Micronutrients: Phosphorus

Dr. Ritamarie Loscalzo

Phosphorus General Info

- **Essential macromineral**
- 2nd most abundant mineral in the body, after calcium
- Makes up about 1% of your body weight
- Stored mostly in the bones and teeth — about 85%

**Phosphorus functions:**
- Bone mineralization
- Energy production
- Acid/alkaline homeostasis
- Manages kidney function and filters waste
- First isolated in 1669 in urine during alchemy trials
- The name is derived from the Greek “Phos” (light) and “Phoros” (bearer), meaning “bringer of light”
- Phosphoric acid in soda drinks can lead to bone issues

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Chemistry of Phosphorus

- 15th element in the periodic table – symbol P
- A vital part of all living things
- A non-metal; part of the nitrogen family
- As a gas, it’s colorless
- As a solid, it’s silvery white or red, depending on how it is bonded
- Burns when exposed to air, so is stored under water
- At least 3 allotropic forms:
  - White (yellow)
  - Black
  - Red

Phosphorus in Living Organisms

- Component of adenosine triphosphate (ATP)
- Phosphorylation activates enzymes, hormones, and cell-signaling molecules
- Human bones are made up of mostly calcium phosphate $\text{Ca}_3(\text{PO}_4)_2$
- Binds to hemoglobin in red blood cells and regulates oxygen delivery to the tissues of the body

Phosphorus Functions

- Major structural component of bone in the form of a calcium phosphate salt called hydroxyapatite
- Phospholipids (e.g., phosphatidylcholine) are major structural components of cell membranes
- Energy production and storage depends on phosphorylated compounds, such as adenosine triphosphate (ATP) and creatine phosphate
- DNA and RNA are long chains of phosphate-containing molecules
- Helps maintain body’s acid-base balance (pH) by acting as an important buffer
Phosphorus Digestion
- Most absorbed in organic form
  - Hydrolyzed enzymatically in small intestine lumen
  - Released as inorganic phosphate
- Phospholipase C
  - Zinc-dependent enzyme
  - Hydrolyzes the glycerophosphate bond in phospholipids
- Alkaline phosphatase
  - Zinc-dependent enzyme
  - Activity is stimulated by calcitriol
  - Functions at the brush border of the enterocyte to free phosphorus from some bound forms
  - It cannot free phytate-bound phosphorus

Phosphorus Absorption
- Phosphorus is readily absorbed in the small intestine
- About 50% - 70% of dietary phosphorus absorbed
  - Animal sources at the upper end of the range
  - Phytate-containing foods at the lower end
- Primarily in duodenum and jejunum
- In its inorganic form throughout small intestine
- Occurs by two processes:
  - A saturable, carrier-mediated active transport system dependent on sodium and enhanced by calcitriol
  - Concentration-dependent passive diffusion process
**Phosphorus Transport**

- Quickly absorbed from intestine into blood
- Appears in blood within about an hour after ingestion
- Found in blood in both organic and inorganic forms
  - 70% - organic phosphate: phospholipids in lipoproteins
  - 30% as HPO$_4^{2-}$ and H$_2$PO$_4^-$ and trace amounts PO$_4^{3-}$
- Inorganic phosphates associated with:
  - Calcium
  - Magnesium
  - Sodium

**Phosphorus Storage**

- Found in all cells of the body; majority in:
  - Bone
  - Muscle
- Circulating phosphate is in equilibrium with skeletal and cellular inorganic phosphate
- Inorganic phosphorus
  - Ultrafilterable phosphate
  - Plasma ranges: 2.5 – 4.5 mg/dL
- Organic phosphates formed in intermediary metabolism
- Variability of serum phosphate concentration as a result of:
  - Dietary phosphate
  - Age and stage growth
  - Time of day
  - Various hormones
  - Renal function
Phosphorus Excretion

- Excess excreted by kidneys, regulated by hormones:
  - Parathyroid hormone (PTH)
  - Vitamin D
  - Fibroblast growth factor-23 (FGF-23)
- Slight drop in blood calcium levels sensed by parathyroids
  - Increased secretion of PTH
  - Urinary excretion of calcium and urinary excretion of phosphorus
  - Stimulates bone resorption

