined with other strategies, dietary modifications can assist in management strategies to help reduce the risk of hyperphosphatemia[56].

(B) Enhancing elimination: removing phosphate with adequate dialysis: Dialysis is the cornerstone of homoeostatic 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. A rapid reduction in serum phosphate is seen at the beginning of dialysis (first 60–90min), but this slows as the concentration gradient between the plasma and dialy sate fluid falls. The rate of phosphate transfer from the plasma consequently decreases and serum phosphate levels plateau. After dialysis, a significant rebound of phosphate can occur resulting in a potential return to the pre- dialysis serum phosphate concentrations[57].Removal of phosphate will also depend on the type and extent of dialysis performed. For example the elimination of phosphate ranges between300 and 1200 mg per day depending of the type of dialysis used: A standard 4hhaemodialys is treatment removes between 600 and 1200mg/day (1800–3600

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mg/week) compared to continuous ambulatory peritoneal dialysis which removes between 300 and 360 mg/day (2100–2520 mg/week).Modifying the dialysis frequency and length of treatment may improve efficiency. Two studies have shown a significant lowering of phosphate levels using innovative dialysis techniques. One study trialed the short daily haemodialysis (six 3-h sessions per week) while the other trialed nocturnal haemodialysis (six night-sessions per week for 8–10 h each while the patient is sleeping)[58]. Both of these dialysis techniques are still investigational and their applicability and effectiveness as alternatives to the conventional dialysis techniques in the management of hyperphosphatemia yet to be determined. In summary, 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.

(C) Minimizing phosphate absorption: reducing intestinal absorption (Phosphate Binders): Using phosphate binders to assist in the management of hyperphosphatemia in patients undergoing dialysis is common with more than 95% of patients being prescribed phosphate binders. Phosphate binders work by binding dietary phosphate and forming insoluble complexes that are excreted by the gut[59].

The most commonly utilized phosphate binders are[60]:

(a) Calcium-based phosphate binders (Calcium Carbonate and Calcium Acetate).
(b) Non-absorbable polymers (Sevelamer).
(c) Heavy metal salts (lanthanum carbonate and aluminium hydroxide).

(a) Calcium-based phosphate binders: Calcium-based phosphate binders are the most widely prescribed phosphate binders. They are more effective than place bo in reducing serum phosphate concentrations and PTH. However, large doses of calcium-based binders(upto 17gperday)are usually required to achieve adequate phosphate management (.This translates to high pill burden (for example a dose of 17 g of calcium carbonate would require approximately 13 tablets) to deliver the required doses. In addition, their use is potentially associated with hypercalcaemia and calcification of vascular tissues. This is of particular concern when these calcium-based phosphate binders are prescribed with vitamin D[61].Several studies have investigated the relationship between increased calcium load serum calcium concentration and overall mortality. A large study of 40,538 haemodialysis patients reported a direct relationship with each 0.25 mmol/l increase in serum calcium associated with a 20% increase in relative risk of death. Other studies have also found a relationship between anincrease in the calcium load and the progression of vascular calcification especially in patients with low-turnover bone diseases[62].

(b) Non-absorbable polymers (Sevelamer): Sevelamer hydrochloride was the first member of its class to be marketed. It is a non-absorbable, synthetic ion-exchange polymer that binds phosphate and inhibits its absorption by the body. Polymers are considered to be as effective as the calcium-based phosphate binders but are much more expensive and have significant gastrointestinal side effects[63].The possibility of hypercalcaemia and lowered concentrations of PTH are less likely to occur with Sevelamer. In addition, the 'Treat to Goal Study'(200haemodialysis patients)found a significant reduction in the progression of vascular calcification in the sevelamer-treated group compared with the calcium-containing binders treated group over the 52-week study period[64].Proposed other benefits with Sevelamer are an anti-inflammatory effect, a favourable effect on the blood lipid profile (due to an ability to bind with cholesterol in the GIT), and a reduction in uric acid[65].Despite these advantages, the relatively high price and high tablet burden as well as the gastrointestinal side effects are the main drawbacks for the use of sevelamer in the management of hyperphosphatemia in CKD patients[66].

