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Review Article

Clinical Implications of Phosphate Metabolism

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Abstract

Phosphate disorders are very common especially in hospitalised patients. As phosphate is not routinely measured with serum electrolytes, it often remains undetected. Phosphate disorders have serious clinical consequences which can be easily avoided or treated if the phosphate abnormalities are detected. This is especially true for patients who are critically ill, ICU patients on ventilators, patients with muscles and bone diseases, patients with renal or intestinal diseases, or endocrine abnormalities, etc. Disease burden, disease-related disability and cost is a significant problem especially when not managed appropriately. The cost and burden on health care is very high, but the treatment of these disorders is simple. Physicians managing these cases need to be mindful of these preventable and treatable disabilities. Junior doctors and trainees often find it hard to understand these issues and manage electrolytes especially phosphate.

This review article focuses on the elaboration of these biochemical changes of phosphate, its clinical implications and management.

Keywords: Hypophosphatemia, Hyperphosphatemia, Phosphate metabolism.

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Introduction

Phosphate Metabolism

Phosphate is mainly present in the bones (85%). Remaining 14% of the total body phosphate is present inside the cells and 1% in the blood. Approximately, 1% of total body weight is phosphate.

Phosphate regulation in human body: Phosphate is regulated by dietary intake, intestinal absorption (jejunum), bones, vitamin D 3, and renal tubules. Jejunum is the main site for absorption of the dietary phosphate. Almost, 70-80% of the dietary phosphate is absorbed. This is both Vitamin D & sodium (Na) dependent & independent.[1]

Vitamin D & phosphate: Vitamin D3 promotes absorption of calcium and phosphate from the small intestine. Vitamin D 3 synthesis in the renal tubules is via 1-alpha hydroxylase which is stimulated by parathyroid hormone (PTH), insulin growth factor (IGF-1), growth hormone (GH), low serum calcium, low serum phosphate, and calcitonin. This enzyme is inhibited by high serum phosphate level, high serum calcium, high levels of vitamin D3, & fibroblast growth factor (FGF23).[2,3]

Hormonal regulation of phosphate: Hormones involved in the phosphate metabolism are insulin, parathyroid hormone (PTH) & fibroblast growth factor (FGF-23). Both PTH & FGF-23 block reabsorption of phosphate from the proximal tubules. Almost 80% of the filtered phosphate is reabsorbed by these tubules. Only 10-20% of the filtered phosphate is normally lost in the urine. High levels of these hormones increase this loss of phosphate in the urine and cause low serum phosphate. FGF-23 also reduces Vitamin D 3 synthesis by inhibiting 1-alpha hydroxylase and indirectly decreases intestinal absorption of calcium and phosphate. High level of PTH or FGF-23 cause low serum phosphate, whereas low levels of PTH or FGF-23 causes high serum phosphate. Deficiency of FGF-23 can cause high phosphate & high Vit D3, and tissue calcification. FGF-23 is produced by mesenchymal cells (osteoblasts, fibroblasts, etc.). Iron infusion induces production of FGF-23 and may cause low serum phosphate.[4,5]

Insulin promotes intracellular shifting of glucose, phosphate, potassium and magnesium. Lack of insulin's effect causes high serum level but deficient intra cellular levels of phosphate. Insulin replacement or glucose intake reduces serum phosphate level due to this intra cellular shifting of the phosphate along with glucose (carbohydrates). This phosphate is needed for trapping these monosaccharides (glucose, fructose, etc.) inside

the cells and also for ATP synthesis.[4,5]

Renal tubules and phosphate: Renal reabsorption is the main & dominant mechanism to regulate the serum level of phosphate. Proximal tubules are the main site of the reabsorption. Its sodium coupled reabsorption. Phosphate reabsorption from the renal tubules is increased by low dietary intake of phosphate, low serum phosphate level, low PTH, low FGF-23, & increased Na (sodium) reabsorption. Whereas, it's reduced by sodium loss, polyuria, high serum level of phosphate, high dietary intake of phosphate, high PTH, & high FGF-23.[6-8]

Hypophosphatemia

Causes of hypophosphatemia:

High fibroblast growth factor (FGF-23): High FGF-23 is present in the following conditions:

- Oncogenic hypophosphatemia
- Hypophosphatemic Ricketts (X-linked, autosomal dominant or autosomal recessive),
- Hypophosphatemic Ricketts due to Klotho gene mutation causing high FGF-23 & high PTH.
- FGF-23 is also high in fibrous dysplasia (McCune Albright Syndrome).

