DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM

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Neither I nor my spouse have anything to disclose.

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Increased Bone resorption

Increased Distal tubule Ca²⁺ reabsorption

Regulation of the serum Ca²⁺ concentration

Vitamin D → Liver → 25 (OH)D → Kidney → 1,25 (OH)₂ D

Increased PTH → Parathyroid gland

Increased Bone resorption

Increased Gut Ca²⁺ absorption

Mechanisms of hypercalcemia

Increased bone resorption

Increased gut absorption

Increased renal reabsorption

Causes of increased bone resorption

- Primary hyperparathyroidism
- Malignancy
- Thyrotoxicosis
  - 8-10% of patients
  - Direct effect to stimulate bone resorption
- Paget’s disease
- Immobilization
- Hypervitaminosis A
  - all trans retinoic acid (vitamin D derivative) in rr of acute promyelocytic leukemia
  - Dialysis patients given nutritional supplements
  - Ingestion of massive doses
- Lithium
  - Due to increased PTH secretion with hypercalcemia in ~5-10%, altered set point
  - Hyperplasia in those with long-term therapy, may unmask adenoma -- more likely with short-term

Malignancy -- Mechanisms

Local osteolytic factors -- account for ~20% of cases of hypercalcemia in malignancy:

- Metastatic solid tumors: IL-1, TNF
- Breast: Locally produced PTHrP increases expression of receptor activator of nuclear factor kappa B ligand (RANKL) in bone
- Myeloma (IL-1, IL-6, IL-3, lymphotoxin, hepatocyte growth factor, and receptor activator of nuclear factor kappa B ligand (RANK ligand)

Humoral -- Most common cause of hypercalcemia in patients with nonmetastatic solid tumors

- PTHrP, 80-90%
- Calcitriol in lymphomas
- Ectopic PTH secretion -- small cell lung ca
Hypercalcemia And Cancer (Series Of 642 Patients)

Causes:
- Cancer: 69%
  - Bone Mets: 53%
  - HHM 35.3%
  - Both 11.7%
- Hyperparathyroidism: 24.6%
- Hyperthyroidism 2.2%
- Sarcoid 0.45%

Hypercalcemia was not due to cancer in 97% of patients who were in complete remission.

PTH-related peptide (PTHrP)

- Expressed in many different non-neoplastic tissues, has multiple physiologic roles
- Close homology with PTH at the amino-terminal end (AA 1-13), binds to PTH receptors and stimulates adenylate cyclase activity
- Immunologically distinct from PTH
- Metabolized similarly to PTH and COOH terminal fragment accumulates in renal failure

Diagnostic value of PTHrP

- Intact PTHrP levels are low (usually undetectable) in patients with primary hyperparathyroidism and in normals
- Intact PTHrP levels are elevated in ~80% of patients with solid tumors; others have multiple myeloma or osteolytic metastases
- 5-10% have high serum concentrations of both PTHrP and PTH, suggesting coexisting primary hyperparathyroidism

Prognostic value of PTHrP in malignancy

- PTHrP concentrations > 12 pmol/L predict:
  - Lesser reduction in Sca++ with bisphosphonate Rx
  - Recurrence of hypercalcemia within 14 days of therapy
  - Shorter median survival times

  Wimalawansa SJ. Cancer 1994;73:2223

Causes of gut hyperabsorption of Ca^{2+}

- Vitamin D overdose (25 OH D)
- 1,25 (OH)2 D overdose
- Milk-alkali syndrome
- Granulomatous disorders (1,25 OH2 D)
- Idiopathic calcitriol induced hypercalcemia
- Idiopathic infantile hypercalcemia

Granulomatous disorders

Mechanism: PTH-independent extrarenal production of 1,25 D from 25-OH D by lymphocytes, macrophages is most common, but in some such as coccidiomycosis, PTHrP may play an important role

- Sarcoïdosis (50-60%)  
- Tuberculosis  
- Berylliosis  
- Histoplasmosis  
- Coccidioidomycosis  
- Lymphomas (15-20%) – calcitriol is the cause of almost all cases of ↑SCa in Hodgkin and 1/3 of cases in non-Hodgkin lymphoma, T, and B cell
- Silicone injections
Vit D overdose with OTC preparations