(c) Heavy metalsalts(lanthanum carbonate and aluminium hydroxide):

- Lanthanum carbonate(LC)[67]
- Aluminium salts[68]

(d) Other significant medications affecting phosphate:

Active vitamin D sterols such as calcitriol and alfacalcidol and their analogues (paricalcitol, doxercalciferol, 22-oxacalcitriol and maxacalcitol)

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are used to treat secondary hyperparathyroidism (SHPT) in CKD patients. They directly inhibit the secretion of PTH through the activation of vitamin D receptors in parathyroid glands. However, they increase the absorption of both calcium and phosphate (vitamin D analogues to a lesser extent) and thus may complicate hyperphosphatemia management and promote calcifications in CKD patients[69].

Cinacalcet is a calcimimetic agent that binds and modulates calcium-sensing receptors in parathyroid glands resulting in reduction of PTH secretion and regression of parathyroid glands proliferation. It is used to treat secondary hyperparathyroidism (SHPT) in patients with CKD. Unlike vitamin D sterols, its use is associated with reduced phosphate concentrations, Ca ×P product and calcium concentrations in haemodialysis patients[70].

Reasons for failure of phosphate control: Ten possible reasons for this failure[71]:

- Pseudo hyperphosphataemia (incorrect sample handling; analytical error).
- High dietary phosphate intake.
- High doses of active vitamin D metabolites.
- Phosphate-containing drugs (enema,infusion).
- In adequacy of haemodialysis.
- Advanced osteitisfibrosa (efflux of P from bone independent of intestinal Puptake).
- Metabolic acidosis (phosphate shift from in tracellular into extracellular space).
- Patient non-compliance with phosphate binders.
- In correct intake of phosphate binders(timing and dosing).
- In efficiency of calcium carbonate because of achlorhydria (spontaneous or after medication).

Drug Profile

Sevelamer Carbonate:

Sevelamer Carbonate is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Sevelamer Carbonate is also indicated for the control of hyperphosphataemia in adult patients with chronic kidneydisease not on dialysis with serum phosphorus. Sevelamer Carbonate should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1, 25-dihydroxy vitamin D3 or one of its analogues to control the development of renal bone disease. Chemically, it is a polymeric resin composed of allylamine and epichlorohydrin cross linked to form a non-absorbed, metal-free hydrogel.

The active ingredient in Sevelamer is sevelamer carbonate, a polymeric amine that binds phosphate and is meant for oral administration. It was developed as a pharmaceutical alternative to sevelamer hydrochloride

Chemical Structure:

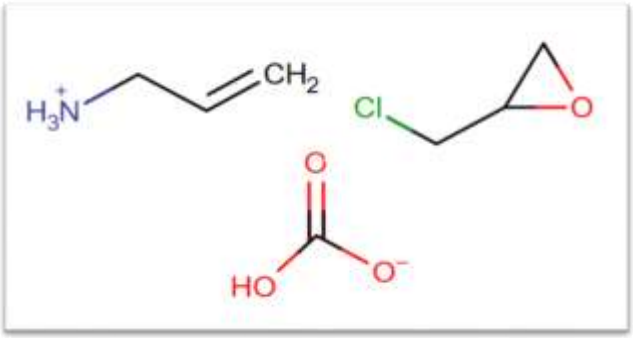

Figure 2: Chemical Structure of Sevelamer Carbonate

IUPAC Name: 2-(chloromethyl) oxiraneprop-2-en-1-a minium hydrogen carbonate

Molecular Formula: $C_7H_{14}ClNO_4$ Molecular Weight: 211.64

Indication: Sevelamer carbonate is indicated for the control of serum phosphorus in adults with chronic kidney disease (CKD) and children 6 years of age on dialysis Pediatric

Category: Hyperphosphatemia; Renal Dialysis

Common side effects include:

- Nausea and vomiting
- Stomach pain and loss of appetite

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- Constipation and diarrhea
- Gas and bloating
- Tired feeling
- Itching and joint pain

Precautions for taking Sevelamer Carbonate

- In form doctor if trouble in swallowing, severe constipation, a blockage in your intestines, slow digestion, or a stomach/intestinal disorder.
- Check for allergies to the medication's in active ingredients.
- Avoid using Sevelamer Carbonate if you have certain medical conditions.
- Pregnant or planning to become pregnant consult doctor.
- Breast feeding is not expected to result in exposure of the child to Sevelamer Carbonate

Calcium Acetate:

Calcium acetate is a calcium salt of acetic acid. It is used as a phosphate binder to control phosphate levels in people with kidney failure who are on dialysis. Calcium acetate attaches to the phosphate in your food before the phosphate can be absorbed by your body, and your body then gets rid of this extra phosphate through your stool. Calcium is also needed for many functions of the body, especially bone formation and maintenance.

