CKD – MBD :
Pathogenesis and Consequences

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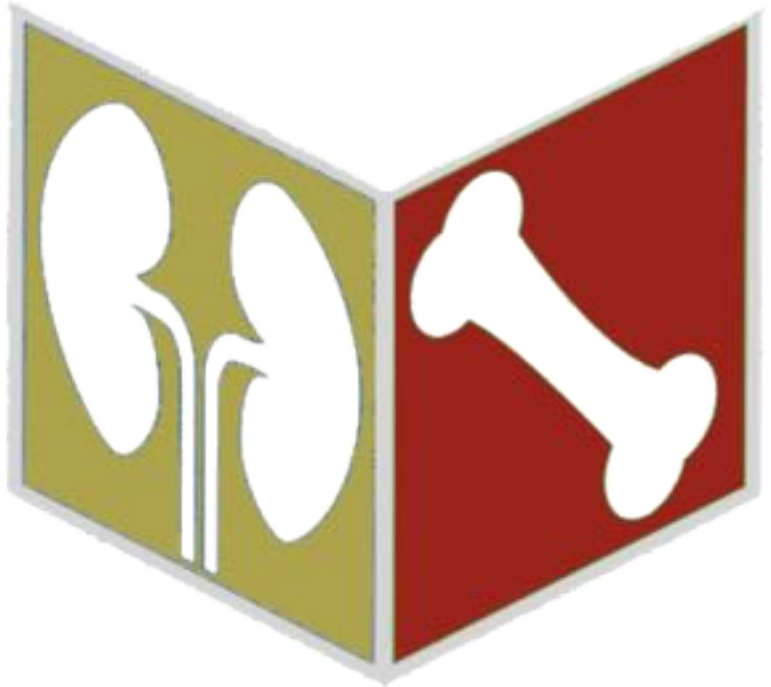

Pediatric Nephrology Center
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Agenda

- Definition
- The bone-renal axis physiology
- Pathogenesis of CKD-MBD
- Abnormalities of bone *T*urnover, *M*neralization and *V*olume
- Consequences of CKD-MBD

Definition

A systemic disorder of bone and mineral metabolism due to CKD manifested by either one or a combination of the following:

Abnormalities in:

Ca, P, PTH and

Vit.D metabolism

Abnormalities in:

-T - M - V

-Linear growth

-Strength

Vascular or

Other soft tissue

CALCIFICATION

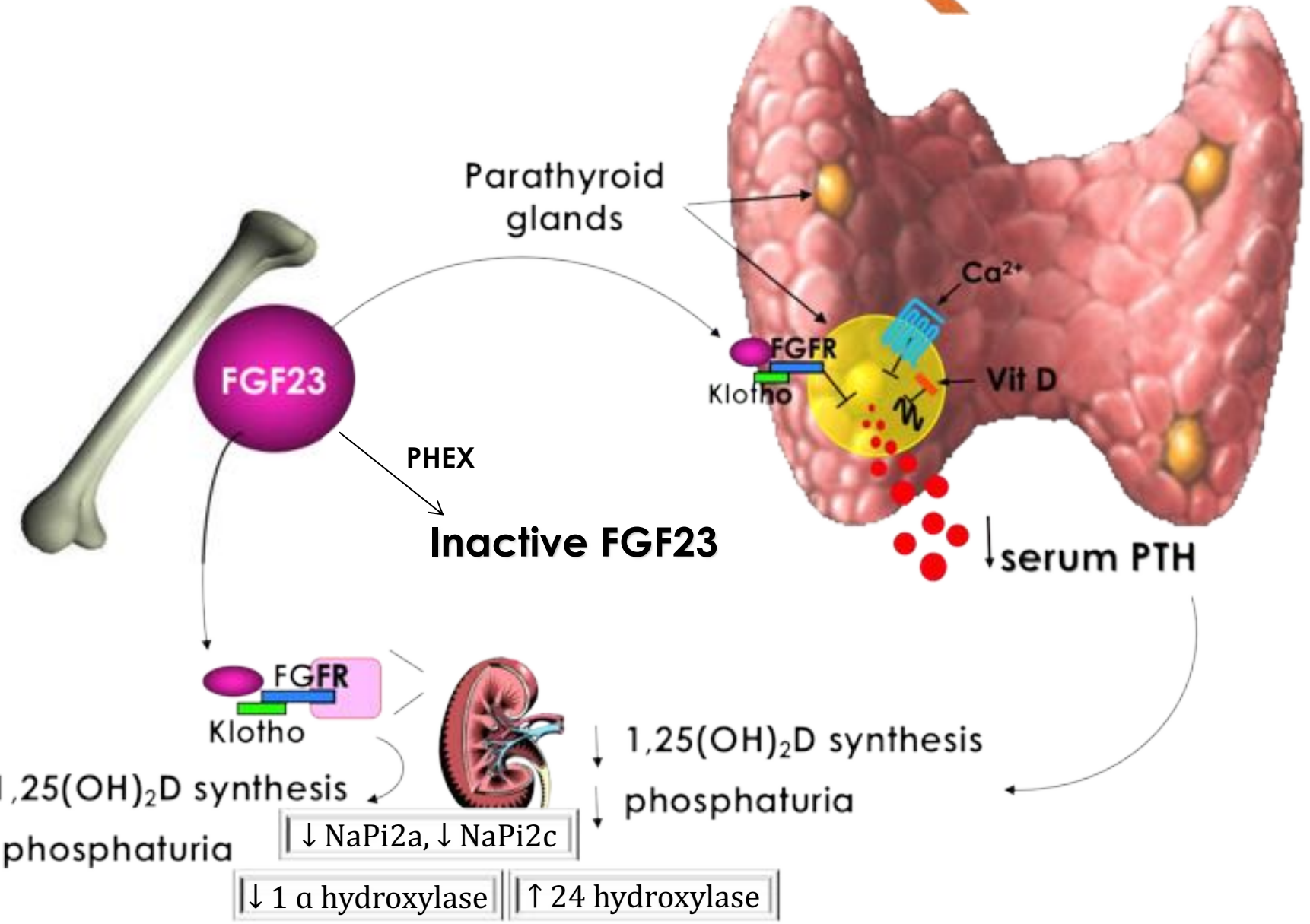
Pediatr Nephrol (2008) 23:195–207

Definition

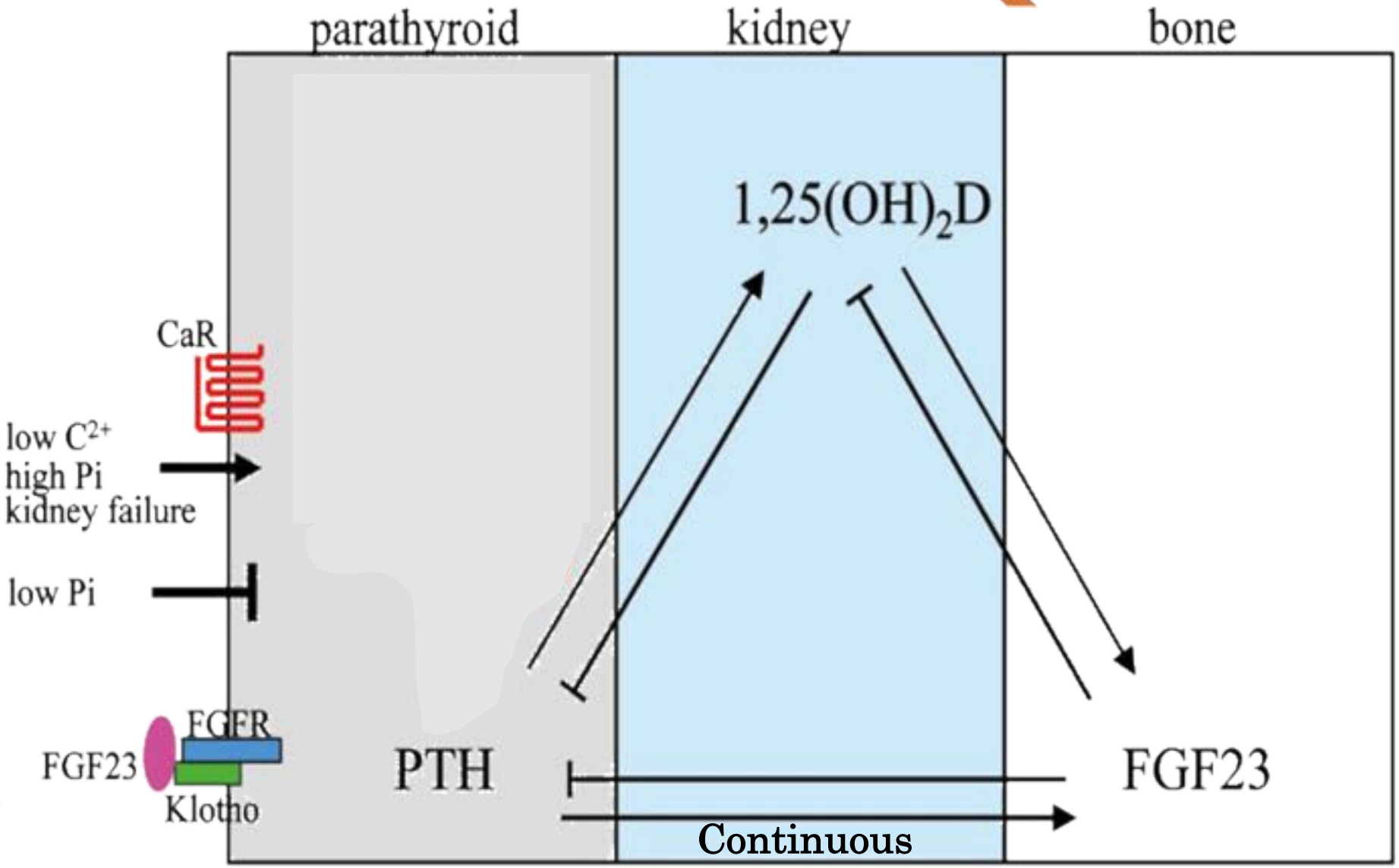
Renal osteodystrophy = CKD-MBD

Renal osteodystrophy is one aspect of CKD-MBD that refers to bone pathology alone

Bone-Renal axis



Bone-Renal axis



Klotho

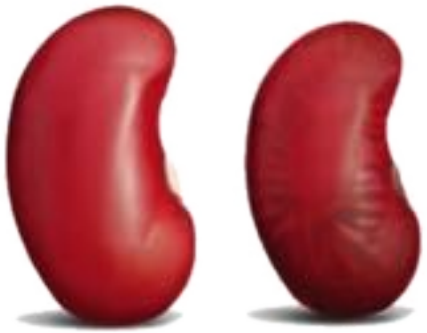
One of the three goddesses of the Moirae

(Greek mythology)

She is the goddess who helps life to unfold, in contrast to the (apoptotic) goddess Atropos, who cuts the thread of life

Early Changes

Pathogenesis



Stage 2

Pi-independent

↓Expression of mm-bound klotho

Fe deficiency-mediated FGF23

Increase osteocyte FGF23 production

↑ FGF23

↓ NaPi2a, ↓ NaPi2c

↓ 1 α hydroxylase

↑ 24 hydroxylase

Pi excretion

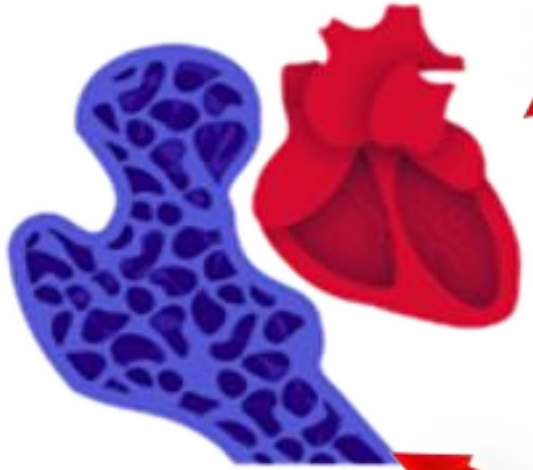
↓Ca

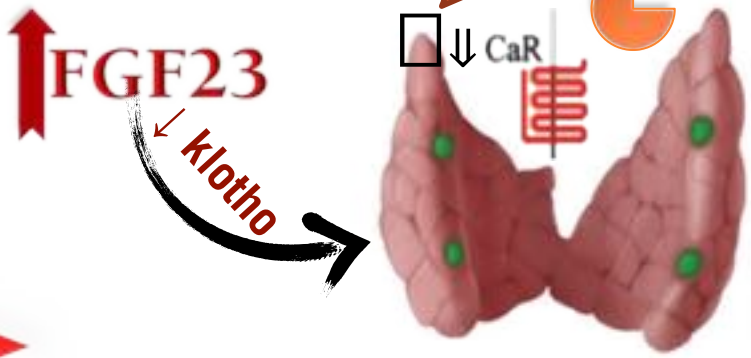
1,25 (OH)2 D3

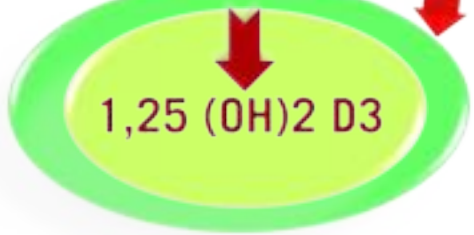
Semin Nephrol. 2013;33(2):169-79

Late Changes

Pathogenesis







Pi retention

↓ Phospholipase A2

↑FGF23 ↓ klotho expression

↑FGF23 ↓ klotho

VDR

⇓ CaR

1,25 (OH)2 D3

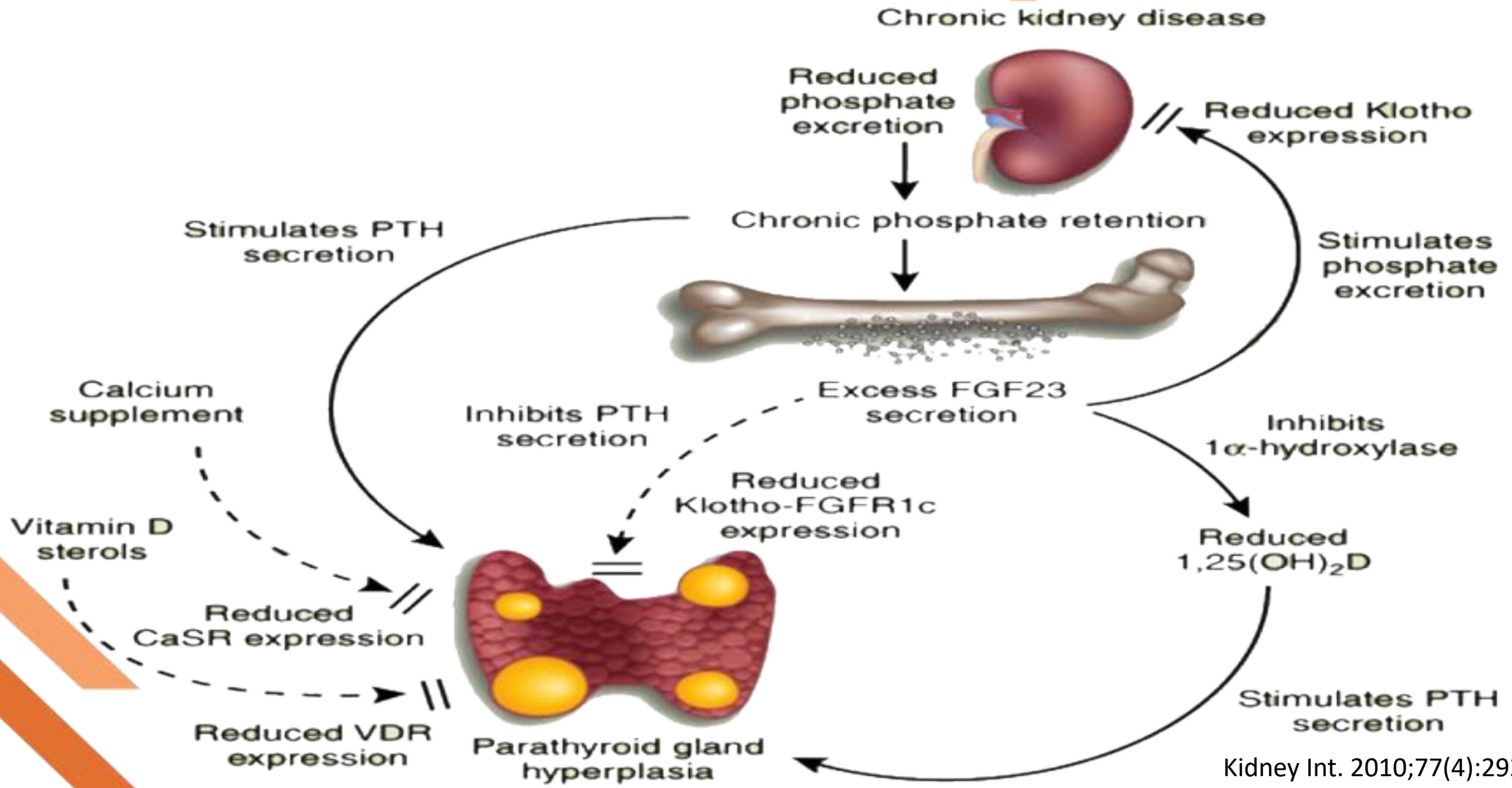
CKD-MBD

2°PTH

Semin Nephrol. 2013;33(2):169-79

To sum

Pathogenesis



Kidney Int. 2010;77(4):292-298

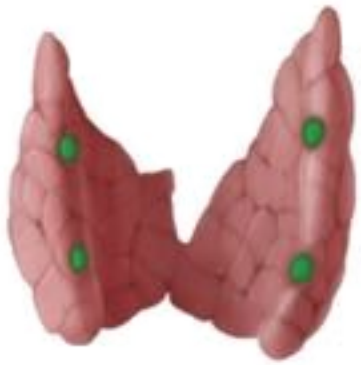