Regulation of Phosphorus: 1

- Concentrations are tightly controlled
  - Intracellularly
  - Extracellularly
- Blood levels maintained between 3.0 and 4.5 mg/dL
- Blood levels not indicative of optimal levels in bone

Regulation of Phosphorus: 2

Source: J Am Board Fam Med © 2003 American Board of Family Medicine
Phosphorus Drug Interactions

- Aluminum-containing antacids form aluminum phosphate, which is not absorbable.
- Proton pump inhibitors may also limit the efficacy of phosphate-binder therapy in patients with kidney failure.
- Excessively high doses of 1,25-dihydroxyvitamin D or its analogs may result in hyperphosphatemia.
- Potassium supplements or potassium-sparing diuretics taken with phosphorus supplements may result in high blood levels of potassium (hyperkalemia), resulting in life-threatening heart rhythm abnormalities.
- HRT in postmenopausal women is associated with higher urinary phosphorus excretion and lower serum phosphorus levels in treated compared to untreated women.

Phosphorus Deficiency

- Inadequate phosphorus intake rarely results in abnormally low serum phosphorus levels (hypophosphatemia) because renal reabsorption of phosphorus increases to compensate for decreased intake.
- Found in cases of near-starvation.
- Inherited disorders, such as Renal Phosphorus Wasting disease, can lead to deficiency.
- Deficiency symptoms include:
  - Loss of appetite
  - Muscle weakness
  - Bone fragility
  - Numbness in the extremities

Bone Mineralization

- 85% of body phosphorus found in bone
  - Of prime importance in development of skeletal tissue.
  - Found in amorphous calcium phosphate forms:
    - Ca₁₀(PO₄)₆(OH)₂
    - Ca₁₀(PO₄)₆.2H₂O
    - Ca₁₀(PO₄)₆.3H₂O
    - Hydroxyapatite: Ca₁₀(PO₄)₆(OH)₂ – crystalline form laid down on collagen in ossification of bone formation.

- Ratio of calcium to phosphorus
  - 13:1
  - Similar to extracellular fluid
  - Crystalline bone – 1.5:1
Bone Metabolism Influenced by

- **Parathyroid hormone (PTH)**
  - Stimulates resorption of phosphate from bone, same as calcium
  - Stimulates excretion of phosphorus in urine
  - PTH-induced urinary excretion of phosphorus
    - Sufficient to override bone resorption of phosphorus
    - Effects a net decrease in plasma phosphate
- **Calcitriol**
  - In conjunction with PTH enhances phosphate resorption from bone
  - Stimulates phosphate absorption in the intestine
    - Through enhanced alkaline phosphatase activity
- **Calcitonin**
  - Promotes bone mineralization
- **Phosphorus that is not part of the bone**
  - Found either in extracellular fluids such as blood or soft tissue
  - Within cells, major anion involved with other processes

Nucleotide/Nucleoside Phosphates

- **Important component of nucleic acids**
- **DNA and RNA**
  - Alternates with pentose sugars to form the linear backbone
- **Intermediary metabolism of energy nutrients in the form of high-energy phosphate bonds**
  - Nucleotide adenosine triphosphate (ATP)
  - Creatine phosphate (phosphocreatine)
    - Synthesized in muscle from ATP and creatine
    - Can provide energy to muscles as needed (e.g., exercise)
      - Transferring its P<sub>O</sub><sub>4</sub> to ADP via creatine kinase
- **Uridine triphosphate (UTP)**
  - Activate substances in intermediary metabolism
  - Hydrolysis provides for the coupling of uridine monophosphate and glucose 1-phosphate to form uridine diphosphate (UDP) glucose
  - UDP-glucose is critical for the synthesis of glycogen

Phosphorus Intracellular Second Messenger

- **Functions as second messenger to affect cellular metabolism**
- **Part of cyclic adenosine monophosphate (cAMP)**
  - Acts within cells by activating certain protein kinases
  - Generated in response to the binding of certain hormones to cell receptors
  - Derived from ATP
- **Inositol triphosphate (IP<sub>3</sub>)**
  - Second messenger to trigger intracellular calcium release
  - Actions mediated by protein kinases
Phosphoproteins
- Intermediary metabolism of the energy nutrients through the phosphorylation of different substrates in the body
- Protein kinases activated by cAMP
  - Function to phosphorylate specific target proteins within the cell
  - Changes cellular activities