All these conditions increase the production of FGF-23 except autosomal dominant hypophosphatemic Ricketts which are due to decreased catabolism of FGF-23. High FGF-23 also suppresses vitamin D3 (calcitriol) except in hypophosphatemic Ricketts which also has high PTH which normalises calcitriol. Similarly oncogenic high FGF-23 may also have normal vitamin D3 due to high PTHrP.

Autosomal recessive and X-linked starts in early childhood and has high urinary phosphate. Autosomal dominant may have delayed onset in teen or early adulthood and therefore more likely to be confused with oncogenic hypophosphatemia. This malignancy related loss of phosphate in urine due to high FGF-23 is seen in mesenchymal tumours. Such cases often have normal phosphate before the onset of tumour. If PTH & parathyroid hormone related protein (PTHrP) levels are normal then FGF-23 should be assessed for the cases of chronic low phosphate levels.[9-14]

Renal phosphate loss with low PTH & low FGF 2315-20

- ***Hereditary Hypophosphatemic Ricketts with hypercalciuria:*** it us due to defective Na-phosphate channels in proximal tubules. As it is without high FGF-23, therefore Vit D 3 synthesis is normal. The low serum phosphate stimulates Vit D 3 synthesis independent of PTH, and cause high serum calcium followed by high urinary calcium which causes renal stones, nephrocalcinosis and / or renal failure too. PTH & FGF-23 are low. High levels of Vit D3 are independent of PTH.
- Hypophosphatemia with renal stones and osteoporosis 1 / (Fanconi syndrome) is impaired reabsorption of phosphate and other chemicals in the proximal tubules. There is loss of phosphate, amino acids, glucose, HCO3, sodium and water in urine. Vitamin D3 synthesis is not affected which causes high vitamin D3 & high serum calcium followed

Table 1: *Causes of hypophosphatemia*

Causes of Hypophosphatemia	Main Mechanism
Renal tubules dysfunction (tubular damage, polyuria, diuresis, reduced sodium absorption, high serum phosphate, hormonal excess, genetic diseases of the tubular channels, etc.).	Reduced renal reabsorption
GIT loss	Reduced absorption, increased loss.
Nutritional deficiency	Reduced intake
Hormones (excess of PTH, PTHrP, FGF-23, Calcitonin)	Reduced renal reabsorption
Vitamin D3 deficiency	Increased reabsorption from the GIT and Kidneys.
Acidosis	Renal tubular loss (phosphate neutralises H-ions in the urine)
HCO3	Renal tubular loss
Alkalosis	Intracellular shifting due to increased glycolysis.
Shifting inside the bones	Hungry bones, growing bones
Shifting inside the cells (refeeding, insulin, glucose, catecholamines, excess of cytokines, recovery from hypothermia)	Phosphate needed for trapping of monosaccharides and for ATP production. Sympathetic activity, insulin, and/or metabolic recovery of the cell are main reasons.
CKD	Excessive removal by dialysis or phosphate binders
Renal transplant	Due to high PTH in the first few weeks before it normalises.

by high urinary calcium, renal stones, nephrocalcinosis, renal failure, etc. PTH & FGF-23 are low. High levels of vitamin D3 are PTH independent. The disease is due to genetic mutation causing NPT2 dysfunction.

