Review Article

Disorders of Phosphate Metabolism: Hypophosphatemia and Hyperphosphatemia

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Abstract

Phosphorus in the body exists as phosphate. Phosphate is the most abundant intracellular anion and exists mostly as organic phosphate compounds critical to cellular functions such as adenosine triphosphate (ATP). The kidneys are the main regulator of phosphate homeostasis. There are three hormonal systems responsible for phosphate homeostasis, the parathyroid hormone (PTH), Fibroblast growth factor-23 (FGF-23)/klotho, and 1,25 dihydroxyvitamin D_3 (1,25 $(OH)_2D_3$, calcitriol). Most cases of hypophosphatemia are acquired and are due to malnutrition as in alcoholism. The kidneys maintain phosphate level in the normal range; therefore, hyperphosphatemia is uncommon until glomerular filtration rate (GFR) falls below 30 ml/min. Hyperphosphatemia is common in patients on renal replacement therapy and is treated with dietary phosphate restriction, and phosphate binders.

Keywords: Hypophosphatemia; Hyperphosphatemia; Electrolyte disorders; Phosphate; Phosphorus

1. Introduction

The focus of this review article is the pathophysiology of phosphate homeostasis in addition to the causes, diagnosis and management of hypophosphatemia and hyperphosphatemia. PubMed database was searched for relevant basic science and clinical articles in addition to the leading journals in nephrology, endocrinology, and internal medicine. The articles reviewed included clinical trials,

comprehensive reviews, and case studies deemed of clinical significance. Major textbook chapters were reviewed as well. Phosphorus is a highly reactive element and is never found free in the body. In the human body phosphorus is bound to oxygen in the form of the polyatomic ion phosphate [$PO4^{3-}$]. There are two forms of phosphate in the body, inorganic phosphate (mineral phosphate) and organic phosphate. Phosphate can exist intracellularly or extracellularly [1]. Most of the body phosphate is in the form of organic phosphate complexed with proteins, lipids, and carbohydrates. Phosphate is the most abundant intracellular anion with a concentration of about 100 mmol/l. Most intracellular phosphate is organic (such as creatine phosphate, adenosine phosphate, and erythrocytes 2,3-diphosphoglycerate [2,3-DPG]). Intracellular phosphate is critical to almost all cellular functions. Inorganic phosphate in the cell is sequestered within intracellular organelles and is complexed with other ions such as calcium (Ca) and magnesium (Mg) [2]. Phosphate is essential to cellular structure, enzymatic processes such as glycolysis, and oxidative phosphorylation (formation of ATP).

Serum phosphate assay is the measurement of inorganic phosphate in the serum. The normal range for serum phosphate is 0.8-1.45 mmol/l (2.5-4.5 mg/dl) [3]. Phosphate should not be expressed as mEq/l. To convert from mmol/l to mg/dl multiply by 31 (the atomic weight of phosphorus) and divide by 10 [i.e., multiply by 3.1]. It is important to emphasize that serum (inorganic) phosphate is a very small fraction (0.3%) of total body phosphate. Most of the inorganic phosphate in the serum exists as free phosphate ions (85%), only 10% is protein-bound and 5% is complexed with Ca, Mg or sodium (Na) [4, 5]. Serum inorganic phosphate consists of two forms of orthophosphate, dihydrogen phosphate ($H_2PO_4^-$) which is a weak acid and monohydrogen phosphate (HPO_4^{2-}) which is a weak base. At the physiologic pH of 7.40, the $HPO_4^{2-}/H_2PO_4^-$ ratio is 4:1 [6]. Phosphate intake varies considerably among individuals depending on their intake of protein and phosphate-rich foodstuffs such as dairy products and processed food. Average daily intake of phosphorus is 22.6-64.5 mmol (700-2000 mg). Serum phosphate follows a circadian rhythm with the lowest level around 11 am and the highest level (about 0.19 mmol/l [0.6 mg/dl] higher) in the afternoon [7].

2. Dietary Phosphate

Most foods contain phosphate especially protein-rich sources. Examples are seeds, legumes, fish, meat, and dairy products. Dietary phosphate is derived from animal protein or plant protein. Organic phosphate in animal protein is easily absorbed after hydrolysis. Phosphate in plant protein such as beans and nuts is stored as phytate. Humans do not have the enzyme phytase. Absence of phytase limits the bioavailability of plant-based phosphate to < 50% [8]. Food additives are an important source of inorganic phosphate in the diet. This source is 90% absorbed and is easily overlooked because phosphorus is not usually included in Nutrition Facts labels. This may have significant implications for patients with advanced chronic kidney disease (CKD) in whom phosphate restriction is routinely recommended. Phosphorus is present in over 10% of medication formulations. Some common medications are high in phosphorus such as amlodipine, lisinopril, sitagliptin, and paroxetine [5]. Not all generic formulations have the same amount of phosphorus. The recommended daily allowance (RDA) of phosphorus in adults is 22.6 mmol (700 mg/day of phosphorus which is equivalent to about 2100 mg of phosphate) [9]. Most adults ingest significantly higher amount of

phosphorus depending on their protein intake. Patients with CKD are advised to ingest approximately 32 mmol (1000 mg) of phosphorus daily.