Phospholipid Structural Roles
- Cell membranes contain phospholipids
- Important to the bilayer structure of cell membranes → Polar and nonpolar regions
- Examples:
  - Phosphatidylcholine
  - Phosphatidylinositol
  - Phosphatidylserine

Acid-Base Balance
- Phosphate functions in acid-base balance
- Main intracellular buffer within cells
- Filtered phosphate reacts with secreted hydrogen ions in kidneys
  - Releases sodium ions
  - Removes free hydrogen ions
  - Increases pH
- Actions can be reversed to lower pH
Assessing Phosphorus Status

- Serum phosphorus is generally part of routine blood chemistry
  - Serum phosphorus is a poor reflection of body stores because <1% is in extracellular fluid
  - Hypophosphatemia (< 3.0 mg/dL)
  - Hypophosphatemia (< 4.5 mg/dL)
  - Vitamin D3
  - Protein status
  - Parathyroid hormone (PTH)
  - PTH-related peptide (PTHrP)
  - Renal function labs (GFR<20-25 ml/min)

**Serum indicates little about phosphorus status**

- Functional Tests:
  - Spectracell
  - NutrEval by Genova/Metametrix
  - NTX or Osteonex – for bone turnover

- Questionnaires and good history taking for signs and symptoms

No routine biochemical method appears to assess phosphorus status accurately

### Phosphorus RDA

#### Table 1. Recommended Dietary Allowance (RDA) for Phosphorus

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males [mg/day]</th>
<th>Females [mg/day]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>100 (AI)</td>
<td>100 (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7-12 months</td>
<td>275 (AI)</td>
<td>275 (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 years</td>
<td>460</td>
<td>460</td>
</tr>
<tr>
<td>Children</td>
<td>4-8 years</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Children</td>
<td>9-13 years</td>
<td>1,250</td>
<td>1,250</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14-18 years</td>
<td>1,250</td>
<td>1,250</td>
</tr>
<tr>
<td>Adults</td>
<td>19 years and older</td>
<td>700</td>
<td>700</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>18 years and younger</td>
<td>-</td>
<td>1,250</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>19 years and older</td>
<td>-</td>
<td>700</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>18 years and younger</td>
<td>-</td>
<td>1,250</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>19 years and older</td>
<td>-</td>
<td>700</td>
</tr>
</tbody>
</table>

### Hyperphosphatemia

#### Tolerable Upper Intake Level (UL) for Phosphorus

<table>
<thead>
<tr>
<th>Age Group</th>
<th>UL (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0-12 months</td>
<td>Not possible to establish*</td>
</tr>
<tr>
<td>Children 1-3 years</td>
<td>3,000 (3.0 g)</td>
</tr>
<tr>
<td>Children 4-8 years</td>
<td>3,000 (3.0 g)</td>
</tr>
<tr>
<td>Children 9-13 years</td>
<td>4,000 (4.0 g)</td>
</tr>
<tr>
<td>Adolescents 14-18 years</td>
<td>4,000 (4.0 g)</td>
</tr>
<tr>
<td>Adults 19-70 years</td>
<td>4,000 (4.0 g)</td>
</tr>
<tr>
<td>Adults 71 years and older</td>
<td>3,000 (3.0 g)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>3,500 (3.5 g)</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>4,000 (4.0 g)</td>
</tr>
</tbody>
</table>

*Source of intake should be from food and formula only.
Hyperphosphatemia Risk

- Kidney disease or stones
- Low PTH
- Kidney trauma/injury
- Transplant recipients
- Dialysis
- Consumption of excessive soft drinks or highly processed foods
- Excessive use of enemas or laxatives containing phosphates

Hyperphosphatemia Symptoms

- Hyperphosphatemia typically asymptomatic
- If acute, symptoms result from hypocalcemia:
  - Joint pain
  - Muscle cramps and spasms
  - Fatigue
  - Perioral numbness
  - Bone pain
  - Pruritus
  - Nausea
  - Vomiting
  - Rash