Chemical Structure:

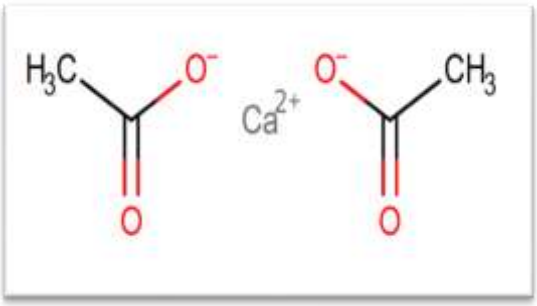

Figure3: Structure of Calcium Acetate Molecular Formula: $C_4H_6CaO_4$

Molecular Weight: 158.166

Synonyms: Acetate of lime, Brown acetate of lime, Calico acetate, Calcium Ethanoate, lime acetate

Indication: Calcium acetate is one of a number of calcium salts used to treat hyperphosphatemia (too much phosphate in the blood) in patients with kidney disease.

Pharmacodynamics: Patients with advanced renal in sufficiency (creatinine clearance less than 30 ml/min) exhibit phosphate retention and some degree of hyperphosphatemia. The retention of phosphate plays a pivotal role in causing secondary hyperparathyroidism associated with osteodystrophy, and soft-tissue calcification. The mechanism by which phosphate retention leads to hyperparathyroidism is not clearly delineated. The rapeutic efforts directed toward the control of hyperphosphatemia include reduction in the dietary intake of phosphate, inhibition of absorption of phosphate in the intestine with phosphate binders, and removal of phosphate from the body by more efficient methods of dialysis. The rate of removal of phosphate by dietary manipulation or by dialysis is insufficient. Dialysis patients absorb 40% to 80% of dietary phosphorus. Therefore, the fraction of dietary phosphate absorbed from the diet needs to be reduced by using phosphate binders in most renal failure patients on maintenance dialysis. Calcium acetate when taken with meals combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Maintenance of serum phosphorus below 6.0 mg/dl is generally considered as a clinically acceptable outcome of treatment with phosphate binders. Calcium acetate is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine.

Mechanism of Action: Calcium acetate and other calcium salts are phosphate binders. They work by binding with the phosphate in the food you eat, so that it is eliminated from the body without being absorbed.

Absorption: About 40% is absorbed in the fasting state and approximately 30% is absorbed in the non fasting state following oral administration.

Route of Elimination: Calcium acetate when taken

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with meals, combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces.

Toxicity : Oral, rat: LD_{50} = 4280 mg/kg. Symptoms of overdose include mild hypercalcemia (constipation; loss of appetite; nausea and vomiting), and severe hypercalcemia (confusion; full or partial loss of consciousness; incoherent speech).

II. CONCLUSION:

Phosphate imbalance is a central concern in the management of Chronic Kidney Disease, especially in its advanced stages. As kidney function deteriorates, hyperphosphatemia contributes to multiple systemic complications including mineral bone disorders, cardiovascular disease, and increased mortality. Understanding the complex interplay between hormones such as PTH, FGF23, and vitamin D is key to unraveling the pathogenesis of CKD-related phosphate dysregulation.

This review emphasizes that management of hyperphosphatemia must be multifaceted—encompassing dietary regulation, dialysis modification, and pharmacologic interventions with phosphate binders. Agents such as Sevelamer and calcium acetate, despite their limitations, remain mainstays in clinical use. However, personalized treatment strategies, considering patient comorbidities and tolerance, are essential for optimal outcomes.

Incorporating patient education and lifestyle modifications plays a pivotal role in enhancing compliance and long-term success. Ultimately, a holistic, interdisciplinary approach remains the cornerstone in addressing phosphate control and improving the prognosis of CKD patients.

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