Calcium and Phosphate

Myles Wolf, MD, MMSc

The “Players”

**ORGANS:**
- Parathyroid
- Bone
- Gut
- Kidney

**HORMONES:**
- Parathyroid Hormone (PTH)
- (PTH-related Peptide)
- Calcidiol (25-OH-D₃)
- Calcitriol (1,25-OH-D₃)
- Fibroblast Growth Factor-23
- Klotho

**Calcium**

- Needed for skeleton
- Excitable tissues
- Action potentials
- Cardiac and muscle contractility

**Calcium balance**

GI absorption: ~20%
Renal reabsorption: ~98%
FeCa: ~2%
Intestinal absorption of calcium

Transporters are highly dependent on 1,25D

Tubular handling of calcium: TAL

Inhibitors: furosemide, activation of CaSR

Tubular handling of calcium: DCT

Phosphate

- Phospholipid bilayers
- Cell signaling
- Glycolysis
- ATP
- DNA, RNA synthesis
- Unloading O₂ (2,3-BPG)
**Phosphate Balance**

- GI absorption: ~67%
- Renal reabsorption: ~85-90%
- FeP: ~10-15%
- Serum P=40 mg/l; GFR 150L/d
- 800 mg/6000 mg = 13%

**Intestinal Phosphate Absorption**

- Linear absorption, nonsaturable function of intake
- Approximately 60-75% of intake
- Primarily in small intestine
- 1,25(OH)2D3 stimulates absorption via NaPi2b
- Most phosphate absorption vitamin D independent via paracellular transport

**Renal Phosphate Handling: Proximal Tubule**

- Apical: NPT2a, NPT2c
- Basolateral: NPT2a, NPT2c

**Main sodium-phosphate co-transporters**

- Gut: NPT2b
  - Active transport of phosphate
  - Less important than passive phosphate transport
  - Human deletion has no phosphate phenotype
- Kidney: NPT2a, NPT2c
  - In PCT
  - NPT2a mutations: Fanconi syndrome
  - NPT2c mutations: HHRT syndrome
  - Relative roles vary in mammalian species
**PTH**

- Primarily regulates: ionized calcium
- Main stimulus: hypocalcemia
- Main effects: raise serum calcium
  - Stimulates bone resorption
  - Stimulates 1,25D production (CYP27B1)
  - Inhibits CYP24
  - Inhibits calciuria
  - Stimulates phosphaturia
- Hyperphosphatemia stimulates parathyroid gland hyperplasia

**1,25-dihydroxyvitamin D**

- Primarily regulates: gut mineral absorption
- Main stimulus: PTH
- Main inhibitor: FGF23
- Main effects:
  - Augment gut calcium absorption
  - Augment gut phosphate absorption
  - Feedback inhibition to suppress PTH
  - Stimulates FGF23
  - Stimulates 24-hydroxylase

**Vitamin D synthesis and hydroxylases**

**Vitamin D Stores and PTH**

- **N** = 1,536 menopausal women on osteoporosis Rx
- 18% had D levels <20
- Inverse association between D and PTH

**RISK FACTORS for D deficiency:** older age, non-white race, obesity, low exercise, low education, insufficient supplementation, certain medications, lack of discussion with MD about vit D

Holick et al., J Clin Endocrinol Metab. 2003; 88: 3210-24
Prevalence of Secondary Hyperparathyroidism by Vitamin D Stores

![Graph showing prevalence of secondary hyperparathyroidism by vitamin D stores.](image)


FGF23

- Primarily regulates: ?
- Main stimulus: 1,25D and high dietary phosphate
- Main effects: lower serum phosphate
  - Stimulates phosphaturia
  - Inhibits 1,25D production (CYP27B1)
  - Stimulates CYP24
  - Inhibits PTH
- Direct effects on bone: ?

Classic Physiological Actions of FGF23

![Diagram illustrating classic physiological actions of FGF23.](image)


FGF23 in normal physiology

![Diagram showing FGF23 in normal physiology.](image)

- 29 healthy males subjected to low phosphate diet with phosphate binder, followed by phosphate loading
- FGF-23 decreased with low phosphate and increased with phosphate load

Ferrari, *J Clin Endocrinol Metab*, 2006
**Illustrative Case Studies: CKD**

- **Features:**
  - Low 1,25D
  - Variable 25D
  - High PTH
  - High FGF23
  - Low klotho expression
  - Low normal calcium
  - High normal phosphate

---

**Calcitriol Deficiency and SHPT in CKD**

![Diagram showing FGF23 levels by CKD stage in CRIC](image)

![Graph showing relationship between GFR and calcitriol levels](image)

---

*Abnormal PTH based on Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in CKD. 2003.