Excessive Phosphate Intake: Adverse Effects on Health
Assessing Bone Mineral Density
Test for those especially at risk for osteoporosis

✓ DEXA aka DXA
  - Dual-energy X-ray absorptiometry is one of the best tools
  - Scan specific sites at two different energy levels

✓ CT scans:
  - Less precise and accurate than DEXA

Dietary Sources of Phosphorus

Plant
✓ Cashews
✓ Sunflower Seeds
✓ Lentils
✓ Almonds

Animal
✓ Chicken
✓ Turkey
✓ Beef
✓ Halibut
✓ Sardines
✓ Salmon
✓ Tuna
✓ Dairy

Herbs High In Phosphorus
✓ Poppy seed
✓ Mustard seed
✓ Caraway
✓ Celery seed
✓ Dill weed
✓ Cumin
✓ Coriander
✓ Fennel seed
✓ Chervil
✓ Anise
✓ Parsley
✓ Onion powder
✓ Paprika
✓ Curry
✓ Chili powder
✓ Fenugreek
✓ Marjoram
✓ Tarragon
✓ Spearmint
✓ Basil
✓ Turmeric
✓ Nutmeg
✓ Saffron
✓ Thyme
✓ Cardamom
✓ White pepper
✓ Ginger
Food Sources of Phosphorus

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Phosphorus (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole grains</td>
<td>85</td>
</tr>
<tr>
<td>Refined</td>
<td>33</td>
</tr>
<tr>
<td>Dark green</td>
<td>29</td>
</tr>
<tr>
<td>Red &amp; orange</td>
<td>25</td>
</tr>
<tr>
<td>Beans &amp; peas</td>
<td>119</td>
</tr>
<tr>
<td>Nuts &amp; seeds</td>
<td>43</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
</tr>
<tr>
<td>Fruits and juices (1/2 cup)</td>
<td>17</td>
</tr>
<tr>
<td>Milk (1 cup)</td>
<td>247</td>
</tr>
<tr>
<td>Meat &amp; beans (1 oz)</td>
<td>63</td>
</tr>
<tr>
<td>Oils (1 tbsp)</td>
<td>9</td>
</tr>
<tr>
<td>Discretionary calories</td>
<td>9</td>
</tr>
<tr>
<td>Solid fats</td>
<td>1</td>
</tr>
</tbody>
</table>

Forms of Phosphorus Supplementation

- **Elemental phosphorus**: Highly toxic; only used as a homeopathic treatment
- **Inorganic phosphates**: Not toxic at typical doses:
  - Dibasic potassium phosphate
  - Monobasic potassium phosphate
  - Dibasic sodium phosphate
  - Monobasic sodium phosphate
  - Tribasic sodium phosphate
  - Phosphatidylcholine
  - Phosphatidylserine

Topical Phosphorus

- Phosphate is the drug (salt) form of phosphorus — combines with other compounds
  - E.g.: Clindamycin phosphate topical
    - Used to treat acne by decreasing the number of acne lesions.
    - Clindamycin is an antibiotic; phosphates allow penetration.
- Phosphates in enemas as laxatives
- Athletes use phosphate supplements before competitions or heavy workouts to help reduce muscle pain and fatigue
Phosphorus/Calcium Ratio

Optimal Intake:
- Ratio of serum calcium to phosphorus 10:4
- A high ratio of phosphorus to calcium sensitizes the body and increases inflammatory tendencies
- Phosphorus level too high:
  - Frequent colds and flu
  - Sensitive skin
  - Caries near gum line
  - Red-rimmed eyes
  - Low blood pressure
  - Sensitive to pain and noise

Resources
- Advanced Nutrition and Human Metabolism – Gropper, Smith and Groff
- Better Bones Blog – Dr. Susan A. Brown, PhD
- Dr. Edward Group DC, NP, DACBN, DCBCN, DABFM
- Last, Walter, DC; The Calcium/Phosphorus Ratio
  [http://www.drribarrie.com/go/CalciumPhosphorusRatio](http://www.drribarrie.com/go/CalciumPhosphorusRatio)
- Linus Pauling Institute:
  [http://www.drribarrie.com/go/LPIPhosphorus](http://www.drribarrie.com/go/LPIPhosphorus)
- University of Maryland Medical Center: