

## CORE CURRICULUM IN NEPHROLOGY

### Disorders of Calcium, Phosphorus, and Magnesium

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#### NORMAL PHYSIOLOGY

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Calcium (Ca), phosphorus (P), and magnesium (Mg) homeostasis is controlled by serum concentrations of the ion and regulating hormones that act on 3 target organs: bone, intestine, and kidney.

#### Regulating Hormones

##### *Parathyroid hormone (PTH)*

- Released in response to lowering of ionized Ca via Ca-sensing receptor inactivation (ionized Ca decreases PTH release)
- Cleaved from pre-pro PTH to pro PTH to PTH in gland, and then secreted and catabolized to *N*-terminal (active) and *C*-terminal fragments. Most of the *C*-terminal fragments are inactive, but some *C*-terminal fragments (sometimes called “7-84” fragments although true sequence is not known) may have antagonistic effects on bone via different receptors.
- Activity:
  - Increases Ca reabsorption (and decreases P reabsorption) from kidney
  - Increases bone resorption by multiple mechanisms
  - Indirectly increases intestinal absorption by enhancing conversion of 25(OH) vitamin D to 1,25(OH) vitamin D
- Regulation:
  - Hypocalcemia stimulates PTH secretion
  - Calcitriol (1,25[OH]<sub>2</sub>D) inhibits PTH secretion, and PTH increases conversion of vitamin D to calcitriol, thereby completing feedback loop for regulation
  - Hyperphosphatemia stimulates PTH secretion
  - Severe hypomagnesemia stimulates PTH secretion

##### *Vitamin D*

- Metabolism:
  - Sources of vitamin D are diet (D<sub>2</sub> ergocalciferol) and skin via conversion of 7-dehydrocholesterol by UV light to D<sub>3</sub> (cholecalciferol)

- D<sub>2</sub> and D<sub>3</sub> are carried by D-binding protein to liver and hydroxylated to 25(OH)D, which is then further hydroxylated by 1- $\alpha$  hydroxylase enzyme in kidney to 1,25(OH)<sub>2</sub>D (calcitriol)
- Some 1- $\alpha$  hydroxylase occurs in extrarenal locations
- 24-Hydroxylase also is present in kidney and catabolizes to 1,24,25(OH)<sub>3</sub>D, which is inert, and converts 25(OH)D to 24,25(OH)<sub>2</sub>D, which may have an effect on bone
- Regulation:
  - 1- $\alpha$  hydroxylase enzyme activity (and thus 1,25[OH]<sub>2</sub>D) is increased by low P, low Ca, low calcitriol, and increased PTH as major regulators; estrogen, prolactin, calcitonin, and growth hormone also increase activity
  - 1- $\alpha$  hydroxylase enzyme activity is decreased by 1,25(OH)<sub>2</sub>D forming feedback loop for regulation
- Activity:
  - Calcitriol acts on intestine to increase Ca and P reabsorption
  - Calcitriol acts on bone to increase mineralization and enhance osteoclast activity
  - Calcitriol acts on PTH gland to inhibit PTH secretion
  - Calcitriol acts on kidney to ensure adequate supply of calcitriol if levels are low and is degraded in the kidney;

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whether it effects Ca and/or P tubular uptake/excretion is controversial

### ***Phosphatonins***

- A group of substances that appear to regulate serum P levels in tumor-induced osteomalacia, X-linked hypophosphatemic rickets, and autosomal dominant hypophosphatemic rickets
- Includes fibroblast growth factor 23, frizzled related protein 4, and matrix extracellular phosphoglycoprotein
- Role in normal physiology of P not yet clear (if any)

### **Balance**

#### ***Calcium***

- Total body stores of approximately 1,000 g: 99% in bone, 0.9% intracellular, and 0.1% extracellular
- Extracellular Ca can be measured as total Ca, of which 50% is free or ionized and physiologically active (and can be measured), 10% bound to anions, and 40% bound to albumin
- Correct total serum Ca for low albumin ( $[(\text{Normal albumin concentration} - \text{patient's albumin concentration}) \times 0.8] + \text{patient's Ca concentration}$ )
- Average dietary intake 500 to 1,000 mg/d, two thirds excreted in stool and one third in urine