3. Phosphate Homeostasis

3.1 Phosphate distribution in the body

The human body contains approximately 700 g of phosphorus (approximately 1% of total body weight) [1]. Most of the organic phosphate in the body (85%) is in the bone. Skeletal phosphate is complexed with Ca as hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] which gives the bone its mechanical strength. About 14% of phosphate resides in soft tissues, and only 1% is in the extracellular (ECF) space [10]. Only 0.5% of phosphate in the bone is exchanged daily with the ECF. There are two forms of ECF phosphate: organic (70%) and inorganic (30%). Organic phosphate in the ECF exists as phospholipids.

3.2 Intestinal absorption of phosphate

Phosphate absorption occurs in the small intestine, Figure 1. This absorption is mainly regulated by calcitriol (the most active form of vitamin D) and dietary phosphate intake itself. Phosphate absorption occurs transcellularly or paracellularly (passively) [7]. Transcellular absorption is an active process mediated by NaPi2b (sodium-phosphate cotransporter type IIb or Npt2b) [3]. Calcitriol stimulates and nicotinamide (due to reduction in Npt2b expression) inhibits transcellular phosphate absorption. A diet low in phosphate (as recommended in CKD patients) increases intestinal absorption of phosphate due to upregulation of Npt2b-dependant phosphate absorption [11]. The reverse is true. In humans the paracellular absorption of phosphate is more important than the transcellular absorption [12]. Paracellular absorption of phosphate occurs passively through the tight junctions between enterocytes. Tight junctions are composed of claudins. Cations such as aluminum, Ca and Mg bind phosphate in the intestine and decrease its absorption. Certain Ca and Mg salts are used as phosphate binders in patients with CKD.

3.3 Renal handling of phosphate

The kidneys are the main regulator of phosphate homeostasis [7]. Phosphate homeostasis is linked to calcium (Ca) homeostasis [13]. The three hormonal systems that regulate phosphate homeostasis are PTH, calcitriol and FGF-23/klotho.

3.3.1 PTH: PTH decreases renal phosphate absorption resulting in phosphaturia. It exerts this action by acting on the proximal tubule [1]. It has the opposite effect on Ca resulting in an increase in renal Ca absorption and hypocalciuria. PTH stimulates calcitriol synthesis by the kidneys. Moreover, it stimulates the release of both FGF-23 and phosphate by bone cells. It is known that hyperphosphatemia stimulates PTH secretion. Recently Centeno et al. elucidated the underlying mechanism [14]. A rise in phosphate concentration inhibits the activity of the CaSR by non-competitive antagonism. This effect was demonstrated in isolated human parathyroid cells, and it results in an increase in PTH secretion. The crystal structure of the extracellular domain of the CaSR revealed 4 anion binding sites [15]. Phosphate or sulfate (SO_4) can occupy these sites resulting in inactivation of the CaSR and stimulation of PTH release. Hyperphosphatemia may block the ability of cinacalcet to activate CaSR and suppress PTH resulting in resistance to the effect of this calcimimetic agent. Therefore, CaSR has binding sites for Ca, Mg and phosphate and it is a calcium and a phosphate sensor [15, 16].

3.3.2 Calcitriol: $1,25(OH)_2D_3$ increases both intestinal and renal absorption of phosphate and Ca. [3]. Calcitriol inhibits PTH production by the parathyroid glands and stimulates FGF-23 production by bone cells.

3.3.3 Fibroblast growth factor-23 (FGF-23)/klotho: FGF-23 is produced in the bone by the osteocytes and osteoblasts [17]. FGF-23 level increases when serum phosphate increases resulting in phosphaturia. FGF-23 decreases phosphate reabsorption in the proximal tubule and the small intestine. FGF-23 requires its cofactor (Klotho) to act on FGF receptor 1 [18]. Both FGF-23 and PTH and are phosphaturic, but they have a contrasting effect on 1*α-hydroxylase and subsequently* calcitriol (FGF-23 decreases the renal production of calcitriol, while PTH increases it). FGF-23 suppresses the synthesis of PTH in the parathyroid glands, and calcitriol production by the kidneys. FGF-23 level increases early in the course of CKD and this increase has been associated with an increase in all-cause mortality, incident heart failure and cardiovascular events [19]. Table 1. Compares the actions of PTH and FGF-23.

3.3.4 The role of acid-base balance: Phosphate ($H_2PO_4^-/HPO_4^{2-}$) is one of the buffer systems in the body that mitigate acid-base disorders [20, 21]. Metabolic acidosis causes phosphaturia which leads to acid removal. Metabolic alkalosis stimulates phosphate reabsorption in the kidney.

