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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

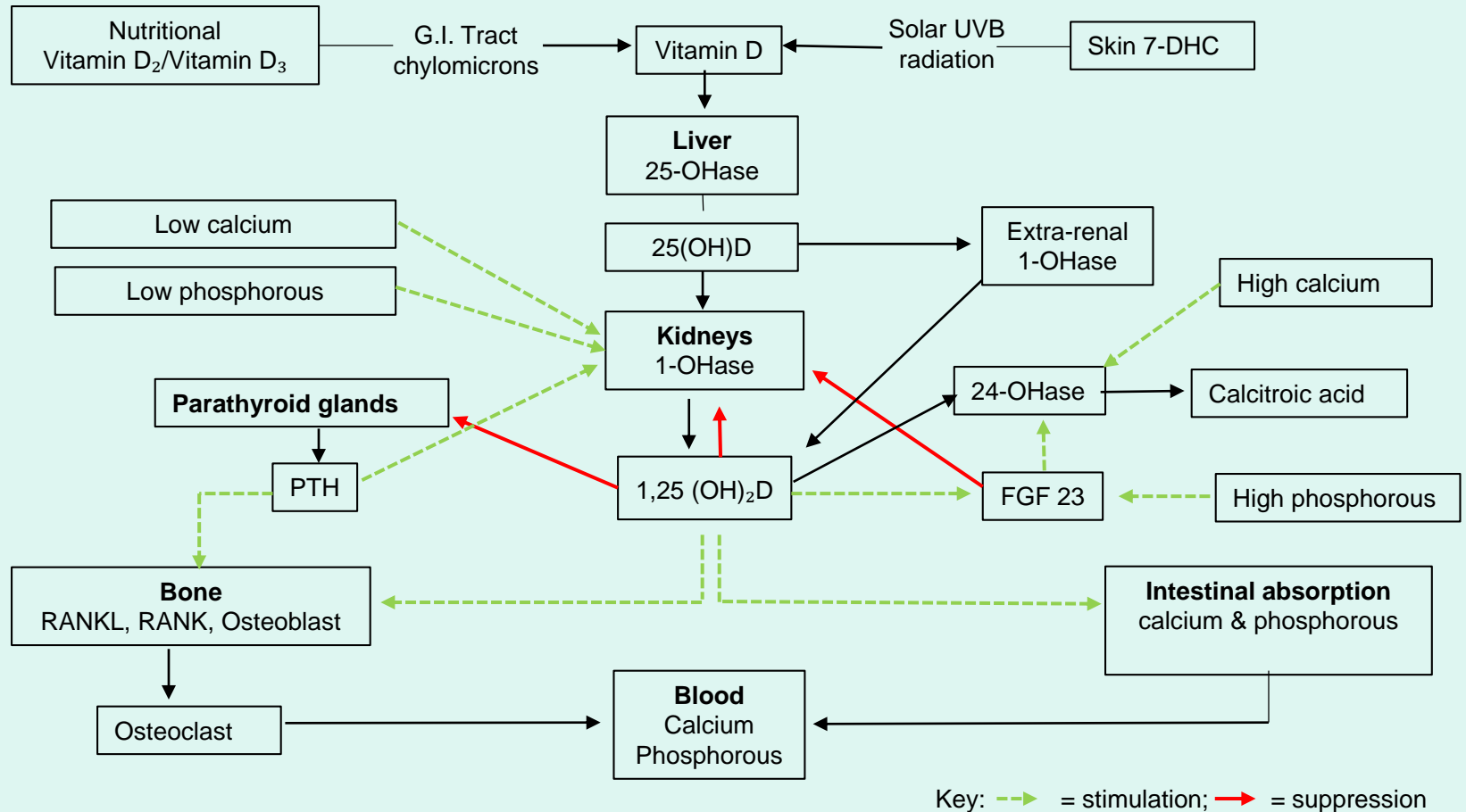
Disclosure

- Speaker for Ultragenyx

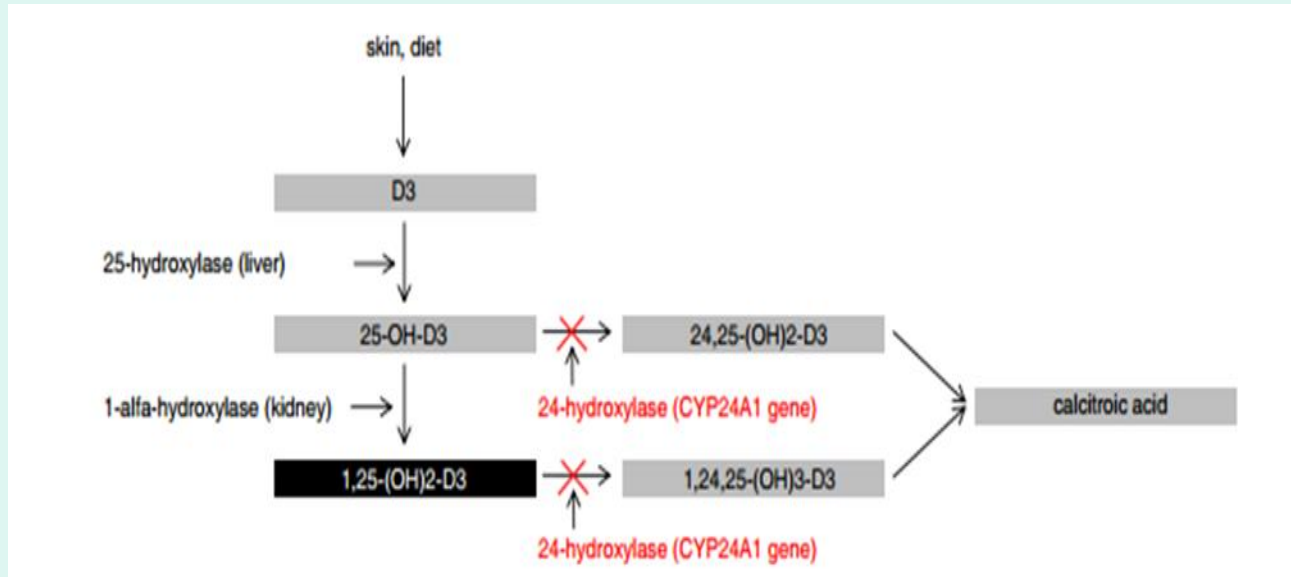
Overview

- 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

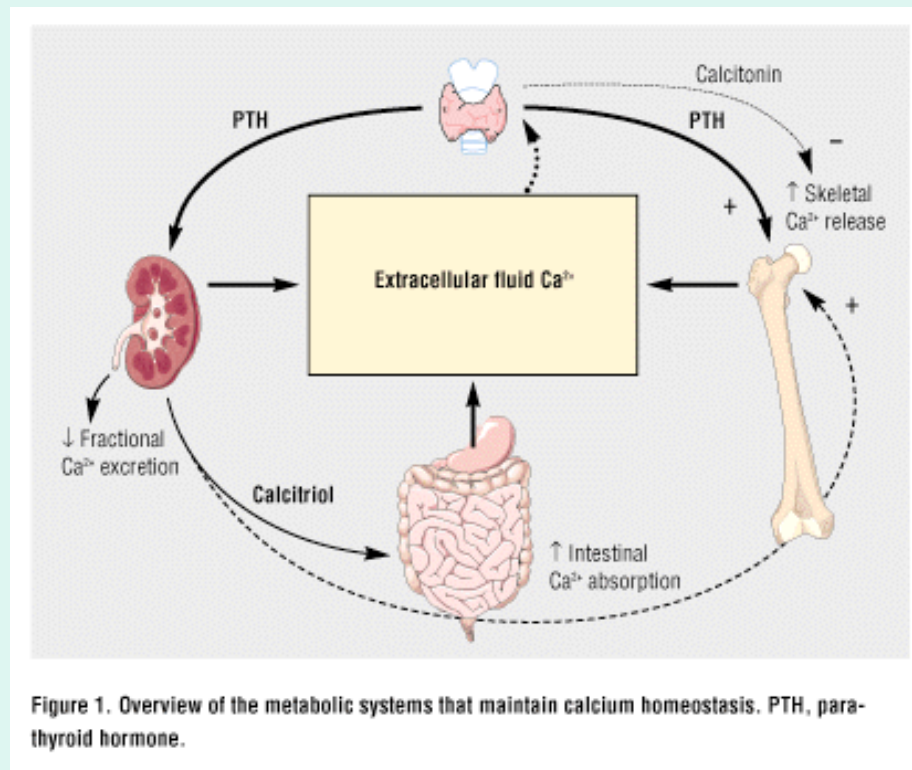


An example of possible aberration in vitamin D metabolism: The role of 24-hydroxylase

