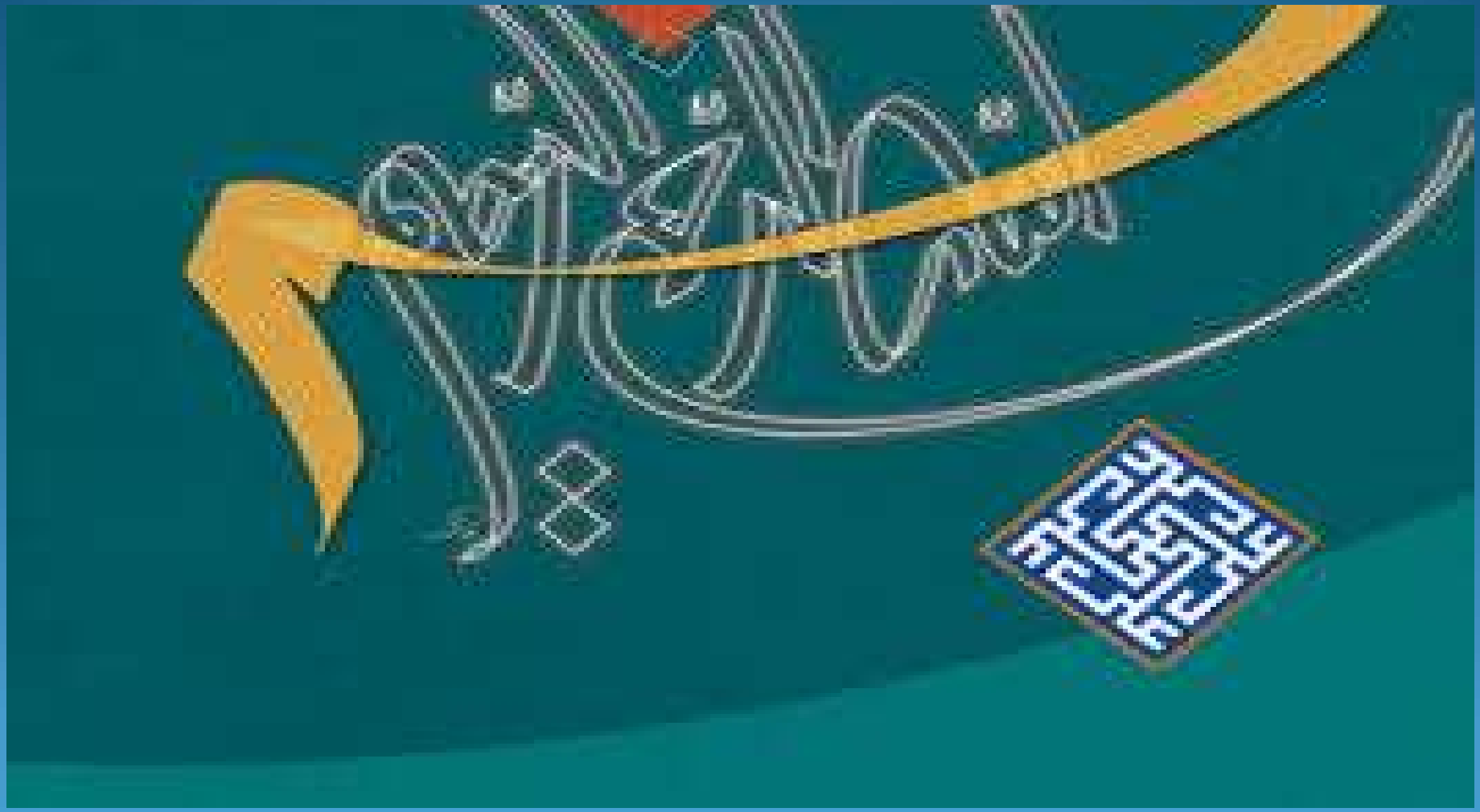

Hypophosphatemia

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- Approximately 80 percent of dietary phosphate is absorbed in the small intestine. In addition, 150 to 200 mg/day is secreted in the colon.
- Poor intake alone is rarely responsible for severe phosphate depletion because of rapid renal adaptation, whereby renal tubular phosphate reabsorption approaches 100 percent, and, therefore, urinary phosphate excretion approaches zero

- Up to 5 percent of hospitalized patients may have low serum phosphate concentrations (less than 2.5 mg/dL
- Profound hypophosphatemia (less than 1 mg/dL [0.32 mmol/L]).