Features in common:
- Moderate to severe hypercalcemia
- 25(OH)D levels 300-700 ng/mL
- Supplements contained 100-1000 X amount of vit D listed by the manufacturer
- Dx delayed due to inadequate hx of intake

Milk-alkali syndrome

- Hypercalcemia, metabolic alkalosis, and renal insufficiency
- Making a comeback (third leading cause of admission for hypercalcemia)
  - Calcium treatment in osteoporosis
  - Over the counter calcium carbonate
  - Use of calcium carbonate to prevent secondary hyperparathyroidism in renal failure


Idiopathic calcitriol induced hypercalcemia

- Hypercalcemia
- Elevated calcitriol with low PTH, normal 25(OH)D
- No evidence of granulomatous disease
- Response to low dose glucocorticoids


Idiopathic infantile hypercalcemia

- Characterized by symptomatic hypercalcemia which can be severe, low levels of PTH, and sensitivity to vitamin D.
- Appears to be due to inactivating mutations in CYP24A1, (24-hydroxylase) responsible for inactivation of 1,25(OH)2D as well as converting 25(OH)D to the inactive metabolite 24,25(OH)2 D
- It has been reported in adults with mild hypercalcemia and hypercalciuric nephrolithiasis and nephrocalcinosis


Causes of increased renal calcium reabsorption/decreased excretion

- Familial hypocalciuric hypercalcemia
- Thiazide diuretics (often with underlying PHPT and Sca >12)
- Renal failure
- Milk-alkali syndrome

Familial hypocalciuric hypercalcemia (FHH)

- Autosomal dominant inactivating mutation in a calcium sensing receptor gene (heterozygous)
- Higher serum Ca2+ is necessary to suppress PTH
- Higher serum Ca2+ is necessary to reduce Ca2+ reabsorption in the CTAL
- Patients homozygous for the FHH gene present with neonatal hyperparathyroidism and severe hypercalcemia
Familial hypocalciuric hypercalcemia (FHH)

- Typically asymptomatic
- Hypercalcemia is not sensed intracellularly by target organs (eg, GI tract)
- PTH usually high nl; 23% sl elevated; calcitriol nl (70%)

**Diagnosis:**
- Family history
- 24 hr urinary calcium excretion <150 mg
- Ca/Cr clearance ratio
  - If 0.02 or less, test for mutations in the CASR gene.
  - Sensitivity of Ca/Cr and then mutation testing is 98%
- Treatment: Family screening

Signs and symptoms of hypercalcemia

- Neuropsychiatric (anxiety, depression, MCI)
- Muscle weakness
- Bowel hypomotility and constipation
- Peptic ulcer disease (?Ca-induced increased gastrin)
- Pancreatitis (Ca deposition in pancreatic duct/ Ca-activation of trypsinogen)
- Renal insufficiency
- Nephrolithiasis
- Nephrogenic DI
- Band keratopathy (subepithelial calcium phosphate corneal deposits)
- Shortening of QT interval

Diagnostic approach to hypercalcemia

- Assess clinical data and draw intact PTH
- Analyze PTH level -- Cut off PTH of > 26 ng/L in a study of 123 patients predicted a non-increased PTHrP in close to 100% of hypercalcemic patients)*
- Measure PTHrP
- Analyze Vitamin D metabolite levels


Useful clinical findings in patients with hypercalcemia

- **History** — childhood radiation, peptic ulcer/pancreatitis, asymptomatic patient with prolonged ↑Ca favor PHPT
- **Serum phosphate** — Hypophosphatemia in PHPT and humoral hypercalcemia of malignancy (PTHrP)
- **24 hr UCa excretion** — Low in milk-alkali, thiazides, FHH
- **25 (OH) D** — often slightly reduced (and 1,25 (OH)2 D increased in PHPT)

Diagnosis of hypercalcemia with hormonal assays

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<tr>
<th>Suppressed PTH assay</th>
<th>Elevated/high normal PTH assay</th>
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<td><strong>Intact PTH assay</strong></td>
<td><strong>Primary hyperparathyroidism</strong></td>
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| Paget’s | Milk-alkali |

Evaluation of vitamin D status in primary hyperparathyroidism

**Usual:**
- 25 (OH)D: normal or slightly low
- 1,25 (OH)2D: high normal or slightly elevated

**Not uncommon (30-35%):**
- 25 (OH)D: low (<20 ng/mL [50 nmol/L])
- 1,25 (OH)2D: normal or slightly elevated
Why look for and Replete low 25(OH)D in Patients with ↑PTH?