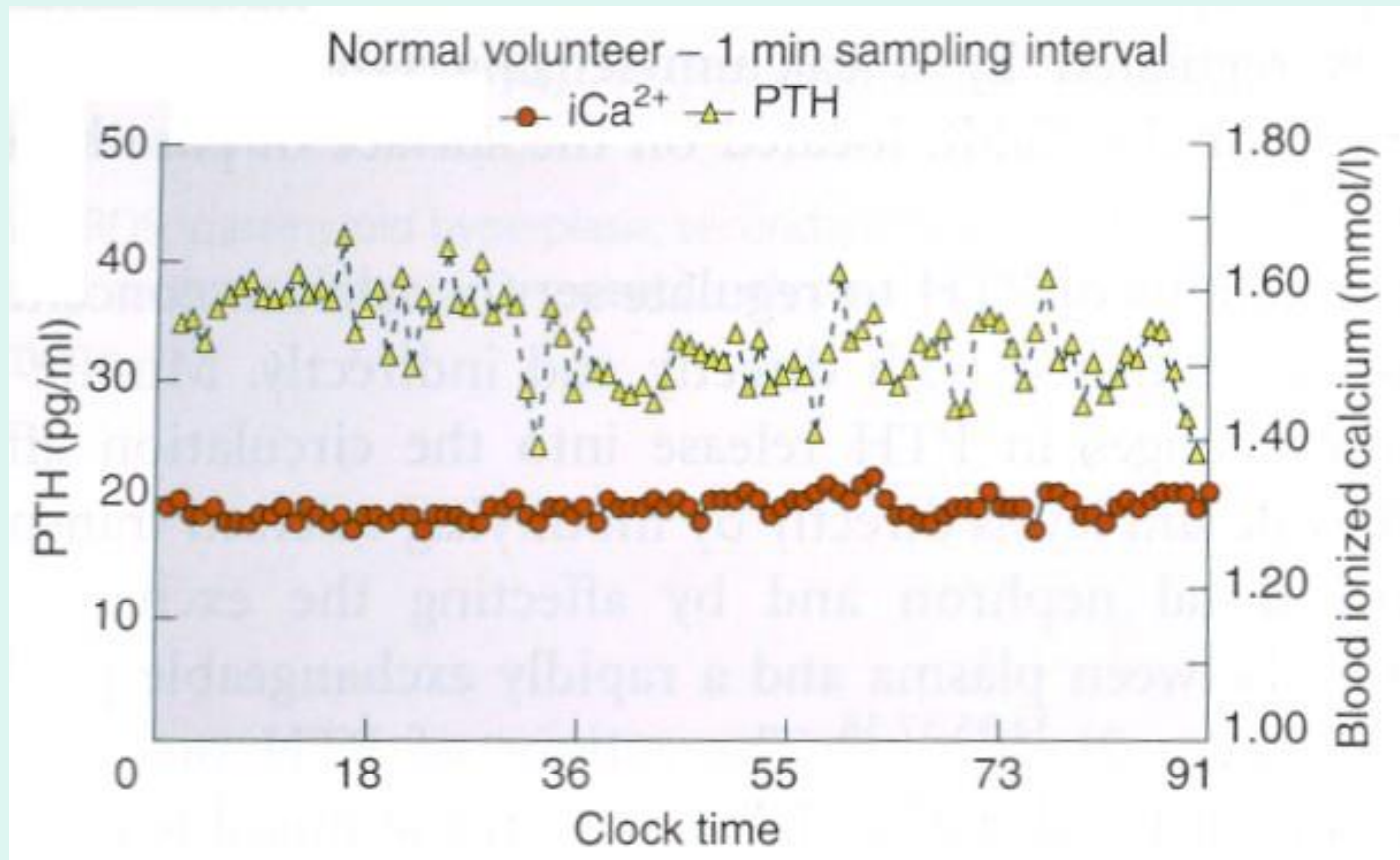


Previously known as Idiopathic Infantile Hypercalcemia, loss of function of the 24-hydroxylase enzyme, caused by mutations in the CYP24A1 gene, will result in high 1,25-(OH)₂D blood level, and consequently hypercalcemia, hypercalciuria and nephrocalcinosis