- ***Hypophosphatemia with renal stones and osteoporosis 2:*** it's defect in phosphate & calcium reabsorption without affecting vitamin D, serum calcium and other functions of proximal tubule. PTH level is normal or low. This is due to mutation in NHEFR gene causing NPT2 dysfunction.
- Hyper active PTH receptors or FGF-23 receptors on the renal tubules will have affect similar to hyperparathyroidism or high FGF-23, respectively. However, the blood levels of PTH or FGF-23 will be lower as the receptors don't need stimulation by the respective hormone., Over active PTH receptor is Jansen's metaphyseal chondrodysplasia. Overactive FGF-23 receptor is Osteoglophonic dysplasia.
- McCune Albright syndrome can cause high PTH level along with high level of other hormones as well due to G-protein mutation.
- High level of PTH, FGF-23 or Calcitonin also increases phosphate loss in urine.
- Drugs: diuretics affecting proximal tubules, loop of Henle or distal tubules. IV iron increases FGF-23 level. Anti epileptics may also cause loss of calcium and phosphate in urine. Corticosteroids increases loss of calcium and phosphate in urine. Drugs damaging tubules such as aminoglycosides, B-Amphotericin, cisplatin, cancer chemotherapeutic drugs, etc. can cause acquired Fanconi's syndrome.
- High HCO3 level also causes phosphate loss in urine.
- Polyuria of any cause decreases tubular reabsorption. Volume expansion also causes low phosphate by causing polyuria.
- Renal tubular damage (tubulointerstitial nephritis (TIN), acute tubular necrosis (ATN), paracetamol toxicity, NSAIDs, hypothermia, drugs, etc.).
- Chronic kidney disease (CKD) cases can have low phosphate due to phosphate removal by dialysis and phosphate binders in addition to poor oral intake and absorption.
- Acidosis of any causes (metabolic, respiratory, salicylate poisoning, DKA, etc.) as phosphate is used to bind with free H-ions in the urine. On the other hand, low phosphate level reduces reabsorption at proximal tubules (due to cell dysfunction) which affects HCO3 reabsorption as well causing RTA 2 like picture.
- Renal transplant causes loss of phosphate especially in the first month due to the high PTH & FGF-23 levels present before the transplant.

Shifting of phosphate into cells &/or bones [1,10]

- Respiratory alkalosis or recovery from the acidosis promotes intracellular shifting of the phosphate. Alkalosis inside the cells stimulates glycolysis by activating the key enzyme for glycolysis, phosphofructokinase (PFK) to produce ATP. Hence, increasing the intra cellular need for phosphate. Hyperventilation causes respiratory alkalosis and low serum phosphate.
- Glucose & insulin: as phosphate demand inside the cells increases to retain the glucose (fructose, etc.) inside the cells and also for ATP production.
- High catecholamines also cause intracellular shifting of phosphate.
- Cytokines stimulate intra cellular shifting of phosphate; examples include sepsis, trauma, burns, ICU patients and bone marrow transplant cases.
- Refeeding syndrome as the cells are hungry.
- Recovery from hypothermia also causes intra cellular shifting for metabolic recovery.
- Hungry bones (especially after parathyroid surgery).
- Rapid cell production such as leukemic blast crisis, severe acute lymphoma, etc. as cells needs phosphate. Erythropoiesis stimulation by erythropoietin (Epo) or other mechanisms can also cause low phosphate.

GIT causes of low phosphate [1,3]

- Malnutrition, anorexia or dietary restrictions.
- Inadequate phosphate in total parenteral nutrition (TPN).
- Vitamin D deficiency or resistance to vitamin D decreased absorption from the intestine.
- Malabsorption (intestinal, biliary or pancreatic causes).
- Chronic alcoholism causes pancreatic and liver disease related malabsorption in addition to low dietary intake.
- Antacids containing Mg, calcium or Aluminium will bind with the phosphate and impairs its absorption.
- Phosphate binders cause loss of phosphate from the intestine

Clinical manifestations of hypophosphatemia

Mechanism of clinical symptoms due to abnormal

phosphate are:

- Cell dysfunction due to lack of ATP,
- Cell death due to severe lack of ATP,
- Non-functioning of ATP-dependent ion-channels and enzymes,
- Low 2-3 diphosphoglycerate in RBC leading to decreased oxygen detachment from the oxygenated haemoglobin. This causes tissue hypoxia.
- Low or high calcium or magnesium levels along with phosphate abnormalities will add to the clinical picture.
- Tissue calcification causes tissue damage due to ischemia and calcium deposition.

Acute phosphate deficiency is usually due to redistribution from the blood into the cells and is often not symptomatic. Symptoms occur when there is phosphate deficiency inside the cells. Chronic deficiency is often either due to renal loss or GIT loss. Renal loss has high level of 24-hour urinary phosphate or spot urinary phosphate. Non-renal causes of low phosphate have low urinary phosphate. Symptoms also depends on the severity of the deficiency,[21-24] Severity of deficiency: Level b/w 2.0-2.5 mg is mild, >1.0 but <2.0 mg is moderate and <1.0 mg is severe deficiency. Mild deficiency is often not symptomatic.