#### ***Phosphorus***

- Total body stores of approximately 600 g: 85% in bone, 14% intracellular, and 1% extracellular
- Extracellular P bound to albumin and cations but, unlike Ca, only measure physiologically active P
- Average dietary intake 900 to 1,400 mg/d, two thirds excreted in urine and one third in stool

#### ***Magnesium***

- Total body stores of approximately 25 g: 66% in bone (not freely exchangeable), 33% intracellular, 1% extracellular
- Serum levels not reflective of total body stores

- Extracellular Mg can be measured as total Mg, of which 55% is free or ionized and physiologically active, 15% bound to anions, and 30% bound to albumin; no test for ionized Mg available clinically
- Average dietary intake of 300 mg/d, two thirds excreted in stool and one third in urine

### **Target Organs**

#### ***Intestine***

- Ca absorption is both passive and active, the latter calcitriol dependent
- P absorption is both passive and active, the latter calcitriol dependent
- Mg absorption is passive only and directly related to dietary intake

#### ***Kidney***

- Calcium:
  - 60% to 70% absorbed in proximal tubule via paracellular uptake in concert with salt/water uptake
  - 20% to 30% absorbed in thick ascending limb of Henle via primarily paracellular uptake energized by luminal Na/K/2Cl transporter, and some transcellular uptake, perhaps mediated by basolateral Ca-sensing receptor
  - 10% absorbed in distal tubule and is active, against both electrical and chemical gradients via luminal Ca channels, and basolateral Ca/adenosine triphosphatase and Ca/Na exchangers
  - Ca reabsorption increased by extracellular volume contraction, PTH, PTH-related peptide (PTHrp), hypocalcemia
- Phosphorus:
  - 85% in proximal tubule via transcellular uptake by Na/P cotransporter; remainder in distal segments
  - Uptake stimulated by extracellular volume contraction and hypophosphatemia, inhibited by PTH, PTHrp, loop diuretics
- Magnesium:
  - 40% absorbed in proximal tubule via paracellular uptake in concert with salt/water uptake
  - 50% absorbed in thick ascending limb of Henle via primarily paracellular uptake

energized by luminal Na/K/2Cl transporter

- 5% absorbed in distal tubule via active transport
- Renal tubular reabsorption increased by extracellular volume contraction, hypomagnesemia, and PTH

### **Bone**

- Bone is dynamic and goes through cycles of remodeling: activation, osteoclast resorption, osteoblasts fill in resorption pit with unmineralized matrix (osteoid), and matrix is then mineralized, cells undergo apoptosis except some osteoblasts that become osteocytes or lining cells
- Primary cells are osteoblasts (build new bone) that derive from marrow stromal cells, osteoclasts (resorb bone) derived from circulating progenitor cells, osteocytes that are “old” osteoblasts embedded in bone and transmit pressure signals
- Osteoblasts regulate osteoclast activity via osteoprotegerin/receptor activator nuclear receptor  $\kappa$  ligand (OPG/RANK-L) system
  - RANK is on osteoclasts and can be activated by RANK-ligand (RANK-L) on osteoblasts
  - OPG is secreted by osteoblasts and can bind to RANK-L on osteoblasts, blocking RANK-L binding to RANK osteoclasts; this serves as a decoy receptor
  - If increased OPG, less binding of RANK-L to RANK and decreased osteoclast activity; if decreased OPG, increased binding of RANK-L to RANK and increased osteoclast activity
  - OPG/RANK system is regulated by nearly all hormones, growth factors, cytokines known to affect bone turnover

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## **HYPERCALCEMIA**

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### **History**

- Malignancy
- Constitutional symptoms
- Medication use (thiazides, lithium)
- Family history

### **Signs and Symptoms**

- Nausea

- Constipation
- Abdominal pain
- Decreased mentation
- Lassitude
- Thirst
- Dehydration
- Reduced urine flow
- Nocturia
- Polyuria
- Volume depletion

### **Differential Diagnosis**

#### **By prevalence:**

- Primary hyperparathyroidism (55%)
- Malignancy (35%)
  - Humoral hypercalcemia of malignancy:
    - PTHrp, usually lung, esophagus, head and neck, renal cell, ovary bladder
  - Local osteolytic hypercalcemia, including:
    - Breast and multiple myeloma
    - Tumors produce factors such as transforming growth factor  $\beta$  or interleukin 1, cytokines such as lymphotoxin, or hormones such as calcitriol
  - Hematologic malignancy (lymphoma) with ectopic production of 1,25-dihydroxyvitamin D
- All other causes (10%) including drugs (thiazides, lithium, vitamin D), immobilization, pheochromocytoma, thyrotoxicosis, milk-alkali