A quick reminder of calcium homeostasis

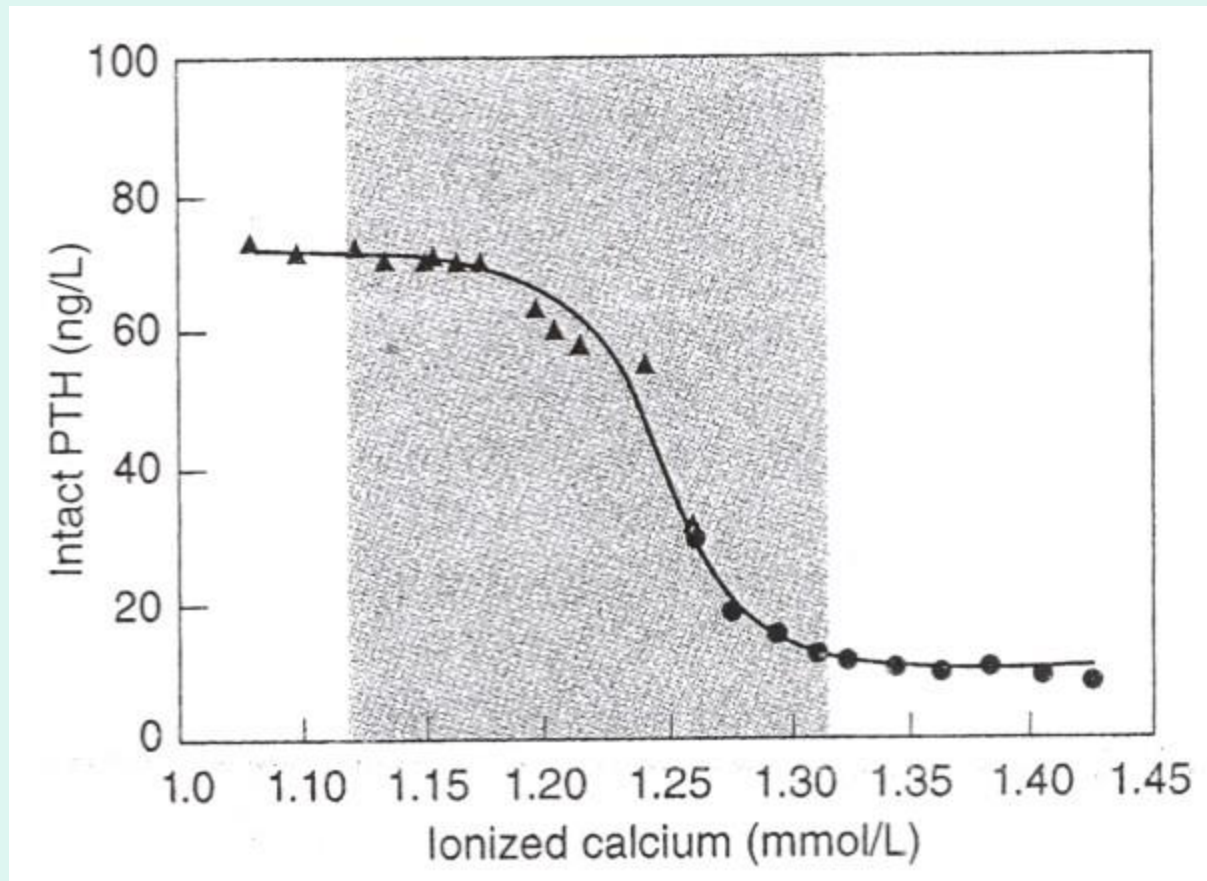


PTH - the actual minute to minute regulator of serum Ca^{++}



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

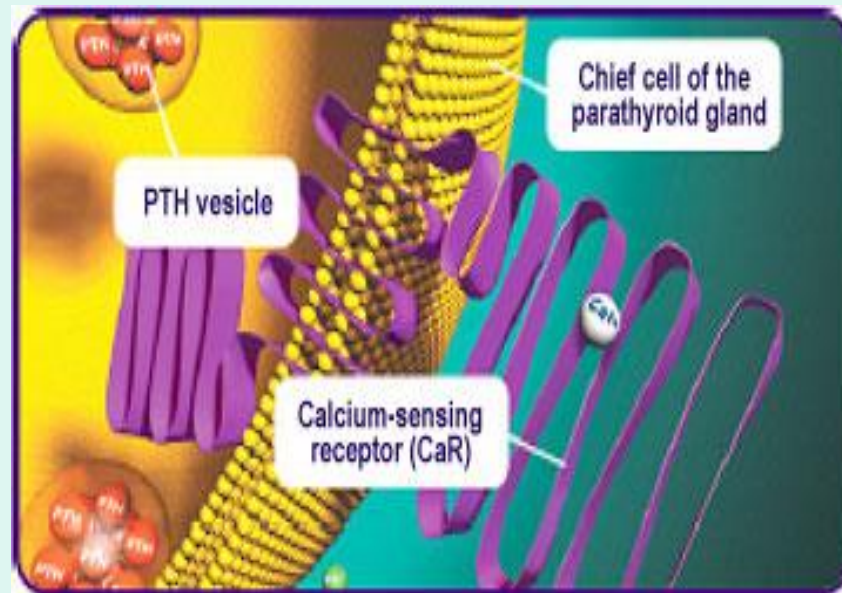
- Brown EM et al.: Cloning and characterization of an extracellular $\text{Ca}(2+)$ -sensing receptor from bovine parathyroid (*Nature* 1993;366:575)