3.4 Phosphate reabsorption along the nephron

Most of the filtered phosphate is reabsorbed in the proximal tubule (PT) [85%]. The loop of Henle reabsorbs 10%, the distal convoluted tubule (DCT) reabsorbs 3%, and the remaining 2% is reabsorbed in the collecting tubule (CD), Figure 2 [3]. The amount of phosphate excreted in the urine equals the net phosphate uptake by the intestine in a steady state. Phosphate reabsorption is the PT is via the transcellular route and it is an active process that requires movement of Na down its concentration gradient. The apical brush border of the PT contains three different Na-phosphate cotransporters: Npt2a, Npt2c, and PiT-2 (phosphate transporter-2). As mentioned above Npt2b exits in the small intestine. Factors that decrease renal phosphate reabsorption such as high phosphate diet, PTH and FGF-23 downregulate these cotransporters. The reverse is true, factors that increase renal reabsorption of phosphate such as low phosphate diet and calcitriol upregulate these cotransporters [7, 22].

3.5 Phosphate pathophysiology in CKD

In patients with CKD the following sequence of events occurs as the disease progresses: serum Ca decreases due to a decrease in renal calcitriol production. Serum phosphate starts to increase due to the decline in GFR [3]. The decrease in Ca and the increase in phosphate stimulates PTH secretion. The increase in phosphate and PTH stimulates FGF-23 secretion. FGF-23 reduces calcitriol synthesis (by inhibiting renal 1-α hydroxylase and stimulating 24-hydroxylase) and subsequently inhibits intestinal phosphate absorption [17]. The rise in FGF-23 occurs early in the course of CKD (as early as CKD-2) [23]. FGF-23 is independently associated with mortality, initiation of dialysis and cardiovascular events in patients with advanced CKD [24]. Increased FGF-23 levels are also associated with mortality in patients starting hemodialysis [25]. The decrease in Klotho expression in the kidney is an early marker of CKD and chronic kidney disease-mineral and bone disease (CKD-MBD) [26]. Klotho may protect against renal fibrosis and may inhibit vascular calcification. PTH and FGF-23 result in phosphaturia due to a decrease

in the number of Na-phosphate cotransporters in the proximal tubule. This will limit the rise in serum phosphate. As renal function worsens, the above mechanism will not be sufficient to mitigate the increase in serum phosphate and hyperphosphatemia ensues. The fractional excretion of phosphate (FE_{phos}) in advanced CKD can surpass 60% [7].

In patients with stage 5 CKD and in patients on renal replacement therapy, it is common to see low or low normal serum Ca, hyperphosphatemia, high PTH, and high FGF-23 levels. These derangements lead to CKD-MBD. Many patients with CKD have secondary hyperparathyroidism due to the rise in PTH resulting from hypocalcemia precipitated by the decrease in calcitriol production. The parathyroid glands become increasingly resistant to FGF-23. The latter will fail to suppress PTH and this will lead to worsening secondary hyperparathyroidism [3]. Secondary hyperparathyroidism is treated with calcitriol or other vitamin D sterols such as doxercalciferol or paricalcitol. Calcimimetics such as cinacalcet and etelcalcetide are effective treatment options for secondary hyperparathyroidism [27].

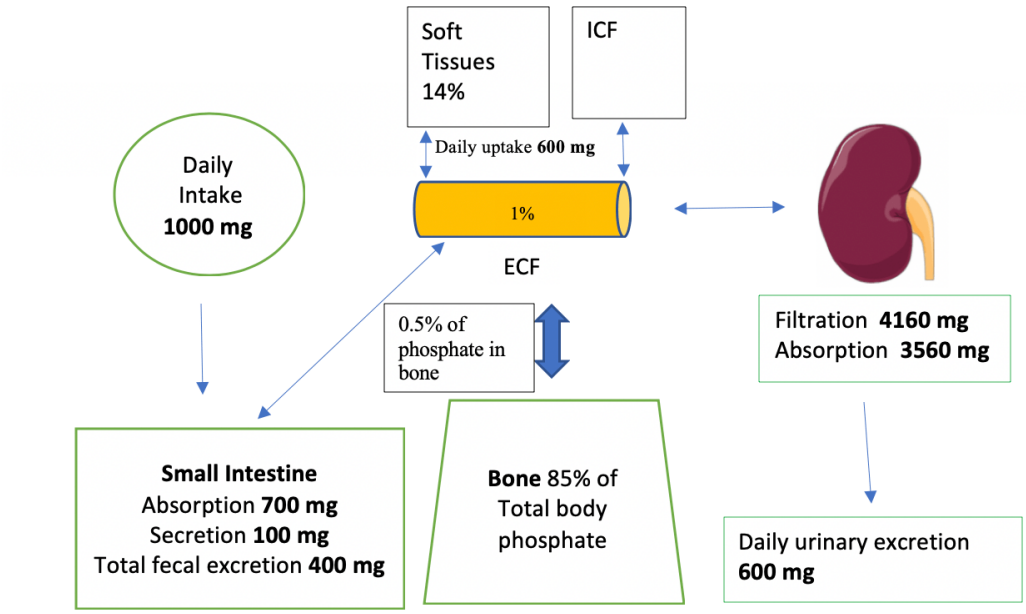

Figure 1: Phosphate homeostasis. Total phosphorus in an average 70 kg adult is about 700 g. ICF is intracellular fluid. Image of kidney is courtesy of Servier Medical Art licensed under a Creative Commons Attribution 3.0 Unported License. https://smart.servier.com