1. Differentiate FHH from mild PHPT with concomitant D def in pts with ↑PTH and SCa and low 24-hour UCa -- in mild PHPT and D depletion, but not FHH, UCa ↑ with D repletion

2. Differentiate 2nd HPT due to D def from normocalcemic PHPT in pts with ↑PTH, nl SCa and low 25OHD – repletion ↓PTH in 2nd HPT but not in normocalcemic PHPT

3. Inform management decision in patients with mild PHPT and D def -- repletion may ↑SCa and UCa significantly

Mild Primary Hyperparathyroidism (80-90% of PHPT)

NIH Consensus Conference Indications for surgery
- SCa 1.0 mg/dL (0.25 mmol/L) above the nl upper limit
- Ccr <60 mL/min
- Bone density at the hip, lumbar spine, or distal radius >2.5 SD below peak bone mass (T score <-2.5)
- Age less than 50 years

Indications for surgery as above (or symptomatic) but medically unfit or refuses
- Medical therapy
- Cinacalcet rather than bisphosphonates (unless osteoporosis or fractures present)

Medical management of mild PHPT
- Avoid aggravating factors thiazide diuretics, volume depletion, prolonged bed rest or inactivity, and a high Ca diet (>1000 mg/day).
- Moderate Ca restriction (eg, <800 mg/day) is probably warranted if calcitriol is high.
- Encourage hydration (>eight glasses of water per day) to minimize the risk of nephrolithiasis.
- Moderate Vit D intake (400 - 600 IU/d) as Vit D def ↑PTH secretion and bone resorption.

Symptomatic hypercalcemia (12-15 mg/dL)
- Volume expansion (Reduce tubular reabsorption)
  - Effective in 6-12 hrs
  - Combination with furosemide is out of favor
- Calcitonin (inhibits bone resorption)
  - Effective within 2 hrs in ~60-70% of patients
  - Escape occurs often after several days
- Bisphosphonates (inhibit bone resorption)
  - Pamidronate, alendronate, zoledronate
  - Effective within 2-5 days
- Glucocorticoids (decrease GI absorption)
  - Vitamin D intoxication, granulomatous disease
  - Effective after 2-3 days
- Gallium (inhibits osteoclastic bone resorption)
  - Potential for nephrotoxicity
  - Need for continuous infusion over five days

Saline plus loop diuretics in the treatment of hypercalcemia

Diuretic therapy plus saline infusion beyond restoration of euvoemia is no longer recommended as:
- Saline therapy rarely normalizes the SCa
- Bisphosphonates and calcitonin inhibit bone resorption, and are effective
- Saline infusion and furosemide-induced diuresis require careful monitoring and replacement to prevent hypok, hypomag, and volume depletion


Treatment of symptomatic moderate or severe hypercalcemia

- Begin saline infusion at 200 to 300 mL/h and then adjust to maintain the UO at 100 to 150 mL/h.
- Begin Salmon calcitonin, 4U/kg, q12h
- Begin infusion of zoledronate (4 mg IV over 15 minutes)
**Rx of severe life-threatening hypercalcemia**  
(Rare, Sca 16-20 mg/dL)

- Intravenous phosphate (potentially lethal)
- EDTA (nephrotoxic)
- Hemodialysis

**Regulation of the serum Ca^{2+} concentration**

[Diagram showing the regulation of serum Ca^{2+} concentration involving Vitamin D, 25(OH)D, 1,25(OH)_{2}D, PTH, increased distal tubule Ca^{2+} reabsorption, increased bone resorption, increased gut Ca^{2+} absorption, and serum Ca^{2+}]

**Hypocalcemia**

- Loss of ionized calcium from the ECF
- Disturbances of PTH secretion
- Vitamin D deficiency

**Loss of ionized Ca^{2+} from ECF**

- Tissue deposition
- Hyperphosphatemia
- Pancreatitis
- Osteoblastic metastases (particularly prostate)
- Hungry bone syndrome
- Intravascular binding (total PCa^{2+} usually normal)
- Respiratory alkalosis
- Citrate (blood transfusions, particularly when liver function is compromised)
- Lactate (shock, sepsis)
- Foscarnet
- Sodium EDTA