- Nemeth EF et al.: Calcimimetics with potent and selective activity on the parathyroid calcium receptor (*Proc Natl Acad Sci USA* 1998;95:4040)

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

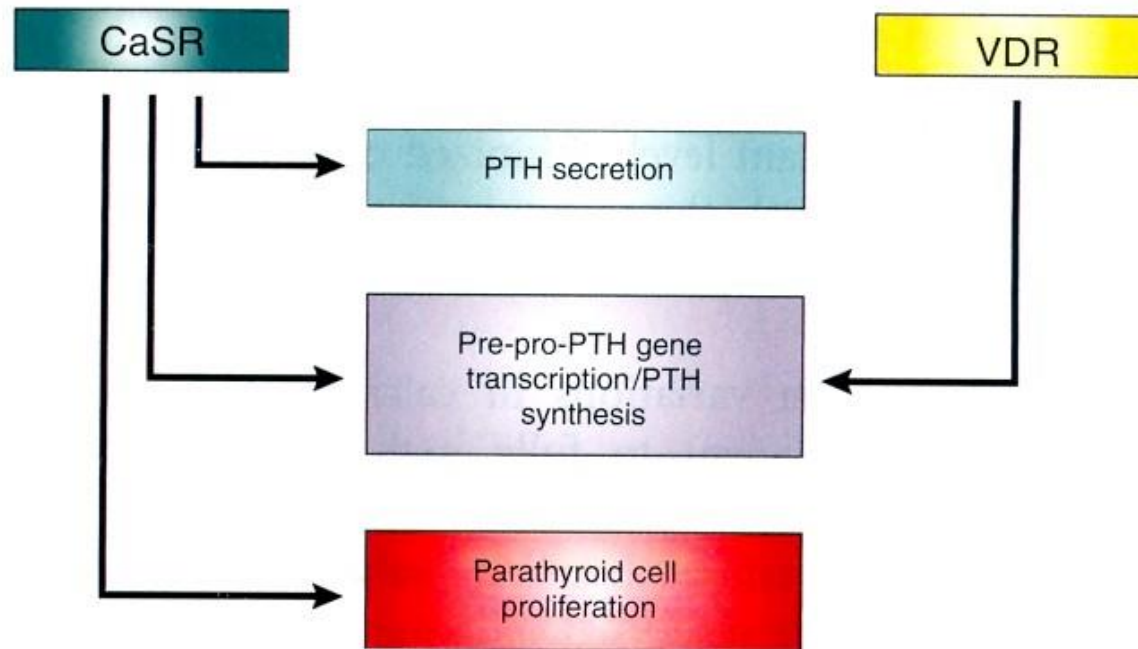
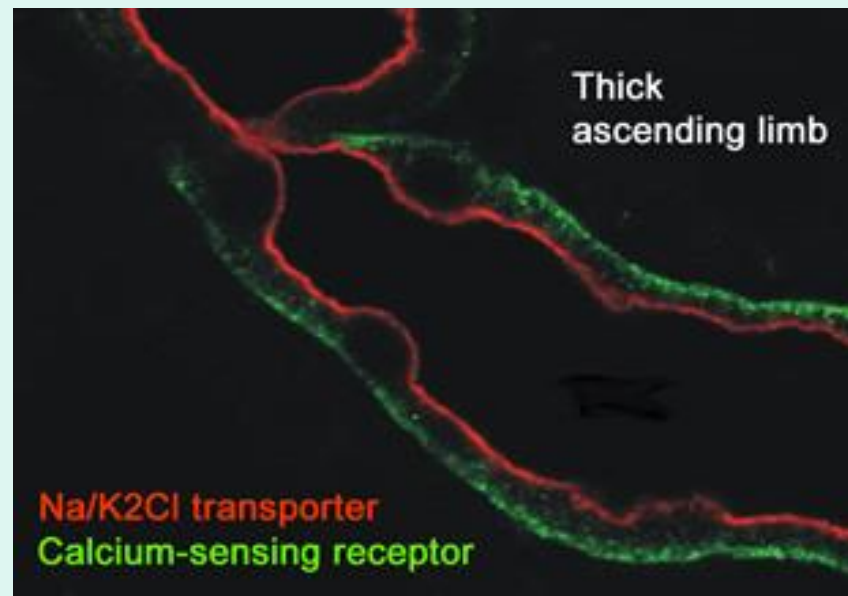


Figure 1 | The respective roles of calcium ions, acting through the CaSR, and vitamin D sterols, acting through the VDR, as direct modifiers of parathyroid gland function.