- Neurological symptoms and signs: Neurological dysfunction leads to paraesthesia, confusion, delirium, irritability and tiredness. Severe deficiency may cause metabolic encephalopathy, seizures, coma, pontine demyelinoses, etc.
- Cardiac: Reduced contractility of the myocardium can worsen heart failure. Reduced ATP can cause arrhythmia due to dysfunction of the cardiac ion channels.
- Skeletal & smooth muscles: Muscle weakness, paralysis, respiratory failure, diaphragmatic weakness, pharyngeal dysphagia, reduced intestinal motility and Ileus are due to paralysis of skeletal and smooth muscles. Rhabdomyolysis can also happen in severe phosphate deficiency.
- Liver: Hepatocytes dysfunction and necrosis can be due to severe phosphate deficiency.
- Blood cells: Hemolysis &/or thrombocytopenia can occur due to severe phosphate deficiency. Dysfunction of the platelets can cause bleeding issues. Immunodeficiency may be due to leucocyte dysfunction.
- Renal tubules: Renal tubular dysfunction leads to reduced reabsorption and increased urinary loss of calcium. Magnesium, HCO3, etc.
- Bones: Reduced phosphate in the bones leads to under mineralisation &/or demineralisation. This causes release of calcium from the bones leading to rickets or osteoporosis. High calcium leads to increased urinary calcium as well,[21-24]

Diagnostic workup for hypophosphatemia

- Serum phosphate level should be measured when low level is suspected or for those with muscle disease, renal failure, endocrinal problems, malnourished or those with malabsorption, severely sick patients, and those on ventilators.
- Serum calcium, renal functions, vitamin D, urinary calcium and phosphate, PTH, PTHrP and FGF-23 levels, etc. are additional tests which help find the cause of low phosphate.
- Those with high serum calcium levels with low phosphate levels, PTH measurement is especially important. Such cases should measure PTHrP if PTH level is low.
- If there is no hypercalcemia and no hyperparathyroidism, measurement of FGF-23 for genetic or oncogenic causes is important. Early age of onset, high FGF-23 with low calcitriol level favours genetic causes and indicates genetic studies. Genetic analysis may not be positive in every case and absence of such abnormalities doesn't exclude the genetic causes. X-linked or autosomal recessive type of hypophosphatemic Ricketts presents at early age. Autosomal dominant cases manifest at late age and hence can confuse with oncogenic high FGF-23. Adult patient with previously normal phosphate would necessitate search for oncogenic causes of high FGF-23. Radiological and nuclear scans (CT / MRI), fluoro-deoxy glucose (FDG) positron emission tomographic (PET)-CT, octreotide scan, etc.) may help localise the tumour.[25,26]
- High urinary phosphate (>100 mg/24-hour hours or <95% reabsorption of phosphate by the renal tubules) means renal loss and low urinary phosphate indicates non-renal aetiology.[26]

Treatment of hypophosphatemia: Mild to moderate deficiency can be treated with oral phosphate, whereas severe deficiency (<1 mg or severely symptomatic case) needs intravenous replacement as well. Those with chronically low phosphate needs replacement for bones, muscles and growth. Oral phosphate can cause diarrhea whereas IV carries the risk of tissue calcification and hypocalcaemia, arrhythmia, and calcification related renal failure.

Usually, dose of the IV phosphate is 0.25-0.5 mmol / kg in 8-12 hours (max up to 80 mmol), whereas oral phosphate dose is 1-4 gm in divided doses. It's important to monitor calcium, phosphate, renal functions and cardiac

rhythm during IV phosphate replacement. Sodium or K phosphate can be used for IV,[27]. Low phosphate due to high FGF-23 has low calcitriol and needs replacement for calcitriol as well along with phosphate. Burosumab is antibody against FGF-23 and can be used for the causes having high FGF-23.27,28

Hyperphosphatemia

Causes of hyperphosphatemia:

High phosphate level is mostly common due to decreased glomerular excretion of the phosphate when the eGFR is 20 or below [29].

Causes of hyperphosphatemia other than chronic kidney disease (CKD)

Increased reabsorption from proximal tubule;

- Hypoparathyroidism,
- Pseudo-hypoparathyroidism (lack of receptor's response to PTH)
- Low magnesium (as it reduces PTH secretion and functions).
- Acromegaly as IGF-1 increases reabsorption from the proximal tubules.
- Lack of FGF-23 due to genetic or acquired causes

Increase intake (especially when kidneys are not working)

- Milk alkali syndrome
- Laxatives containing phosphate
- Drugs containing phosphate: lipophilic Amphotericin, fosphenytoin, foscarnet, etc.