#### **By target organ:**

- Parathyroid gland: Excess release of PTH in hyperparathyroidism, lithium, familial hypercalcemia hypocalciuria
- Intestine: Vitamin D toxicosis, sarcoidosis, granulomatous disorders, milk-alkali syndrome, some tumors
- Bone: Hyperparathyroidism, thyrotoxicosis, immobilization

### **Diagnostic Tests**

- Ca, PTH, 25(OH)D and 1,25(OH)<sub>2</sub>D levels, PTHrp

**Treatment****Acute**

- Volume repletion with saline, loop diuretics, careful monitoring ins/outs, bisphosphonate and/or calcitonin if severe

**Granulomatous disorders**

- Corticosteroids

**Chronic/preventive**

- Bisphosphonates for bone etiology, calcimimetics for hyperparathyroidism and parathyroid malignancy

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**HYPOCALCEMIA**


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**History**

- Previous thyroid, parathyroid, or neck surgery
- Chronic kidney disease
- Diarrhea
- Steatorrhea
- Previous bowel surgery
- Lack of sunlight
- Low dietary Ca and vitamin D

**Signs and Symptoms**

- Neck scar
- Positive Chvostek's, positive Trousseau's signs
- Carpal-pedal spasm
- Perioral numbness
- Tetany
- Dyspnea
- Stridor
- Wheezing
- Seizures
- Bone pain
- Muscle weakness
- Cataracts
- Rachitic deformities

**Differential Diagnosis**

- Low albumin (correct Ca level for albumin to make sure true hypocalcemia)
- Hypoparathyroidism: postsurgical, postradiation, congenital, autoimmune
- Vitamin D deficiency: renal failure, poor nutrition, malabsorption, short bowel, cirrhosis

- Pancreatitis
- Pseudohypoparathyroidism
- Hypomagnesemia
- Increased P (binds more Ca): rhabdomyolysis, tumor lysis syndrome
- Hungry bone syndrome

**Diagnostic Tests**

- Ca, albumin, Mg, P, PTH, 25(OH)D, and 1,25(OH)<sub>2</sub>D levels

**Treatment**

Treat symptoms, not numbers:

**Severe**

- Parenteral Ca salts for severe or life-threatening symptoms (2 ampules Ca gluconate 90 mg Ca/10 mL) or intravenous Ca infusion: 60 mL in 500 mL D5W (1 mg/mL), infuse at 0.5 to 2.0 mg/kg/h to control symptoms

**Chronic or not severe**

- Oral Ca supplements and vitamin D as soon as feasible

**Mg depleted**

- Replace with Mg salts before giving calcium

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**HYPOPHOSPHATEMIA**


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Low serum P does not necessarily indicate total body depletion as only 1% of body P is in blood.

**History**

- Observed in 10% of hospitalized alcoholics
- Gastrointestinal disorders, diarrhea, recent severe illness, weight change
- Diabetic ketoacidosis
- Critical illness/ventilated: Observed in 3% of all hospitalized patients, up to 70% of intensive-care-unit patients
- On total parenteral nutrition
- New medications, renal transplant

**Symptoms**

- Muscle weakness
- Hypoventilation
- Confusion
- Seizures
- Osteomalacia

**Differential Diagnosis**

Usually occurs due to combination of 1 of these 3 causes:

- Decreased intestinal absorption: Antacid abuse, malabsorption, chronic diarrhea, vitamin-D deficiency, starvation, anorexia, alcoholism
- Increased urinary losses: Primary hyperparathyroidism, post-renal transplant, extracellular fluid volume expansion, glucosuria (after treating diabetic ketoacidosis), post-obstructive or resolving acute tubular necrosis diuresis, acetazolamide, Fanconi's syndrome, X-linked and vitamin-D-dependent rickets, oncogenic osteomalacia
- Extracellular to intracellular shift: Respiratory alkalosis, alcohol withdrawal, severe burns, total parenteral nutrition, recovery from malnutrition when inadequate P is provided (post-feeding syndrome), leukemic blast crisis