	PTH	**FGF-23**
Production site	Parathyroid gland	Osteocytes and osteoblasts
Main function	Ca and phosphate regulations	Phosphate regulation
Main stimulus	Hypocalcemia	Hyperphosphatemia
Renal effect	Phosphaturia	Phosphaturia
Effect of calcitriol synthesis	Increases	Decreases

Table 1: PTH and FGF-23 comparison.

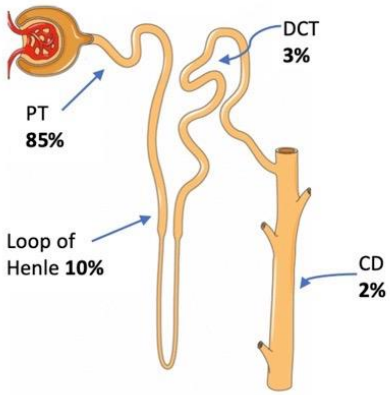

Figure 2: Fraction of phosphate reabsorption in different segments of the nephron. Nephron image is courtesy of Servier Medical Art licensed under a Creative Commons Attribution 3.0 Unported License. https://smart.servier.com Labels added to illustrate the sites of phosphate reabsorption along the nephron.

4. Diagnosis of Phosphate Metabolism Disorders

Diagnosis of hypophosphatemia and hyper-phosphatemia requires a high index of suspicion because phosphate is not included in all routine chemistry panels. Measurement of serum phosphate is easy and available in all laboratories. Other tests are needed including Na, K, Mg and Ca, renal function tests and PTH [28]. Alkaline phosphatase is elevated in mineral and bone diseases such as rickets. FGF-23 assay is only available in reference laboratories. *25-hydroxyvitamin D* level is ordered if vitamin D deficiency is suspected. Urine phosphate measurement is needed if urine phosphate wasting is suspected. Normal fractional excretion of phosphate (FE_{phos}) is 5-20%. In other words, the kidneys excrete 5-20% of the total filtered phosphate [7]. In patients with hypophosphatemia FE_{phos} is < 5% unless it is the result of renal phosphate wasting. Renal wasting of phosphate is the excretion of > 3.2 mmol (100 mg) of phosphate daily.

FE_{phos} = 100 x (Urine $_{phos}$ x Serum $_{creatinine}$) / (Serum $_{phos}$ x Urine $_{creatinine}$)

5. Hypophosphatemia

5.1 Manifestations

Hypophosphatemia can be mild: serum phosphate 0.5-0.75 mmol/l (1.5-2.4 mg/dl), moderate: serum

phosphate 0.32-0.49 mmol/l (1-1.4 mg/dl), or severe: serum phosphate < 0.32 mmol/l (1 mg/dl). Hypophosphatemia is seen in up to 5%-10% of hospitalized patients. The incidence increases to 20%-80% in patients presenting to the emergency department with diabetic ketoacidosis, sepsis and alcohol-related emergencies [29]. Mild hypophosphatemia is usually asymptomatic. Moderate hypophosphatemia is associated with metabolic encephalopathy, hemolysis, thrombocytopenia, seizures, poor appetite, myopathy and rhabdomyolysis [28]. Severe hypophosphatemia can result in respiratory depression, respiratory acidosis, and difficulty in weaning patients off mechanical ventilation [30]. The manifestations of hypophosphatemia are due to intracellular depletion of ATP and erythrocyte 2,3-DPG [31].

5.2 Causes of hypophosphatemia

Hypophosphatemia results from decreased dietary intake of phosphate, decreased intestinal phosphate absorption, transcellular shift of phosphate, or renal phosphate wasting (increased excretion). Most cases of hypophosphatemia are acquired and are due to malnutrition [28]. Genetic causes are rare. Table 2.

