The Physiology and Hormonal Control of Calcium, Phosphate and Vitamin D

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The Physiology and Hormonal Control of Calcium, Phosphate and Vitamin D

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Russ

- I always learned something new from friendly, smiling Russ
- Most importantly, I learned that there is no substitute to loving what you are doing
- There was no need to look for (other) giants in our field of Pediatric Nephrology in general, and Mineral Metabolism in particular, whenever Russ was around
- It is thus a real honor to be here today
Disclosure

• Speaker for Ultragenyx
Overview

• The physiology of the players in mineral metabolism is closely intertwined, with common final goals of:
  (a) maintenance of mineral homeostasis
  (b) in pediatrics - tissue buildup (bone and soft)
• The main minerals involved:
  Calcium and phosphorus
• The main hormones regulating them:
  Vitamin D, PTH and FGF23
**Principles of vitamin D metabolism**

- **Nutritional Vitamin D₂/Vitamin D₃**
- **G.I. Tract chylomicrons**
- **Vitamin D**
  - **Liver**
    - 25-OHase
    - 25(OH)D
  - **Kidneys**
    - 1-OHase
    - 1,25 (OH)₂D
  - **Extra-renal 1-OHase**
  - **24-OHase**
  - **FGF 23**

- **Parathyroid glands**
  - PTH

- **Bone**
  - RANKL, RANK, Osteoblast
  - Osteoclast

- **Intestinal absorption**
  - Calcium & phosphorous

- **Blood**
  - Calcium
  - Phosphorous

- **Solar UVB radiation**
  - Skin 7-DHC

- **Key:** → = stimulation; ← = suppression

- **Low calcium**
- **Low phosphorous**
- **High calcium**
- **High phosphorous**

**Pathways:**
- **Low calcium** to **Parathyroid glands**
- **Parathyroid glands** to **Bone**
- **Bone** to **Intestinal absorption**
- **Intestinal absorption** to **Blood**
- **Blood** to **Liver**
- **Liver** to **Kidneys**
- **Kidneys** to **Extra-renal 1-OHase**
- **Extra-renal 1-OHase** to **Calcitriolic acid**
- **Calcitriolic acid** to **Skin 7-DHC**
- **Skin 7-DHC** to **G.I. Tract chylomicrons**
- **G.I. Tract chylomicrons** to **Vitamin D**
- **Vitamin D** to **Liver**
- **Liver** to **Kidneys**
- **Kidneys** to **Extra-renal 1-OHase**
- **Extra-renal 1-OHase** to **Calcitriolic acid**
An example of possible aberration in vitamin D metabolism: The role of 24-hydroxylase

Previously known as Idiopathic Infantile Hypercalcemia, loss of function of the 24-hydroxylase enzyme, caused by mutations in the CYP24A1 gene, will result in high 1,25-(OH)$_2$D blood level, and consequently hypercalcemia, hypercalciuria and nephrocalcinosis.
A quick reminder of calcium homeostasis

Figure 1. Overview of the metabolic systems that maintain calcium homeostasis. PTH, parathyroid hormone.
PTH - the actual minute to minute regulator of serum Ca\(^{++}\)

Note the exceptional stability of Ca\(^{++}\) within a very narrow range.
Effect of serum Ca\(^{++}\) on PTH

Note that minor changes in serum Ca\(^{++}\), well within its normal range, result in significant changes in serum PTH.
Ca sensor receptor (CaSR) - History


- Nemeth EF et al.: Calcimimetics with potent and selective activity on the parathyroid calcium receptor (*Proc Natl Acad Sci USA* 1998;95:4040)
CaSR Distribution

- Bone, cartilage, pituitary, placenta, intestine, pancreas, calcitonin-producing cells
- Parathyroid glands
- Kidney
CaSR in the Parathyroid Glands

- When the CaSR is inactive (low serum Ca\(^{++}\)), vesicles move to the cell membrane and release their stores of PTH. When the CaSR is activated by high serum Ca\(^{++}\) (or Mg\(^{++}\) at 1/3 potency), the release of PTH is inhibited.
Roles of CaSR and VDR in the parathyroid glands

Figure 1 | The respective roles of calcium ions, acting through the CaSR, and vitamin D sterols, acting through the VDR, as direct modifiers of parathyroid gland function.