**Diagnostic Tests**

- Based on history and trend in values, and blood pH (to distinguish acute shift) and urine P (<100 mg/d = gastrointestinal loss or shift)

**Treatment**

- Phosphate comes as Na-phosphate or K-phosphate; choice dictated by other illnesses such as heart or renal failure
- Only treat symptomatic severe hypophosphatemia with intravenous agents
- Otherwise choose oral agent; oral repletion best done with milk

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**HYPERPHOSPHATEMIA**


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**History**

- Renal failure
- Tumor lysis syndrome
- Rhabdomyolysis

**Symptoms**

- Asymptomatic unless hypocalcemia occurs due to precipitation of insoluble Ca-P complexes and decreased calcitriol synthesis
- Chronic hyperphosphatemia in renal failure is associated with vascular calcification and increased mortality

**Differential Diagnosis**

- Hyperphosphatemia occurs almost exclusively with impaired glomerular filtration rate
- Other rare causes:
  - Increased renal reabsorption: hypoparathyroidism, acromegaly, thyrotoxicosis
  - Massive release from intracellular stores in tumor lysis syndrome, rhabdomyolysis
  - Overdose of vitamin-D derivatives, phosphate-containing enemas

**Diagnostic Tests**

- Serum P and creatinine/glomerular filtration rate

**Treatment****Acute symptomatic hyperphosphatemia**

- Intravenous volume repletion with normal saline will enhance renal excretion, add 10 U insulin and 1 ampule D50 to enhance cellular uptake; best removal is obtained with dialysis but this is limited due to intracellular location of P

**Chronic**

- Dietary restriction and phosphate binders

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**HYPERMAGNESEMIA**


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**History**

- Medication use
- Laxative abuse
- Kidney disease

**Signs and Symptoms**

- Lethargy
- Nausea
- Confusion
- Hypoventilation
- Hypotension
- Arrhythmias
- Muscle weakness
- Decreased deep-tendon reflexes

**Differential Diagnosis**

(Occurs almost exclusively with chronic kidney disease)

- Increased intake: Antacids, laxatives, enemas, or treatment of preeclampsia with Mg salts

- Decreased renal function
- Cellular shifts: Pheochromocytoma, acidosis

#### Diagnostic Tests

- Mg, creatinine

#### Treatment

- Ca can be given if life-threatening arrhythmias, otherwise dialysis

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### HYPOMAGNESEMIA

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#### History

- Alcohol use
- Diarrhea/malabsorption
- Medications (cisplatin, aminoglycosides, amphotericin, loop diuretics, digoxin)

#### Signs and Symptoms

- Tremor of extremities and tongue, myoclonic jerks, Chvostek sign, Trousseau sign, tetany, general muscular weakness (particularly respiratory muscles), coma, vertigo, nystagmus, movement disorders
- Electrocardiogram: Increased susceptibility to digoxin-related arrhythmias; ventricular arrhythmias: premature ventricular contractions, ventricular tachycardia, Torsade de Pointes, ventricular fibrillation

#### Differential Diagnosis

##### *Reduced intake*

- Starvation, alcoholism, prolonged postoperative state

##### *Redistribution from extracellular to intracellular fluids*

- Insulin administration post-therapy of diabetic ketoacidosis, hungry-bone syndrome postparathyroidectomy, catecholamine excess states such as ethanol-withdrawal syndrome, acute pancreatitis, excessive lactation

##### *Reduced absorption*

- Specific gastrointestinal Mg malabsorption, generalized malabsorption syndrome, post-extensive bowel resections, diffuse bowel disease or injury, chronic diarrhea, laxative abuse

#### Diagnostic Tests

- Determining Mg deficiency
  - Only parameter to consistently predict Mg depletion is retention of >75% of Mg after a Mg infusion
  - Low urine fractional excretion of Mg indicative of deficiency
- Very low serum value (<1 mg/dL [0.41 mmol/L]) always indicates significant deficits that require therapy
- Other findings: Hypocalcemia, hypokalemia

#### Treatment

##### *Symptomatic*

- Intravenous Mg sulfate

##### *Asymptomatic*

- Oral repletion with Mg supplement (Mg oxide, Mg lactate)