Release from the cells or the bones

- Lack of insulin (hyper catabolic states).
- Tissue damage releasing phosphate from the cells (tumour lysis, cancer chemotherapy, aggressive haematological tumours, tissue trauma, burns, haemolysis, severe hepatic necrosis, rhabdomyolysis, etc.).
- Bone demineralisation; metastatic bone diseases, immobilisation.

Spurious hyperphosphatemia is due to interference of various other chemicals with the assay; globulins, lipids, bilirubin, heparin or tPA, or liposomal Amphotericin.[29,30]

Clinical manifestations of hyperphosphatemia: Clinical presentation depends on severity and chronicity of the high serum phosphate. Underlying renal functions and associated calcium or magnesium levels also contribute & determine the clinical picture. Hypocalcaemia is due to binding of the phosphate with calcium leading to tissue calcification. Hypocalcaemia causes neuromuscular hyper excitability such as tremors, tetany, seizures, etc. QT prolongation and cardiac arrhythmia, etc. are cardiac risks of low calcium.

Tissue calcification occurs in arterioles, capillaries, AV or SA nodes, cornea, skin and subcutaneous tissues, tendons, periarticular soft tissues, etc. Various clinical findings can be tissue ischemia such as ACS, cardiac arrhythmia, skin necrosis, tendon rupture, itching and skin nodules, band keratopathy, etc. Brain calcification in the basal ganglia can cause extra-pyramidal manifestations. Secondary hyperparathyroidism is another serious consequence as high phosphate is very strong stimulus for parathyroid hormone. This leads to parathyroid bone disease and renal failure (or worsening of renal failure).[1,3,29,30].

Diagnosis of hyperphosphatemia: Serum phosphate level more than 4.5 mg/dl indicates hyperphosphatemia.

Table 2: *Causes of hyperphosphatemia.*

Mechanism	Clinical conditions
Renal failure (GFR < 20)	CKD is the most common cause. Decreased filtration through glomerulus.
Increased reabsorption from renal tubules.	Hypoparathyroidism, Pseudo-hypoparathyroidism (lack of receptor's response to PTH) Low magnesium (as it reduces PTH secretion and functions). Acromegaly as IGF-1 increases reabsorption from the proximal tubules. Lack of FGF23 due to genetic or acquired causes
Increased intake	Milk alkali syndrome Laxatives containing phosphate Drugs containing phosphate lipophilic Amphotericin, fosphenytoin, foscarnet, etc.).
Release from the cells or the bones.	Lack of insulin (hyper catabolic states). Tissue damage releasing phosphate from the cells (tumour lysis, cancer chemotherapy, aggressive haematological tumours, tissue trauma, burns, haemolysis, severe hepatic necrosis, rhabdomyolysis, etc.). Bone demineralisation; metastatic bone diseases, immobilisation.
Spurious	Interference of various other chemicals with the assay; globulins, lipids, bilirubin, heparin or tPA, or liposomal Amphotericin

Measurement of urinary phosphate is important to exclude renal vs. non-renal causes. Fractional excretion of phosphate <5% indicates renal cause of high phosphate., Renal functions, calcium, magnesium, vitamin D3, pH, & PTH measurement are helpful finding the cause.

Low PTH indicates hypoparathyroidism & low eGFR for renal failure. Low calcium with high phosphate means hypoparathyroidism. High calcium and high phosphate mean tertiary hyperparathyroidism in renal failure, vitamin D intoxication, high intake such as milk-alkali syndrome, etc.[1,3,29]

Treatment of hyperphosphatemia: Remove the cause when possible: stop oral or IV phosphate intake. Acute hyperphosphatemia without renal failure is treated with IV fluids and diuresis. IV insulin and glucose can help shift the phosphate into the cells. Dialysis is needed for those who don't respond to medical treatment especially those with low calcium.

Phosphate binders such as calcium based (calcium carbonate, calcium citrate), and non-calcium phosphate binders (sevelamer, lanthanum) are available to remove phosphate from the intestinal fluid. Calcium based binders can cause high calcium and more tissue calcification. Non-calcium based reduces mortality 20-39% more than calcium-based binders but are costly. Serum calcium level, availability of the drugs, side effects and cost are the main factor to choose the phosphate binders. Those on regular dialysis may not need phosphate binders.[30-32]

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