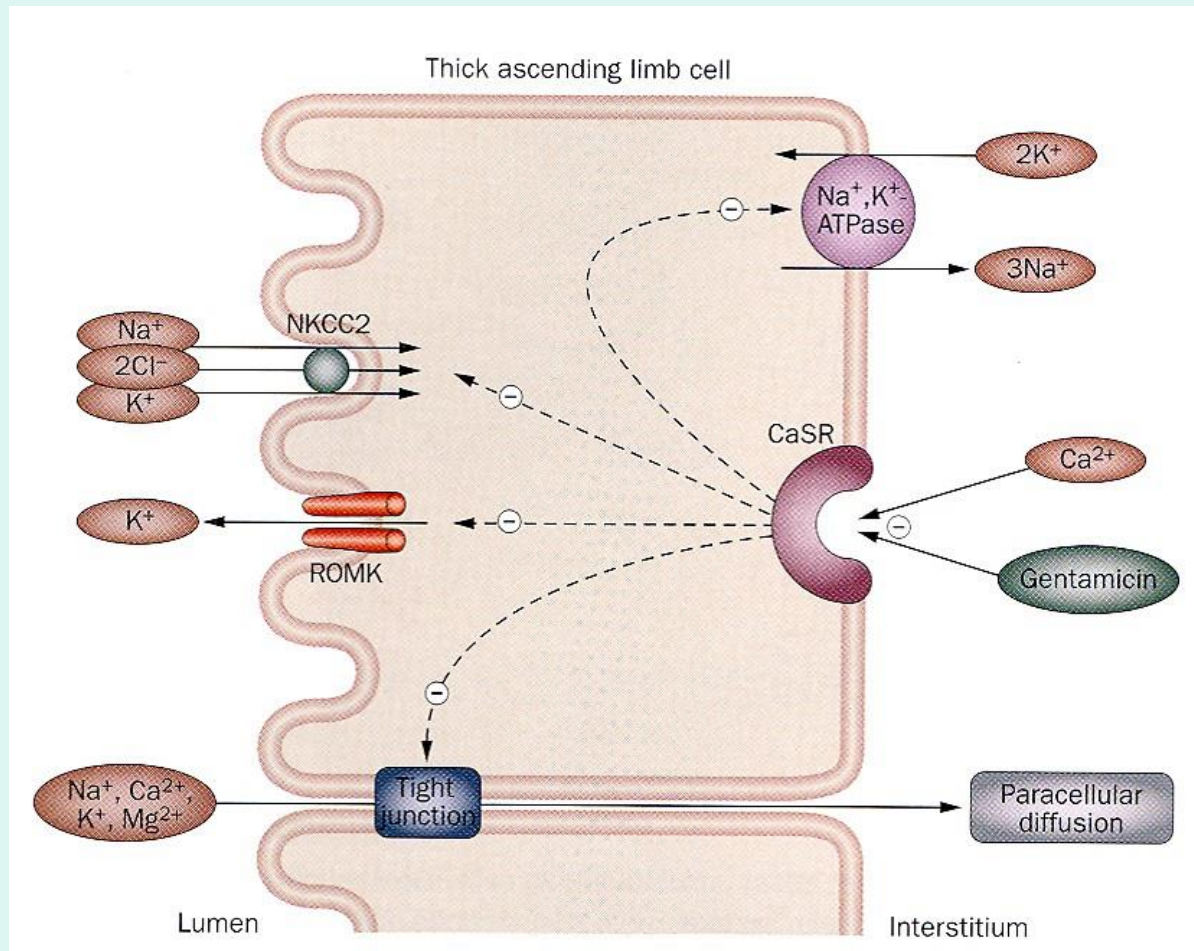
Note the role of CaSR in gland proliferation, a common problem in the CKD population

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

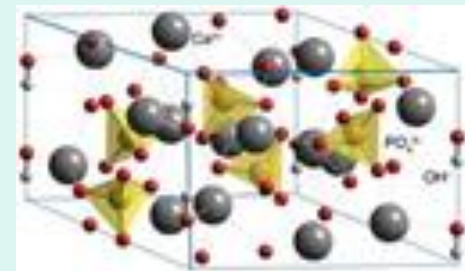


CaSR in the kidney (2)

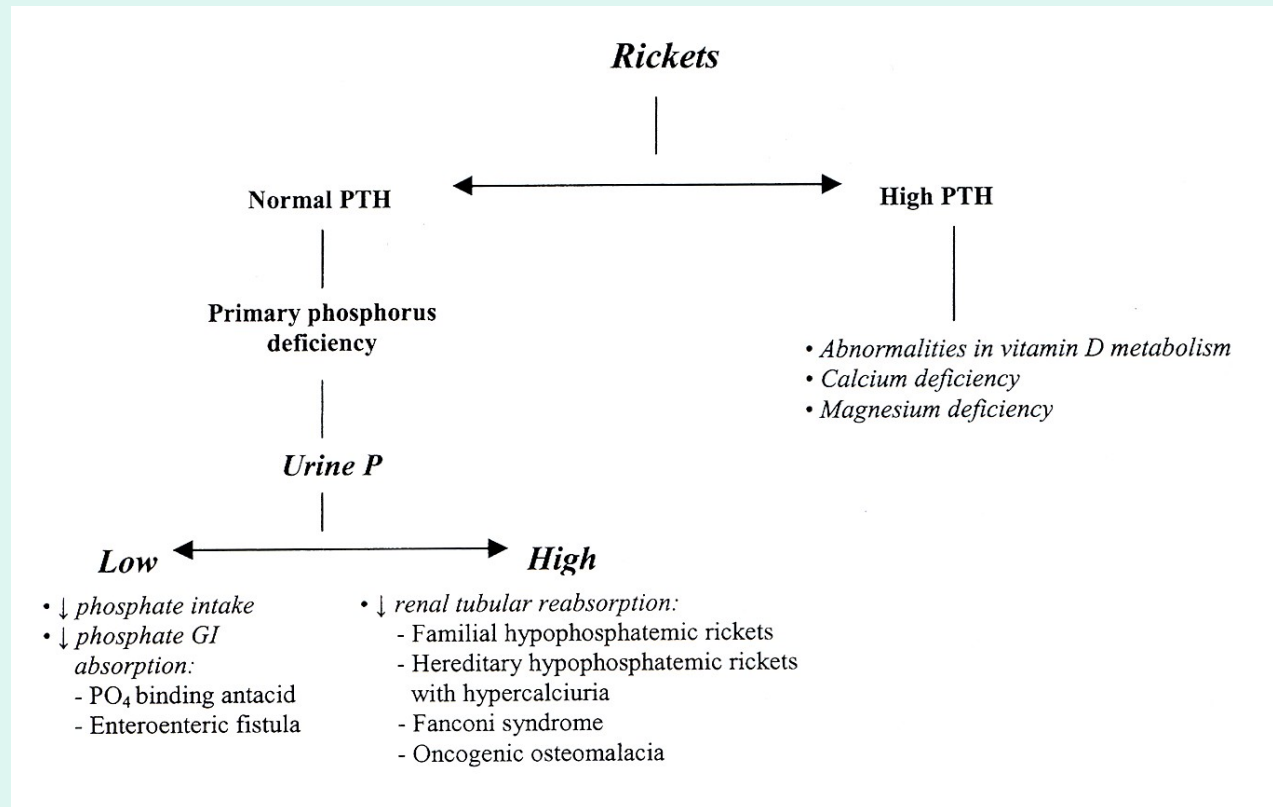
- In the cTAL, CaSR activation inhibits the activity of Na/K₂Cl co-transporters and, consequently, sodium reabsorption
- This leads to decrease in lumen-positive transepithelial voltage and consequently to decrease in passive, paracellular Ca (+Mg) reabsorption, resulting in ↑ in calciuria (& magesuria)
- 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

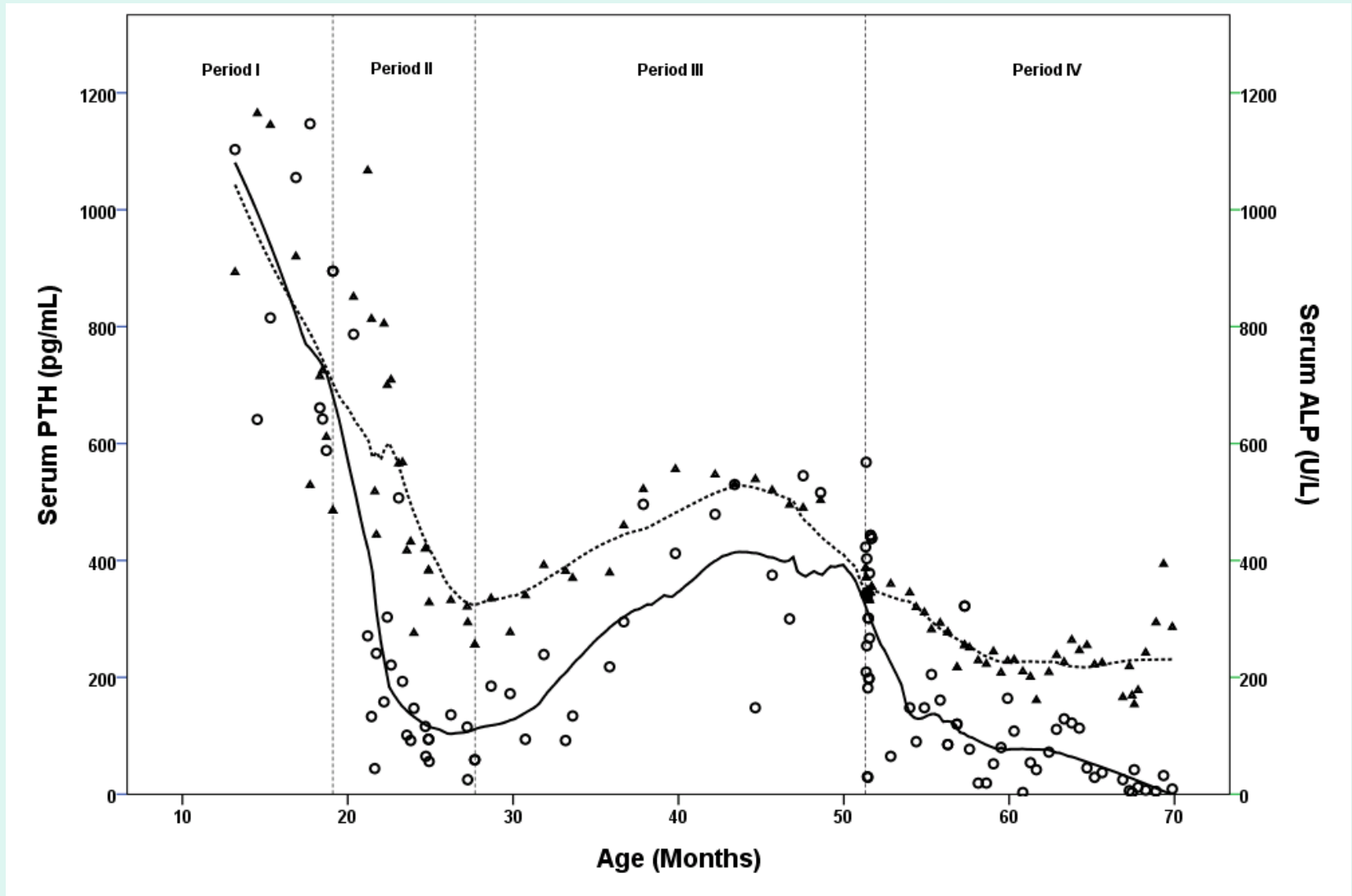
Hereditary vitamin D resistant rickets (HVDRR): PTH and calcimimetics ⁽¹⁾

- 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 $1,25(\text{OH})_2\text{-D}$
- It presents in early life with hypocalcemic tetany and rickets
- Biochemically serum Ca and P are low, and $1,25(\text{OH})_2\text{-D}$ 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)

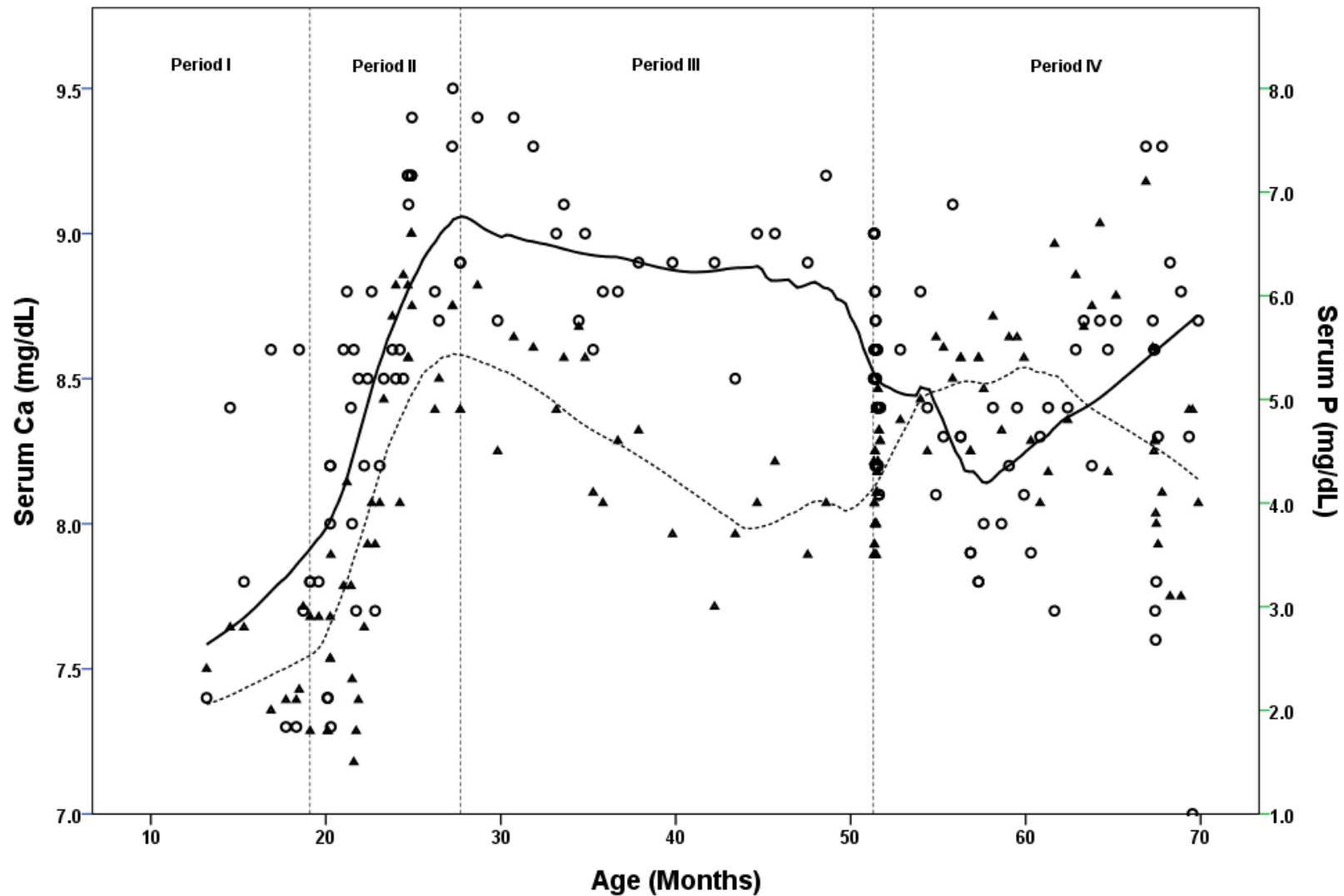
- We speculated that the rickets is the result of low serum phosphate resulting from the excessive phosphaturic effect of high serum PTH
- As such (and after treatment with IV calcium became life threatening, due to recurrent infections of the central line), in order to suppress PTH secretion, we applied cinacalcet

Treatment of a child with HVDRR: IV calcium (Period II) followed by Cinacalcet (Period iV)



PTH _____, Alk Phosph - - - - -

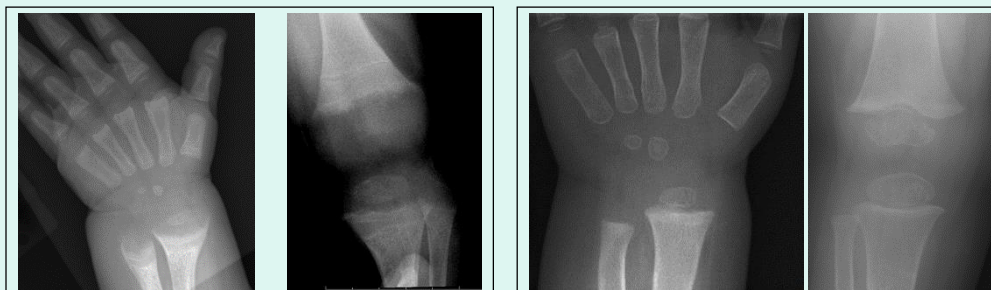
Treatment of a child with HVDRR: IV calcium (Period II) followed by Cinacalcet (Period IV)