Decreased Dietary Intake or Absorption
• Malnutrition, starvation, chronic diarrhea, steatorrhea, intestinal malabsorption, and bariatric surgery • Alcoholism and alcohol withdrawal • Vitamin D deficiency • Vitamin D-dependent rickets type IA (VDDR-1A) • Vitamin D-dependent rickets type 1B (VDDR-1B) • Hereditary vitamin D-resistant rickets (HVDRR)
Intracellular Shift
• Diabetic ketoacidosis (DKA) and nonketotic hyperglycemia • Total parenteral nutrition (TPN) and refeeding syndrome • Increased insulin secretion • Acute respiratory alkalosis • Cellular uptake of phosphate • Hungry bone syndrome • Cannabinoid hyperemesis syndrome • Salicylate poisoning
Increased Renal Phosphate Excretion
• Primary and secondary hyperparathyroidism • Post renal transplantation hypophosphatemia due to high level of PTH and FGF-23 • Diuretics, the diuretic phase of acute tubular necrosis (ATN) and post-obstructive diuresis • Acquired Fanconi syndrome • Tumor-induced osteomalacia (TIO) with high FGF-23 level • Continuous renal replacement therapy (CRRT)

Drug-mediated hypophosphatemia • Corticosteroids, imatinib, carbonic anhydrase inhibitors, theophylline, estrogens, acyclovir, diuretics, phosphate binders, antacids, phenobarbital, phenytoin, IV iron
Genetic Causes of Hypophosphatemia (Familial Hypophosphatemia) Familial Hypophosphatemia Due to FGF-23 Excess • X-Linked hypophosphatemic rickets (XLH) • Autosomal dominant hypophosphatemic rickets (ADHR) • Autosomal recessive hypophosphatemic rickets (ARHR) • McCune-Albright Syndrome (fibrous dysplasia), autosomal dominant, somatic mosaicism FGF-23-Independent Familial Hypophosphatemia • Fanconi Syndrome and type I (proximal renal tubular acidosis [RTA]) • Hereditary hypophosphatemic rickets with hypercalciuria (HHRH), autosomal recessive

Table 2: Causes of Hypophosphatemia.

5.2.1 Decreased dietary intake or absorption:

5.2.1.1 Malnutrition, chronic diarrhea, steatorrhea, and intestinal malabsorption: malnutrition is a common cause of hypophosphatemia especially with concomitant poor protein intake and vitamin D deficiency [28]. Fat malabsorption reduces absorption of fat-soluble vitamins such as vitamin D, which results in concomitant hypocalcemia.

5.2.1.2 Alcoholism and alcohol withdrawal: these are common causes of severe hypophosphatemia and are associated with malnutrition and multiple electrolyte disorders [32]. Patients with alcoholism commonly have multiple causes of hypophosphatemia including poor intake of phosphate and protein, vitamin D deficiency, administration of phosphate-free intravenous fluids (IVF) and hyperventilation [33].

5.2.1.3 Vitamin D deficiency: this is a common cause of hypophosphatemia and is due to inadequate nutrition or lack of sun exposure [28]. Vitamin D deficiency or resistance decreases intestinal phosphate absorption. It also decreases intestinal calcium absorption resulting in hypocalcemia, secondary hyperparathyroidism and subsequently phosphaturia.

5.2.1.4 Vitamin D-dependent rickets type IA (VDDR-1A): VDDR-1A is an autosomal recessive disorder due to an inactivating mutation in the *CYP27B1* gene that encodes *1*α-hydroxylase. Calcitriol level is low with subsequent rise in PTH, hypocalcemia, hypophosphatemia and hyperphosphaturia [34]. This disorder is treated with calcitriol.

5.2.1.5 Vitamin D-dependent rickets type 1B (VDDR-1B): VDDR-1B is due to loss-of-function mutation of *CYP2R1*, the gene that encodes the enzyme responsible for 25-hydroxylation of vitamin D [35]. It is treated with calcidiol (*25-hydroxyvitamin D*) and not with nutritional vitamin D compounds such as ergocalciferol and cholecalciferol because they are *25-hydroxyvitamin D* precursors.

5.2.1.6 Hereditary vitamin D-resistant rickets (HVDRR): HVDRR is extremely rare and is due to an inactivating mutation in the vitamin D receptor gene [34].

5.2.2 Intracellular shift:

5.2.2.1 Diabetic ketoacidosis (DKA) and nonketotic hyperglycemia: Initially patients manifest with normal or high phosphate (and potassium). After initiation of IVFs and intravenous (IV) insulin, hypophosphatemia (and hypokalemia) ensue due to intracellular shift [7]. Osmotic diuresis and phosphate-free IVFs aggravate hypophosphatemia.

5.2.2.2 Total parenteral nutrition (TPN): Insulin in TPN causes intracellular shift of phosphate. Hypophosphatemia will worsen if phosphate is not included in the TPN [7].

5.2.2.3 Increased insulin secretion: Hypophosphatemia due to increased insulin secretion is seen upon refeeding patients with malnutrition as in anorexia nervosa or alcoholism [36, 37]. Epinephrine and glucagon also drive phosphate intracellularly and can cause mild hypophosphatemia.

5.2.2.4 Acute respiratory alkalosis: as in hyperventilation from any cause, mechanical ventilation, sepsis, and salicylate poisoning. This is a common cause of hypophosphatemia in hospitalized patients [36].