Note the role of CaSR in gland proliferation, a common problem in the CKD population.
CaSR in the kidney (1)

- The CaSR is most abundant in the basolateral cell surface of the cortical thick ascending limb of the loop of Henle (cTAL) (but is present also in most other tubular segments)
CaSR in cTAL
CaSR in the kidney

• In the cTAL, CaSR activation inhibits the activity of Na/K2Cl co-transporters and, consequently, sodium reabsorption
• This leads to decrease in lumen-positive transepithelial voltage and consequently to decrease in passive, paracellular Ca (+Mg) reabsorption, resulting in \( \uparrow \) in calciuria (& magesuria)
• It is therefore of clinical relevance, when using calcimimetics (thus stimulating the CaSR), to monitor for hypercalciuria (amenable to thiazide diuretics)
Rickets – a disease of phosphate insufficiency

- The common denominator of all types of rickets is hypophosphatemia (leaving aside bone disease in CKD)
- Hypophosphatemia prevents apoptosis of mature chondrocytes at the growth plate, and consequently the chain of events that includes invasion of blood vessels and generation and mineralization of new bone
- Elevated alkaline phosphatase activity, seen in all cases of rickets, is an indicator of activity of osteoblasts, trying to recruit phosphate, for the formation of hydroxyapatite, by breaking down pyrophosphate
Differential Diagnosis of Rickets Based on Serum PTH

Note that serum P is always low, either due to high PTH or abnormalities in P metabolism.
Hereditary vitamin D resistant rickets (HVDRR): PTH and calcimimetics (1)

- HVDRR is a rare autosomal recessive disorder which results from loss of function mutation in vitamin D receptor (VDR) gene, leading to target organ resistance to $1,25(OH)_2$-D
- It presents in early life with hypocalcemic tetany and rickets
- Biochemically serum Ca and P are low, and $1,25(OH)_2$-D and PTH are very high
- Traditional treatment: high doses of calcium, provided IV in infancy (20/24 hours daily) and PO later in life
Vitamin D resistant rickets: PTH and calcimimetics (2)

- We speculated that the rickets is the result of low serum phosphate resulting from the excessive phosphaturic effect of high serum PTH

- As such (and after treatment with IV calcium became life threatening, due to recurrent infections of the central line), in order to suppress PTH secretion, we applied cinacalcet
Treatment of a child with HVDRR:
IV calcium (Period II) followed by Cinacalcet (Period IV)

PTH ______, Alk Phosph -------
Note the increase in serum P (----) as PTH was suppressed by either IV calcium (Period II), or cinacalcet (Period IV)
Period I: Age 15 months (left) and 19 months (right)

Period II: Age 22 months (left) and 27 months (right)

Period III: Age 36 months (left) and 42 months (right)

Period IV: Age 57 months (left) and 70 months (right)
Differential Diagnosis of Rickets Based on Serum PTH

- Normal PTH
  - Primary phosphorus deficiency
    - Urine P
      - Low
        - ↓ phosphate intake
        - ↓ phosphate GI absorption:
          - PO₄-binding antacid
          - Enteroenteric fistula
      - High
        - ↓ renal tubular reabsorption:
          - Familial hypophosphatemic rickets
          - Hereditary hypophosphatemic rickets with hypercalciuria
          - Fanconi syndrome
          - Oncogenic osteomalacia
  - High PTH
    - Abnormalities in vitamin D metabolism
    - Calcium deficiency
    - Magnesium deficiency
X-linked (dominant) hypophosphatemic rickets

- The most common inherited rickets caused by mutations in the PHEX gene, leading to elevated serum levels of FGF23, and consequently suppression of proximal tubule P reabsorption and 1,25 (OH)$_2$D production, resulting in hypophosphatemia and rickets
- Traditional treatment includes calcitriol and high repetitive doses of oral phosphate
- However, complications are frequent and include nephrocalcinosis and secondary hyperparathyroidism, at times progressing to tertiary hyperparathyroidism and damage to the kidneys to the point of ESKD
FGF23-blocking Agents

• The development of a human antibody to FGF23 opened a new field of treatment of XLH

• Indeed studies showed that a SQ injection, q2W, in children with XLH, resulted in normalization of TP/GFR, serum phosphate and 1,25 (OH)₂-D levels, and healing of rickets, with no adverse effects

• Interestingly in my patient, following treatment serum FGF23 went up from 230 to 99,500 RU/ml

• Will the medication have a place in our ESKD population (protecting their hearts)?
Grandpa, Dad, Grandkids and Cessna 206 are ready to go flying

Thanks for your attention