- Spurious hypophosphatemia can be caused by interference of paraproteins with the phosphate assay

Major causes of hypophosphatemia

Internal redistribution
Increased insulin secretion, particularly during refeeding
Acute respiratory alkalosis
Hungry bone syndrome
Decreased intestinal absorption
Inadequate intake
Inhibition of phosphate absorption (eg, antacids, phosphate binders, niacin)
Steatorrhea and chronic diarrhea
Vitamin D deficiency or resistance
Increased urinary excretion
Primary and secondary hyperparathyroidism
Vitamin D deficiency or resistance
Hereditary hypophosphatemic rickets
Oncogenic osteomalacia
Fanconi syndrome
Other - acetazolamide, tenofovir, IV iron, chemotherapeutic agents
Removal by renal replacement therapies

INTERNAL REDISTRIBUTION

- Stimulation of glycolysis increases the formation of phosphorylated carbohydrate compounds in the liver and skeletal muscle. The source of this phosphate is the inorganic phosphate in the extracellular fluid; as a result, serum phosphate concentrations (and urinary phosphate excretion) fall rapidly.
- during carbohydrate refeeding in malnourished patients with alcoholism or anorexia nervosa ; and in patients receiving hyperalimentation.

Increased insulin secretion

- Administration of insulin or glucose (which stimulates endogenous insulin release) results in only a small decrease in serum phosphate concentrations,except If there is underlying phosphate depletion diabetic ketoacidosis, malnourished patients with alcoholism or anorexia nervosa , severe hypophosphatemia may ensue.

Acute respiratory alkalosis

- The fall in partial pressure of carbon dioxide during acute respiratory alkalosis results in a similar change in the cells because carbon dioxide readily diffuses across cell membranes.
- The resulting rise in intracellular pH stimulates phosphofructokinase activity which in turn stimulates glycolysis
- Extreme hyperventilation (to PCO_2 <20 mmHg) in normal subjects can lower serum phosphate concentrations to below 1 mg/dL (0.32 mmol/L) , and it is probably the most common cause of marked hypophosphatemia in hospitalized patients

- Total starvation alone does not cause hypophosphatemia, because of the lack of insulin and the associated increase in cell catabolism that results in phosphate release from cells.
- Refeeding of starved patients, however, can cause hypophosphatemia, unless phosphate is provided.

Medications

- Antacids, particularly those that are aluminum and magnesium based,
- Niacin and its derivatives can also promote fecal phosphate losses by reducing intestinal expression of the type 2b sodium-phosphate cotransporter (NaPi-IIb)

Steatorrhea and chronic diarrhea —

- Steatorrhea or chronic diarrhea can cause mild to moderate hypophosphatemia due to decreased phosphate absorption from the gut and renal phosphate wasting, the latter caused by secondary hyperparathyroidism induced by concomitant vitamin D deficiency.

INCREASED URINARY EXCRETION

- Renal phosphate transport occurs in the proximal tubule (60 to 70 percent of the filtered load being reabsorbed) and in the distal tubule (10 to 15 percent of the filtered load being reabsorbed)
- Phosphate reabsorption is linked to sodium reabsorption via sodium-phosphate cotransporters in the luminal membrane.

Physiologic regulators of renal tubular phosphate reabsorption include the following:

- Serum phosphate concentration – Mild phosphate depletion stimulates phosphate reabsorption via the sodium-phosphate cotransporters in the proximal tubule
- Parathyroid hormone (PTH) – PTH increases phosphate excretion by diminishing activity of sodium-phosphate cotransporters
- Phosphatonins – Phosphatonins such as fibroblast growth factor 23 (FGF-23), fibroblast growth factor 7 (FGF-7), matrix extracellular phosphoglycoprotein (MEPE), and secreted frizzled-related protein-4 (sFRP-4) decrease phosphate reabsorption by sodium-phosphate cotransporters

Primary and secondary hyperparathyroidism

- Most patients with primary hyperparathyroidism have mild hypophosphatemia.
- It may be more severe in those with vitamin D deficiency and secondary hyperparathyroidism.

Vitamin D deficiency or resistance

- Vitamin D deficiency can cause hypophosphatemia both by decreasing gastrointestinal phosphate absorption and by causing hypocalcemia and secondary hyperparathyroidism, resulting in increased urinary phosphate excretion.