5.2.2.5 Cellular uptake of phosphate: as in rapidly proliferating malignancies such as Burkitt's lymphoma and acute myelogenous leukemia [38].

5.2.2.6 Hungry bone syndrome: this disorder is seen post parathyroidectomy and can result in hypophosphatemia and severe hypocalcemia [36].

5.2.2.7 Cannabinoid hyperemesis syndrome: Hypophosphatemia probably results from intracellular shift due to hyperventilation [39].

5.2.3 Increased renal phosphate excretion:

5.2.3.1 Primary and secondary hyperparathyroidism: PTH causes hypercalcemia and hypophosphatemia [40]. The latter is due to its phosphaturic effect.

5.2.3.2 Post renal transplantation hypophosphatemia: renal phosphate wasting is common post renal transplantation [41]. It is due to elevated FGF-23 level and residual secondary hyperparathyroidism due to end stage renal disease (ESRD).

5.2.3.3 Diuretics, the diuretic phase of acute tubular necrosis (ATN), and post-obstructive diuresis: short-term hypophosphatemia can be seen due to profound diuresis [42].

5.2.3.4 Acquired fanconi syndrome: hypophosphatemia due to impaired proximal tubule phosphate reabsorption is one of the manifestations of Fanconi syndrome [7]. Some cases are induced by medications, most commonly aminoglycosides, tenofovir, or ifosfamide. A recent report described a case of severe hypophosphatemia due to Fanconi syndrome induced by the checkpoint inhibitor nivolumab [43, 44].

5.2.3.5 Tumor-induced osteomalacia (TIO): Mesenchymal tumors can cause hypophosphatemia due to secretion of FGF-23 [45]. Surgical resection will lead to resolution of hypophosphatemia.

5.2.3.6 Continuous renal replacement therapy (CRRT): hypophosphatemia is common in patients receiving CRRT [46]. Phosphate is routinely added to dialysate or replacement fluids.

5.2.4 Drug-mediated hypophosphatemia:

Multiple mechanisms are at play in this category. Several medications increase phosphate excretion in the urine including corticosteroids, imatinib mesylate, carbonic anhydrase inhibitors such as acetazolamide, theophylline, estrogens, acyclovir, and diuretics such as hydrochlorothiazide [42]. Phosphate binders are used frequently in patients with advanced CKD for the management of hyperphosphatemia. They bind phosphate and decrease its intestinal absorption. Hypophosphatemia is seen if the patient continues to take phosphate binders during periods of poor intake of phosphate-rich foods. Antacids containing aluminum, calcium, or magnesium can cause hypophosphatemia by the same mechanism. Phenobarbital and phenytoin can cause hypophosphatemia due to vitamin D deficiency. There has been several case reports of IV iron-induced hypophosphatemia [47]. The proposed mechanisms are elevated FGF-23 and low calcitriol levels in addition to direct proximal tubule toxicity.

5.2.5 Genetic causes of hypophosphatemia (Familial Hypophosphatemia):

Vitamin D dependent and resistant rickets were discussed above. Familial hypophosphatemia is rare. Hypophosphatemia is due to renal phosphate wasting in all of these disorders. Renal phosphate wasting is either FGF-23 dependent or FGF-23 independent.

5.2.5.1 Familial Hypophosphatemia Due to FGF-23 Excess

X-Linked hypophosphatemic rickets (XLH): XLH is an autosomal dominant disorder responsible for more than 80% of the cases of familial hypophosphatemia. This form of rickets is due to a loss-of-function mutation in the PHEX gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) with subsequent rise in FGF-23 level and renal phosphate wasting [48]. Calcitriol is low or normal in this disorder. Affected children have impaired growth, osteomalacia, rickets, lower extremities pain, and deformities. Burosumab is a recombinant human monoclonal antibody that blocks FGF-23. It was approved by the US Food and Drug Administration (FDA) in 2018 for the treatment of X-linked hypophosphatemia [49].

Autosomal dominant hypophosphatemic rickets (ADHR): ADHR is due to one of several mutations in the FGF-23 gene which makes FGF-23 resistant to cleavage with subsequent rise in FGF-23 level [50].

Autosomal recessive hypophosphatemic rickets (ARHR): ARHR is due to inactivating mutations in the genes for dentin matrix protein 1 (DMP1) or ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) [50].

McCune-Albright syndrome: in this disorder hypophosphatemia is associated with polyostotic (i.e. involving many bones) fibrous dysplasia of the bone [51]. Patients usually have café-au-lait spots on their skin.

5.2.5.2 FGF-23-Independent familial hypophosphatemia

Fanconi syndrome and type I (proximal renal tubular acidosis) RTA: this syndrome manifests with hyperphosphaturia, glucosuria, aminoaciduria, and bicarbonaturia. Renal K wasting is seen as well [50, 52]. Some cases are idiopathic, others are

associated with diseases such as Wilson disease, hereditary fructose intolerance, cystinosis, Lowe syndrome, and Dent disease.