**Disturbances in PTH secretion**

- Anatomic hypoparathyroidism
- Post-surgical
- Idiopathic
- Auto-immune
- Post-irradiation
- Glandular infiltration
- Functional hypoparathyroidism
  - Marked hypomagnesemia (<1 mg/dL)
  - Marked hypermagnesemia (5-6 mg/dL)
- End-organ resistance
  - Pseudohypoparathyroidism (Type I: decreased cAMP production, Type II: Resistance to cAMP)
IV MgSO₄ for premature labor
(n=7; Mg²⁺ = 4.8-6.3 mg/dL)

Cholst, IN, et al. NEJM 1984; 310:1221

Vitamin D metabolism

Causes of vitamin D deficiency

Measurement of vitamin D levels
- Vit D sufficiency is estimated by measuring total 25OHD concentration (not 1,25(OH)₂D). Maximal PTH suppression by vit D occurs in the 30 to 40ng/mL range.
- Vit D insufficiency -- usually defined as 25OHD concentration of 20 -- 30 ng/mL; deficiency is defined as 25OHD < 20 ng/mL.
- The IOM -- 20 ng/mL is the level needed for good bone health for practically all individuals.
- Latest recommendations of the Endocrine Society -- serum levels >30 ng/mL have been acceptable, but now should target 40 -- 60 ng/mL.

Mean levels of vitamin D-binding protein (VDBP) were also significantly lower (168±3 vs. 337±5 μg/mL)

Genetic polymorphisms independently appeared to explain 79.4% of the variation in levels of vitamin D-binding protein

Among homozygous participants, blacks and whites had similar levels of bioavailable 25-OH D overall (2.9±0.1 ng per milliliter and 3.1±0.1 ng per milliliter, respectively; P=0.71) and within quintiles of parathyroid hormone concentration.


Vit D–Binding Protein And Vit D Status Of Black And White Americans

Dose response to vit D supplementation in AA (winter, boston, MA)

Mean levels of total 25-OH D were significantly lower in blacks than in whites (15.6±0.2 vs 25.8±0.4 ng/mL) but higher bone mineral density
Problems With Interpretation

- Potential issues with the assay used to measure vitamin-D binding proteins and lack of direct measure of "bioavailable" 25-OHD
- The complex of 25-OH D and vitamin-D-binding protein is taken up by renal proximal tubule epithelial cells through receptor-mediated (megalin) endocytosis. The 25-OH D component of the endocytosed complex then becomes the major precursor for circulating 1,25-(OH)2 D

Other causes of hypocalcemia

- Sepsis
  - hypoalbuminemia
  - impaired secretion of both PTH and calcitriol
  - end-organ resistance to the action of PTH (due to hypomagnesemia and cytokines)
- Fluoride poisoning (inhibition of bone resorption)
- Bisphosphonates
- Pseudohypocalcemia (Gadolinium, interferes with the colorimetric assays for calcium)


Signs and symptoms of hypocalcemia

- Acute hypocalcemia
  - Tetany: paresthesias, muscles spasms, cramps (Trousseau's sign, Chvostek's sign)
  - Seizures
  - Hypotension
- Chronic hypocalcemia
  - Cataracts
  - Mental retardation
  - Impaired insulin release
  - Basal ganglia calcifications, movement disorders
  - Myopathy (vitamin D deficiency)
  - Myocardial dysfunction and congestive heart failure

Diagnostic approach to hypocalcemia

Correct for serum albumin
Draw serum Mg++, PO4, PTH
Give Mg++ if renal function is normal
Hypocalcemia is corrected and SMg++ is low
Diagnosis of hypomagnesemia
High PTH Low PTH
Vitamin D deficiency
Measure 25 OHD and 1,25 (OH)2 D

Treatment of acute hypocalcemia

- Mild hypocalcemia (PCa++ > 8.0mg/dL)
  - Typically asymptomatic
  - Maintain dietary Ca > 1000 mg/day
- Symptomatic hypocalcemia
  - IV Ca: 100-200 mg/10-20 minutes then
  - Slow IV infusion: 0.5-1.5 mg/kg/hr (gluconate less likely to cause tissue necrosis)
  - Start calcitriol 0.25-0.5 µg/day

Treatment of chronic hypocalcemia (Hypoparathyroidism)