Primary renal phosphate wasting (Inherited dx)

- **In X-linked hypophosphatemic rickets:** the defect in proximal tubular phosphate transport is due to a mutation in the PHEX gene
- This gene encodes an endopeptidase that indirectly alters the degradation and production of FGF-23, a phosphatonin that promotes urinary phosphate excretion and suppresses calcitriol synthesis.

- Autosomal dominant hypophosphatemic rickets and results from mutations in the FGF-23 gene on chromosome 12p13.
- A number of autosomal recessive mutations

Autosomal recessive mutations

- Mutations in the sodium-phosphate cotransporter gene SLC34A3 produce striking dysfunction of the type 2c sodium-phosphate cotransporter and lead to hereditary hypophosphatemic rickets with accompanying hypercalciuria
- Mutations in the SLC34A1 gene encoding the type 2a sodium-phosphate cotransporter are associated with hypophosphatemia in conjunction with nephrolithiasis and osteomalacia,

- Defects in the sodium-hydrogen exchanger regulatory factor 1 (NHERF1) are associated with impaired phosphate reabsorption and hypophosphatemia
- Mutations in the genes encoding dentin matrix protein 1 ,
  ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) , and klotho are also linked to hypophosphatemic syndromes in humans

Tumor-induced osteomalacia

- These patients usually have tumors of mesenchymal origin, often a sclerosing type of hemangiopericytoma, that produce a phosphaturic hormone(s) ,such as FGF-23, MEPE, and sFRP-4.
- Rarely, significant renal phosphate wasting is observed in patients with fibrous dysplasia and/or McCune-Albright syndrome, disorders that result from

fibrous dysplasia and/or McCune-Albright syndrome

- Mutations in the alpha subunit of the stimulatory G protein. Excess production of FGF-23 has been found in some of these patients
- (Hypophosphatemia and hyperphosphaturia are common in patients who have undergone a partial hepatectomy)

Fanconi syndrome

- The Fanconi syndrome refers to a generalized impairment in proximal tubular function leading to urinary wasting of compounds normally reabsorbed in the proximal tubule.
- In children, cystinosis, Wilson's disease, and hereditary fructose intolerance are the most common causes of this syndrome.

Miscellaneous

- Osmotic diuresis (most often due to glucosuria);
- Proximally acting diuretics (acetazolamide and some thiazide diuretics that also have carbonic anhydrase inhibitory activity, such as metolazone);
- Acute volume expansion (which diminishes proximal sodium reabsorption);
- Intravenous iron formulations containing carbohydrate moieties may increase phosphate excretion by causing an increase in circulating levels of FGF-23

- Chemotherapeutic agents, including tyrosine-kinase inhibitors
- Target of rapamycin (m-tor) inhibitors (especially temsirolimus)
- And vascular endothelial growth factor (VEGF) inhibitors (such as sorafenib)

symptoms

- While overt symptoms of hypophosphatemia rarely occur unless the serum phosphate concentration is less than 2 mg/dL (0.64 mmol/L), some evidence suggests that even mild hypophosphatemia may be associated with poor clinical outcomes
- Serious symptoms such as muscle weakness and rhabdomyolysis are generally not observed until the serum phosphate concentration falls below 1 mg/dL

EFFECTS OF HYPOPHOSPHATEMIA ON MINERAL METABOLISM

- Prolonged hypophosphatemia produces a number of effects on both the kidney and bone. Distal tubular reabsorption of calcium and magnesium are inhibited, and striking hypercalciuria ensues
- The initial response of bone to hypophosphatemia is increased resorption; the associated release of bone calcium contributes to the hypercalciuria. This effect may be mediated, in part, by the phosphate depletion-induced rise in the synthesis of calcitriol (1,25-dihydroxyvitamin D)

OTHER EFFECTS OF PHOSPHATE DEPLETION

- Red cell 2,3-diphosphoglycerate (DPG) levels fall, thereby increasing the affinity of hemoglobin for oxygen and reducing oxygen release at the tissue level
- Intracellular adenosine triphosphate (ATP) levels fall with severe hypophosphatemia, and cell functions dependent upon energy-rich phosphate compounds begin to fail.
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Central nervous system