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH): HHRH is an autosomal recessive disorder due to mutations in the gene for Npt2c resulting in renal phosphate wasting [53]. FGF-23 is appropriately suppressed in this disorder.

5.3 Treatment

Phosphate is replaced orally (PO) in patients with mild hypophosphatemia. Milk contains 0.9 mg of phosphorus per ml. Commonly 1-2 g is administered daily divided in three doses. Each tablet of K-Phos® Neutral contains 250 mg (8 mmol) of phosphate, 298 mg (13 mmol) of Na and 45 mg (11 mmol) of K. A starting dose is 1-2 tablets 3-4 times daily. Gastrointestinal side effects including diarrhea are the limiting factor. Patients with moderate and severe hypophosphatemia require IV and PO replacement (if feasible) [41]. IV phosphate is available as Na phosphate and K phosphate. The rate should not exceed 7.5 mmol/h. K phosphate should be avoided in patients with hyperkalemia. Serum phosphate is monitored every 12-24 h during IV phosphate replacement.

6. Hyperphosphatemia

Hyperphosphatemia is defined as serum phosphate > 1.45 mmol/l (4.5 mg/dl). Individuals with normal renal function do not develop hyperphosphatemia solely due to increased phosphate intake. Phosphorus intake up to 130 mmol/d (4000 mg/d) will not result in hyperphosphatemia due to the great ability of normal kidneys to increase phosphate excretion. The tolerable upper daily intake level for phosphorus set by the US Food and Nutrition Board is 130 mmol (4000 mg) in individuals 9-70 years of age [9]. Over 50% of patients on renal replacement therapy have hyperphosphatemia despite use of phosphate binders [54].

6.1 Causes of hyperphosphatemia

Common causes of hyperphosphatemia are listed in table 3.

Compromised renal function: acute kidney injury and advanced CKD
Cellular release of phosphate: rhabdomyolysis and tumor lysis syndrome
Increased gastrointestinal or renal phosphate absorption: hypoparathyroidism, vitamin D toxicity, acute phosphate nephropathy, fibroblast growth factor receptor inhibitors such as pemigatinib
Phosphate shift to extracellular fluid: lactic acidosis, diabetic ketoacidosis, acute and chronic respiratory acidosis
Genetic: familial tumoral calcinosis
Pseudohyperphosphatemia: hyperlipidemia, liposomal amphotericin B, hyperglobulinemia, hyperbilirubinemia

Table 3: Causes of Hyperphosphatemia.

6.1.1 Compromised renal function: hyper-phosphatemia is primarily seen in patient with compromised renal function, namely acute kidney injury (AKI) and CKD [55]. The diagnosis is easily made due to concomitant rise in serum creatinine. Chronic hyperphosphatemia is seen in patients with advanced CKD (stage 4 and 5 and in patients on renal replacement therapy). Serum phosphate starts to increase once GFR is < 30 ml/min/1.73 m^2 (CKD stage 4 or higher) [56].

6.1.2 Cellular release of phosphate: Acute hyperphosphatemia is seen in patients with cell lysis (such as rhabdomyolysis, malignant hyperthermia, and tumor lysis syndrome [TLS]) due to acute increase in phosphate that overwhelms the excretory ability of the kidneys [57]. Admission hyperphosphatemia is a risk factor for the development of TLS in the appropriate setting [58].

6.1.3 Increased phosphate absorption: as in hypoparathyroidism (increased renal tubular absorption), and vitamin D toxicity (increased GI and renal tubular absorption). Hyperphosphatemia is seen in some patients after taking PO sodium phosphate bowel preparation solution prior to colonoscopy. Acute phosphate nephropathy has been described in some patients taking this bowel preparation manifesting as AKI [59, 60]. Ca phosphate deposits were seen in renal biopsy specimens. These solutions should be avoided in general, particularly in patients with CKD. Pemigatinib is a kinase inhibitor used for the treatment of advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement [61]. It results in hyperphosphatemia in over 90% of patients due to FGFR inhibition. Hyperphosphatemia can be severe, and it is due to increased phosphate reabsorption in the proximal tubule. Hyperphosphatemia is seen with other FGFR inhibitors such as infigratinib.

6.1.4 Phosphate shift to extracellular fluid: as in lactic acidosis and diabetic ketoacidosis (prior to initiation of treatment) [62, 63]. The same effect is seen in acute and chronic respiratory acidosis.

6.1.5 Genetic: Familial tumoral calcinosis is a rare autosomal recessive disorder. Hyperphosphatemia is due to increased proximal tubular reabsorption. Mutations in GALNT3 and FGF-23/Klotho genes have been described leading to a decrease in FGF-23 level, increase in calcitriol level and subsequent hyperphosphatemia [64]. This is the opposite of autosomal dominant and X-linked hypophosphatemic rickets mentioned above.