- Goals
  - Relieve symptoms
  - Maintain Sca++ 8-8.5 mg/dL to avoid hypercalciuria and nephrocalcinosis
- Therapy
  - Oral calcium, 1.5 - 2.0 g of elemental calcium
  - Lower phosphate in diet
  - Add vitamin D preparation
  - ?Add thiazides and Na restriction
Hypophosphatemia

**Phosphate balance**

**Mechanisms of hypophosphatemia**

- **Internal redistribution**
  - Stimulation of glycolysis – ↑ formation of phosphorylated carbohydrate compounds in liver and skeletal muscle
  - Insulin and glucose IV (45%)
  - Respiratory alkalosis (5-10%) – phosphofructokinase
  - Hyperalimentation or post-op refeeding (7-10%)
  - Hungry bone syndrome

- GI loss (10-15%)
  - Inadequate intake with continued secretory losses (unusual)
  - Diminished absorption – principally aluminum and magnesium phosphate binders
  - Increased losses – steatorrhea and diarrhea

- Renal loss (5%)
  - Decreased proximal tubular reabsorption
    - Diamox
    - Glycosuria (osmotic diuresis)
    - Fanconi syndrome (glycosuria, RTA, aminoaciduria)
  - Multiple myeloma in adults
  - Cystinosis, Wilson's disease, and hereditary fructose intolerance in children

- Hereditary hypophosphatemic rickets
  - X-linked hypophosphatemic rickets (PHEX mutation) (low 1,25D)
  - Autosomal dominant hypophosphatemic rickets (Abnormal FGF23) (low 1,25D)
  - Hereditary hypophosphatemia with hypercalciuria (elevated 1,25D) (Mutations in the Na-Pi cotransporter)

- Oncogenic osteomalacia (TIO) (very low 1,25D) (↑FGF23, MEPE, frizzled-related protein 4)

Primary renal PO₄ wasting with normocalcemia

- Decreased proximal tubular reabsorption
- Hereditary hypophosphatemic rickets
- Oncogenic osteomalacia (TIO)
Phosphatonin metabolism

- Autosomal-dominant FHM
- Abnormal FGF23 mutation
- Locally produced FGF23 and other phosphatoninns
- Cleaved by endopeptidase
- Proximal renal tubule cell
- PO₄ transport
- Calcitriol production
- Inactive metabolites
- XLH
- Inactivating mutations

FGF23 Overproduced in TIO

Quares, LD. Am J Physiol Endocrinol Metab 2003; 285: E1

Signs and symptoms of hypophosphatemia (typically <1.0 mg/dL) with intracellular phosphate depletion (mostly due to tissue hypoxia due to reduced levels of ATP and 2,3 DPG)

- Muscle
  - Muscle weakness (chronic)
  - Rhabdomyolysis
- Respiratory paralysis
- Central Nervous System
  - Irritability
  - Paraoxonias
  - Confusion
  - Seizures
  - Delirium
  - Coma
- Hemolytic anemia
- Myocardial dysfunction
- Osteomalacia (chronic)

Diagnosis of hypophosphatemia

Measure urine phosphate excretion

- yes: 24 hr urine < 100 mg
  - FEPO₄ < 5%
  - Check serum calcium

Is there respiratory alkalosis or insulin/glucose infusion?

- No
  - GI loss
  - Redistribution
  - 1st Renal PO₄ wasting
- Yes
  - 1st HPT
  - VIT D deficiency

Hereditary
- X-linked (FGF23)
- Autosomal dominant (FGF23)
- Na-PO₄ cotransporter mutation (hypocalciuria)

Acquired
- Fanconi Syndrome
- Diuretics/glucosuria
- TIO (FGF23)
- IV iron (FGF23)
- Imatinib (?)

FGF 23 Levels In Hypophosphatemia


Hypophosphatemia in the alcoholic

Baseline

- Poor diet
- Vitamin D deficiency
- Inadequate PO₄ intake
- GI absorption
- Secondary hyperparathyroidism
- Diarrhea
- GI loss
- Renal phosphate loss

12 hrs after admission

- Cellular PO₄ uptake
- Severe hypophosphatemia
- Insulin release
- ATP depletion
- Rhabdomyolysis
- Phosphate depletion with mild hypophosphatemia
- Cellular PO₄ uptake
- Increase in glycolysis
- Stimulates phosphofructokinase
- Acute respiratory alkalosis
  - Alcohol withdrawal
  - Sepsis
  - Hepatic failure
Prophylaxis in alcoholic

1. Use valium/tranquilizers to prevent development of DTs
2. Avoid carbohydrate loading – use saline instead of D5W as volume repleting and replacement fluid
3. Provide oral PO₄ in hypophosphatemic patients on admission

Hypophosphatemia in DKA – Why treat?