- Severe hypophosphatemia can lead to a metabolic encephalopathy that results from ATP depletion.
- A broad spectrum of neurologic symptoms have been associated with prolonged phosphate depletion, ranging from mild irritability and paresthesias to more severe manifestations such as delirium, generalized seizures, and coma
- Severe phosphate depletion is also speculated to contribute to the development of central and extrapontine myelinolysis

Cardiopulmonary system

- Myocardial contractility may be impaired with ATP depletion and phosphate administration appears to improve cardiac function, especially in patients with severe hypophosphatemia, defined as a plasma phosphate below 1 mg/dL (0.32 mmol/L)
- In addition, hypophosphatemia has been associated with a higher incidence of ventricular arrhythmias in the setting of acute myocardial infarction
- Diaphragmatic contractility can be substantially impaired in this setting , and several studies suggest that hypophosphatemia is associated with prolonged ventilator dependency in critically ill patients

Skeletal and smooth muscle

- Hypophosphatemia-induced manifestations of muscle dysfunction include a proximal myopathy (affecting skeletal muscle) , dysphagia, and ileus (affecting smooth muscle).
- Rhabdomyolysis

Hematologic dysfunction

- **Red blood cells** — A reduction in intracellular ATP levels increases erythrocyte rigidity, predisposing to hemolysis, which can be seen when the plasma phosphate concentration falls below 0.5 mg/dL (0.16 mmol/L)
- **White blood cells** — Diminished intracellular ATP levels reduce both phagocytosis and granulocyte chemotaxis . This complication is also rare and only seen with severe hypophosphatemia.
- **Platelets** — Defective clot retraction and thrombocytopenia can occur, which can aggravate mucosal hemorrhage.

Evaluation and

Evaluation

- ●A 24-hour urine phosphate excretion less than 100 mg or a $FEPO_4$ less than 5 percent indicates appropriate low renal phosphate excretion, suggesting that the hypophosphatemia is caused by internal redistribution (eg, refeeding syndrome, acute respiratory alkalosis) or decreased intestinal absorption (eg, chronic antacid therapy, steatorrhea).
- ●A 24-hour urine phosphate excretion greater than or equal to 100 mg or a $FEPO_4$ greater than or equal to 5 percent indicates renal phosphate wasting, suggesting that the hypophosphatemia is caused by hyperparathyroidism, vitamin D deficiency, or a variety of other conditions.
- The formula used to calculate the $FEPO_4$ is the same as that for the fractional excretion of sodium (FENa):
- $FEPO_4 = [UPO_4 \times PCr \times 100] \div [PPO_4 \times UCr]$

- Serum calcium,PTH, 25-dihydroxyvitamin D,calcitriol level (1,25-dihydroxyvitamin D).
- Hypophosphatemia can be seen with either primary or secondary hyperparathyroidism. The triad of hypercalcemia, hypophosphatemia, and urinary phosphate wasting is often present in primary hyperparathyroidism.

- Isolated urinary phosphate wasting is rare but can be observed in patients receiving ferric carboxymaltose therapy for treatment of iron deficiency anemia [7], in children with certain genetic mutations leading to vitamin D-resistant rickets, or in adults with oncogenic osteomalacia, a condition characterized by the overproduction of phosphaturic substances from a mesenchymal tumor (usually a hemangiopericytoma).

- One clue to the presence of oncogenic osteomalacia is a very low plasma calcitriol level (1,25-dihydroxyvitamin D).
- Normally, hypophosphatemia results in stimulation of calcitriol levels, which would tend to raise the serum phosphate by increasing intestinal phosphate absorption and, perhaps, via bone resorption.

Treatment of hypophosphatemia

- For these reasons, most hypophosphatemic patients will not require therapy other than that aimed at the underlying cause. As examples:
- Diabetic ketoacidosis
- Patients who have hypophosphatemia due to gastrointestinal losses should correct spontaneously once there is resolution of the underlying cause (eg, diarrhea, chronic antacid therapy, or vitamin D deficiency which should be treated with vitamin D supplementation).