6.1.6 Pseudohyperphosphatemia: as in hyperlipidemia, prolonged treatment with liposomal amphotericin B, hyperglobulinemia (especially multiple myeloma), and hyperbilirubinemia [65]. Phosphate level should be analyzed using a different assay.

6.2 Complications of hyperphosphatemia

Most patients are asymptomatic. Some patients develop pruritus. Hyperphosphatemia is associated with vascular calcifications, calciphylaxis (calcific uremic arteriolopathy), and increased morbidity and mortality in CKD patients [66, 67]. Hyperphosphatemia is potentially associated with increased morbidity and mortality in the general populations as well; however, this issue needs further study [68]. Severe and acute hyperphosphatemia can result in hypocalcemia. The latter can result in muscle cramps, arrhythmias, hypotension, and seizures.

6.3 Treatment of hyperphosphatemia

Acute hyperphosphatemia is treated by addressing the underlying cause such as rhabdomyolysis and TLS. Patients may benefit from IVFs. As in hyperkalemia, IV dextrose and insulin shift phosphate intracellularly [7]. Acetazolamide increases urinary phosphate excretion. Hemodialysis and CRRT are effective in the management of acute severe hyperphosphatemia seen in the course of AKI as in patients with TLS. Chronic hyperphosphatemia is treated with dietary phosphate restriction and phosphate binders. Dialysis patients are advised to

restrict their phosphorus intake to 32 mmol/d (1000 mg/day). If the daily net uptake of phosphate is 60% and dietary compliance is 100%, the weekly phosphorus intake amounts to 135 mmol (4200 mg). A standard 4-hr hemodialysis session removes 22.5-29 mmol (700-900 mg) of phosphorus. If the patient undergoes the customary thrice weekly dialysis, total weekly hemodialysis phosphorus removal is 68-87 mmol (2100-2700 mg) or 50-64% of net phosphorus uptake [5]. In reality this percentage is significantly lower due to non-adherence to low phosphorus diet and phosphate binders. Increasing the frequency and/or the duration of hemodialysis will result in better control of hyperphosphatemia [69]. Peritoneal dialysis (whether continuous ambulatory, automated or continuous cycling) removes approximately 90 ± 32 mmol (2800 ± 1000 mg) of phosphorus weekly [70].

Most patients on renal replacement therapy will need phosphate binders [71]. The role of phosphate binders in patients with CKD who are not on renal replacement therapy remains to be defined. The recently published IMPROVE-CKD trial randomized 278 individuals with stage 3b or 4 CKD and serum phosphate > 1 mmol/l (3.10 mg/dl) to lanthanum carbonate or placebo [72]. After 96 weeks, there was no significant differences between the two groups with regard to arterial stiffness, abdominal aortic calcification, FGF-23, or serum phosphate levels. Phosphate binders limit phosphate intestinal absorption. These binders may upregulate Npt2b in patients with CKD which leads in increased intestinal phosphate absorption in a manner similar to low phosphate diet [11, 73]. This effect may limit the effectiveness of phosphate binders. Commonly used phosphate binders include calcium carbonate, calcium acetate, magnesium carbonate, sevelamer carbonate, sucroferric oxyhydroxide, lanthanum carbonate, and ferric citrate [74]. Non-calcium binders are preferred [61, 62]. Phosphate binders add to the high pill burden in patients on renal replacement therapy. Renal dietitians play a crucial role in the management of hyperphosphatemia in patients on renal replacement therapy [70, 71]. Nicotinamide did not significantly lower FGF-23 or serum phosphate level in a study involving 205 patients with stage 3b/4 CKD over 12 months [79]. Tenapanor is under investigation as a novel treatment for hyperphosphatemia. It is a minimally absorbed inhibitor of sodium hydrogen exchanger 3 (NHE-3). It lowers intestinal phosphate absorption by targeting the paracellular pathway of phosphate absorption. A phase 3 randomized double blind trial in 219 hemodialysis patients showed a mean phosphate reduction of 0.32-0.39 mmol/l (1.0-1.2 mg/dl) over an interval of 8 weeks [80]. The main adverse effect of tenapanor is diarrhea.

7. Conclusion

- There are three main phosphate regulating hormonal systems: PTH, vitamin D, and FGF-23/klotho.
- Phosphate level is maintained by the interplay between the above hormones and the bowel (phosphate absorption), the kidneys (phosphate reabsorption and excretion), phosphate shift between ICF and ECF, and bone (phosphate uptake and release).
- Hypophosphatemia is the result of poor dietary intake, decreased intestinal phosphate absorption, renal phosphate wasting, or intracellular shift of phosphate.
- The most common causes of hypophos-phatemia are malnutrition and vitamin D deficiency.
- Hyperphosphatemia is mainly seen in patients

with AKI, stage 4 or 5 CKD, and patients on renal replacement therapy. It is treated with dietary phosphate restriction and phosphate binders.

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