1. They typically develop significant hypophosphatemia during insulin therapy and if they have pre-existing phosphate depletion from glycosuria, should have the same problems as the alcoholic
2. In fact, severe symptoms have been described including:
   - Rhabdomyolysis
   - Hemolytic anemia
   - Respiratory failure
3. Data suggesting insulin resistance as consequence of hypophosphatemia

Hypophosphatemia in DKA – Why not treat?

1. Characteristics of patients with symptomatic hypophosphatemia during treatment of DKA:
   - Rare
   - Preceding protracted course with days of hyperglycemia and glycosuria
   - Most treated with high-dose insulin
   - Serum phosphate <3.0 mg/dL
2. Prophylaxis with IV phosphate as KPhos has been shown to not have beneficial effects upon outcome and has been associated with deleterious effects

Recommendations for therapy in DKA

The routine use of phosphate is NOT recommended in the treatment of DKA or HHS with mild or moderate hypophosphatemia. Patients who remain hypophosphatemic after recovery can be treated with oral phosphate.

However, to avoid cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may be indicated:

- In patients who develop cardiac dysfunction, hemolytic anemia, or respiratory depression,
- In those with a serum phosphate concentration below 1.0 mg/dL.
- In patients on a respirator

When needed, 20 to 30 meq/L of KPhos can be added to replacement fluids.

Causes of hyperphosphatemia

- Decreased GFR (<25 mL/min)
- Massive phosphate infusion
  - Endogenous:
    - Tumor lysis
    - Rhabdomyolysis
  - Exogenous: Phosphate enemas, laxative abuse
- Increased tubular reabsorption
- Hypoparathyroidism
- Acromegaly
- Some diphosphonates (etidronate used in Paget’s)
- Tumoral calcinosis (↑ FGF 23)
- Lactic and ketoacidosis – acidosis inhibits glycolysis
- Pseudohyperphosphatemia – interference with analytical methods may occur with hyperglobulinemia, hyperlipidemia, hemolysis, and hyperbilirubinemia

Acute phosphate nephropathy

Associated with ingestion of sodium phosphate laxatives (solution or tablets) as bowel preparation for colonoscopy (or enemas)

- Formerly sold without prescription as “Fleet Phosho-soda”
- December 2008, voluntarily withdrawn from the market and currently available only by prescription in pill form

Pathogenesis – Hyperphosphatemia (dose dependent) + volume contraction (diarrhea) and/reduced GFR (CKD, ACEI, diuretics) which limit PO₄ excretion

Presentation:

- Acute reversible renal failure (pro-renal?) within hours with hyperphosphatemia and symptoms of hypocalcemia (can be fatal)
- Acute renal failure in asymptomatic patients documented days to months following phosphate administration, typically not reversible (biopsy – nephrocalcinosis)
Primary Hyperparathyroidism vs FHH

Treatment of Hyperparathyroidism

Diagnosis of Hypercalcemia

Zolendronic Acid in Hypercalcemia of Malignancy
- Major, P. The Oncologist 2002; 7:481
- Cines, GA. Curr Opin Endocrinol Diabetes Obes. 2011; 18:339

Saline Plus Loop Diuretic In The Treatment Of Hypercalcemia

Phosphatonin Metabolism
- Quarles, LD. Am J Physiol Endocrinol Metab 2003; 285: E1

FGF 23 levels in Hypophosphatemia

Phosphate depletion and hypophosphatemia

Acute Phosphate Nephropathy

Vitamin D insufficiency in US

Endocrine Society Guidelines

Pseudohypocalcemia

Hyperventilation and Serum PO4

Insulin and glucose and hypophosphatemia
- Juan, D, et al. JAMA. 1979; 242: 163

Vitamin D overdose with OTC preparations

Milk-Alkali Syndrome

Idiopathic Infantile Hypercalcemia