Phosphate repletion regimens

- Our approach to phosphate repletion takes into account the serum phosphate concentration, the presence or absence of overt symptoms of hypophosphatemia, and whether the patient can take oral therapy.
- If possible, we prefer oral rather than intravenous phosphate therapy since intravenous repletion can lead to hyperphosphatemia that may result in serious complications such as hypocalcemia, acute kidney injury, and arrhythmias

- We suggest the following approach:
- In **asymptomatic** patients with a serum phosphate less than 2.0 mg/dL
- ●The treatment of **symptomatic** patients varies with the severity of the hypophosphatemia:
- •We treat with oral phosphate if the serum phosphate is 1.0 to 1.9 mg/dL
- •We treat with intravenous phosphate if the serum phosphate is less than 1.0 mg/dL and switch to oral replacement when the serum phosphate exceeds 1.5 mg/dL (0.48 mmol/L)
- ●We stop phosphate repletion when the serum phosphate is greater than or equal to 2.0 mg/dL unless there is an indication for chronic therapy such as persistent urinary phosphate wasting

- Eff.tablet sodium phosphate(phosphate sandose) 500 mg
- Ampule sodium phosphate
- Ampule potassium phosphste
- Tab 500 mg monobasic potassium phosphate
- Bulk monobasic potassium phosphate
- Powder Monobasic sodium phosphate
- Powder Dibasic sodium phosphate
- Glycerophosphoric acid or glycophos. 20 mg
- Jouile solution:136 gr dibasic sodium phosphste +58.8 gr phosphoric acid +up to 1 liter water:1cc=30 mg phosphore

Oral dosing

- PHOSPH.RRICH DIET :meats, poultry, fish, nuts, beans and dairy products.
- When oral dosing is used, we initiate therapy with 30 to 80 mmol of phosphate per day in divided doses.
- Phosphate may also be supplemented with skim milk, which contains approximately 15 mmol of phosphate per 480 mL serving.
- The following regimen is a reasonable approach :
- ●If the serum phosphate is greater than or equal to 1.5 mg/dL , 1 mmol/kg of elemental phosphorus (minimum of 40 mmol and a maximum of 80 mmol) can be given in three to four divided doses over a 24-hour period.
- ●If the serum phosphate is less than 1.5 mg/dL (0.48 mmol/L), 1.3 mmol/kg of elemental phosphorus (up to a maximum of 100 mmol) can be given in three to four divided doses over a 24-hour period.
- ●Patients with a reduced glomerular filtration rate should receive approximately one-half of the suggested initial dose.
- The serum phosphate concentration should be rechecked 2 to 12 hours following the last of the divided doses to determine whether repeated doses are required. If so, the same approach may be reapplied.
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Intravenous dosing

- Intravenous phosphate is potentially dangerous since it can precipitate with calcium and produce a variety of adverse effects including hypocalcemia due to binding of calcium, renal failure due to calcium phosphate precipitation in the kidneys, and possibly fatal arrhythmias.
- If intravenous therapy is necessary in patients with severe symptomatic hypophosphatemia or an inability to take oral therapy, We suggest the following regimen :
- ●If the serum phosphate concentration is greater than or equal to 1.25 mg/dL (0.40 mmol/L), we give 0.08 to 0.24 mmol/kg over six hours (up to a maximum total dose of 30 mmol)
- ●If the serum phosphate concentration is less than 1.25 mg/dL (0.40 mmol/L), we give 0.25 to 0.50 mmol/kg over 8 to 12 hours (up to a maximum total dose of 80 mmol)

- In addition, we do not usually give phosphate replacement when the serum phosphate is above 2.0 mg/dL (0.64 mmol/L).
- The serum phosphate concentration should be monitored every six hours when intravenous phosphate is given, and the patient should be switched to oral replacement when the serum phosphate concentration reaches 1.5 mg/dL (0.48 mmol/L)

In critically ill patients receiving nutritional support

میزان الکترولیت های مورد نیاز کودکان در روز		
سدیم	کودکان و نوزدان	2–4 mEq/kg
پتاسیم	کودکان و نوزدان	2–3 mEq/kg
کلر	کودکان و نوزدان	2–4 mEq/kg
منیزیم	نوزادان	0.25–0.5 mEq/kg
	کودکان بیشتر از 1 سال یا 12 کیلوگرم	4–12 mEq
کلسیم	نوزادان	2–3 mEq/kg
	کودکان بیشتر از 1 سال یا 12 کیلوگرم	10–20 mEq
فسفر	نوزادان	1.0–1.5 mmol/kg
	کودکان بیشتر از 1 سال یا 12 کیلوگرم	10–20 mmol

THANKS FOR YOUR ATTENTION