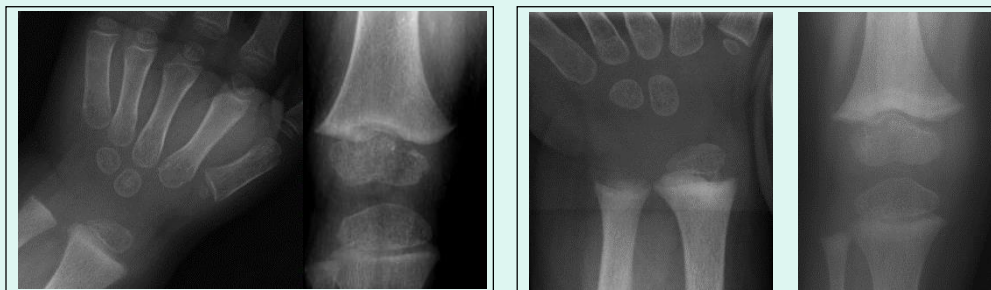
Note the increase in serum P (----) as PTH was suppressed by either IV calcium (Period II), or cinacalcet (Period IV)



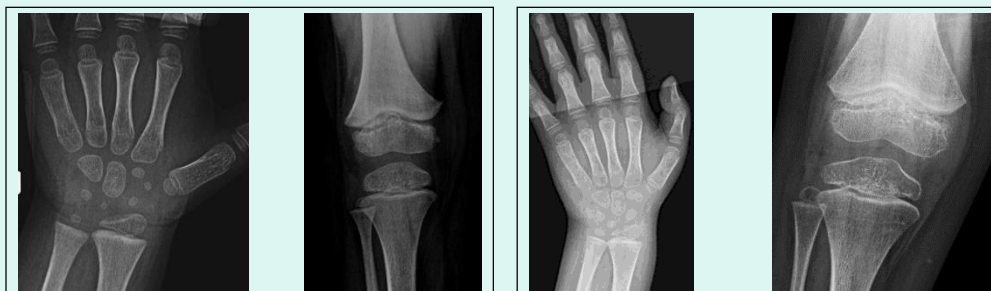
Period I: Age 15 months (left) and 19 months (right)



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

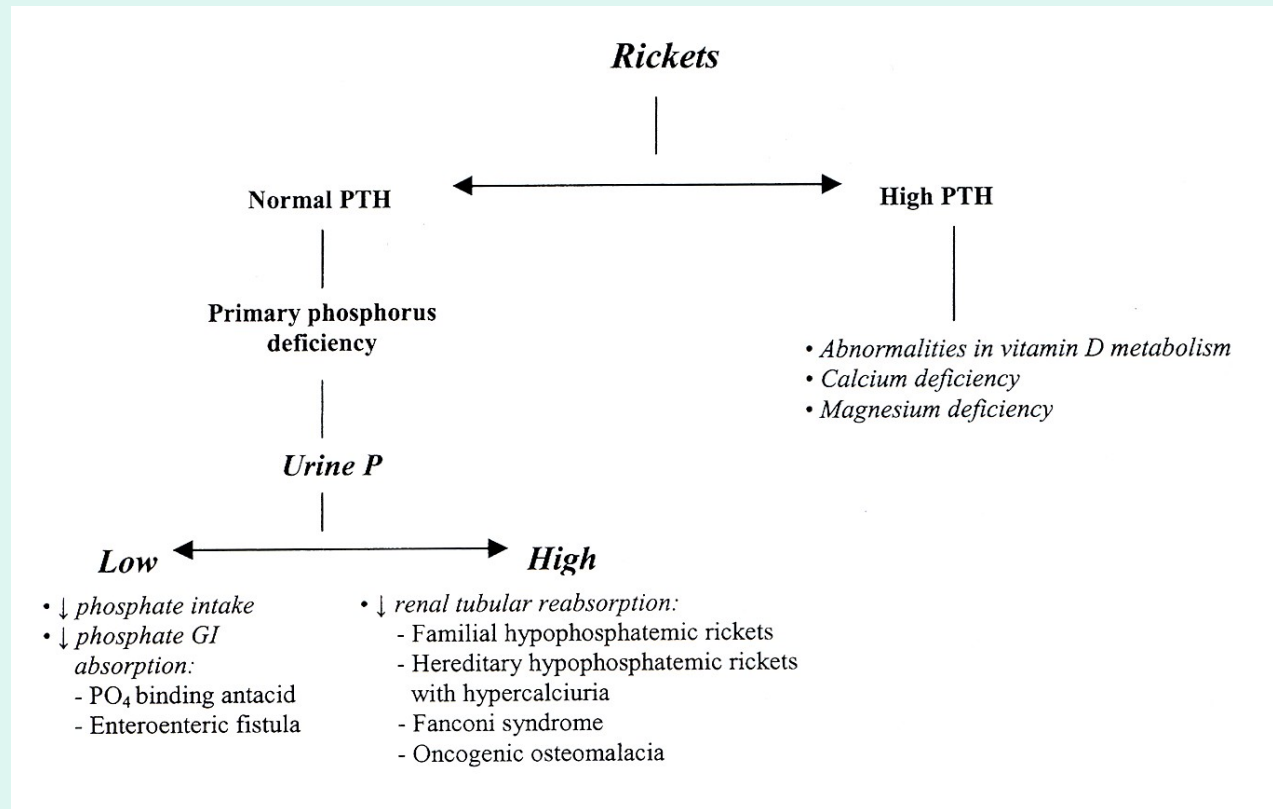


Period III: Age 36 months (left) and 42 months (right)



Period IV: Age 57 months (left) and 70 months (right)

Differential Diagnosis of Rickets Based on Serum PTH



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)₂D 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