FGF23 and PTH in CRIC

Effects of Anti-FGF23 Antibodies

Disordered Mineral Metabolism in Rat CKD

Cascade of disordered mineral metabolism in CKD
FGF23 and mortality in incident ESRD

Cumulative incidence of death, %

FGF23 and mortality in CKD 2-4: 266 events, 20.3/1000 person-years

FGF23-Induced Hypertrophy of NRVM: FGFR-dependent but klotho independent

Blocking FGFRs prevents LVH in uremic rats
Anti-FGF23 Ab: Increased calcification & mortality

Disordered phosphate homeostasis and cardiovascular disease in CKD

Illustrative monogenic case studies 1

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)

- Biochemical phenotype:
  - Rickets
  - Hypophosphatemia
  - Normal serum calcium
  - Low FGF23
  - Normal PTH
  - Hypercalciuria
  - High 1,25D

- Where is the primary lesion?

- Key finding: Hypophosphatemia that is not FGF23 or PTH mediated
- Primary defect: NaPi2c deficiency
- Phosphate wasting → rickets
- FGF23 suppression → 1,25D activation
- Hypercalciuria
- NaPi2a deficiency was recently described in humans for the first time (Magen D, N Engl J Med 2010)
Illustrative monogenic case studies 2

- Biochemical phenotype:
  - Ectopic calcification
  - Hyperphosphatemia
  - Normal serum calcium
  - Low intact FGF23
  - Low PTH
  - Hypercalciuria
  - High 1,25D

- Where is the primary lesion?

Tumoral calcinosis: FGF23 deficiency

- Key finding: hyperphosphatemia with low FGF23 and low PTH
- Absence of biologically active FGF23 or FGF23 action due to klotho deficiency \(\Rightarrow\) elevated 1,25D
- Positive calcium balance + defective phosphate excretion = calcifications
- Elevated 1,25D and calcium absorption suppress PTH and permit hyperphosphatemia

Illustrative monogenic case studies 3

- Biochemical phenotype:
  - Hypercalcemia
  - Normal serum phosphate
  - High-normal PTH
  - Hypocalciuria
  - High 1,25D

- Where is the primary lesion?

Familial hypocalciuric hypercalcemia (FHH)

- Key finding: hypercalcemia with non-suppressed PTH = primary hyperparathyroidism
- Inactivating mutation of calcium sensing receptor
  - Persistent PTH production despite hypercalcemia
  - Upward reset of calcium set point
  - PTH induces hypercalcemia
  - Activation of TAL and DCT calcium transport by partially inactive calcium sensing receptor

- Boards claim to fame:
  - Looks like primary hyperparathyroidism on serum
  - Don’t resect FHH
  - Urine calcium differentiates
Illustrative monogenic case studies 4

• Biochemical phenotype:
  – Hypocalcemia
  – Hyperphosphatemia
  – Low PTH
  – Hypercalciuria
  – Low 1,25D

• Where is the primary lesion?

Autosomal dominant hypoparathyroidism

• Key finding: Hypocalcemia + low PTH = hypoparathyroidism
• Activating mutation of calcium sensing receptor
• Mirror image disease of FHH
  – Absent PTH production despite hypocalcemia
  – Downward reset of calcium set point
  – Lack of PTH induces hypocalcemia
  – Lack of PTH (and likely inappropriately low FGF23) contribute to hyperphosphatemia
  – Reduced TAL and DCT calcium transport by activated calcium sensing receptor leads to calcium dumping, hypercalciuria

Illustrative monogenic case studies: 5

• Biochemical phenotype:
  – Hypocalcemia
  – Hypophosphatemia
  – High PTH
  – Normal 25D
  – Undetectable 1,25D

• Where is the primary lesion?

Vitamin D-dependent rickets type 1

• Key finding: hypocalcemia + hypophosphatemia with secondary hyperparathyroidism = defective vitamin D signaling
• 1-alpha hydroxylase deficiency (autosomal rec)
• Lack of 1,25D → hypocalcemia → secondary hyperpara and hypophosphatemia
• Vitamin D-dependent rickets type 2 = VDR deficiency
  – Difference is 1,25D level and response to 1,25D therapy
• FGF23 should be very low in type 1 and 2
• Vitamin D resistant rickets = primary FGF23 excess (XLH, ADHR, TIO)
Questions