Pathogenesis

Intermittent PTH

1. Increase in bone mass
2. Suppress FGF23

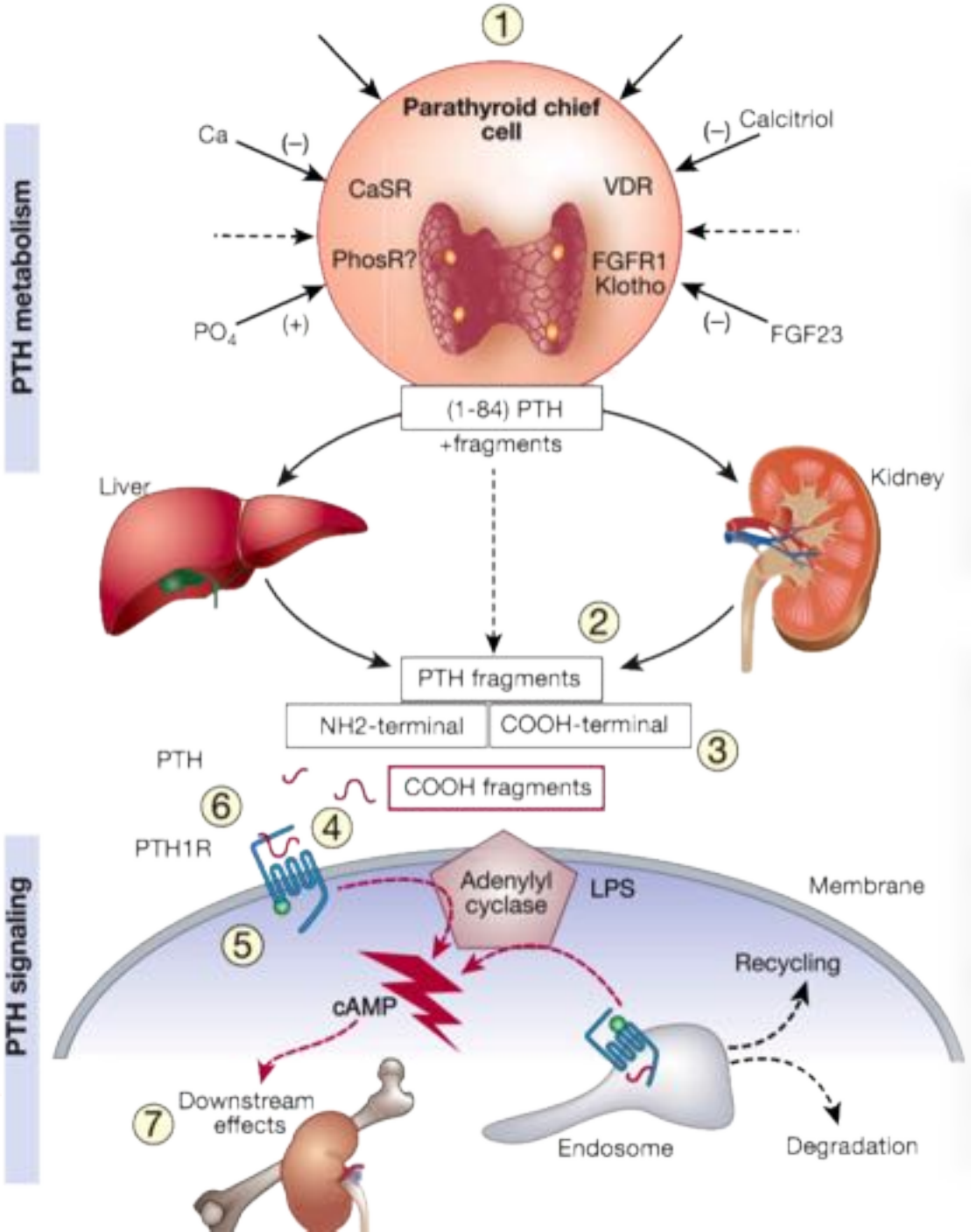
Continuous PTH

1. Bone resorption
2. Increase FGF23



PTH

PTH resistance



1) ⇧ Synthesis & secretion of PTH– accumulation of C-terminal PTH
2) Posttranslational modification PTH
3) VDR & CaSR downregulation

4) Competitive inhibition between PTH & its fragments
5) PTH1R downregulation
6) PTH1R dysfunction
7) Competing downstream signals

Kidney International (2016) 90, 1184–1190

Turnover, Mineralization & Volume

Turnover

It reflects the rate of skeletal remodeling (bone resorption & bone formation)

Mineralization

It reflects how well bone collagen becomes calcified during the formation phase of skeletal remodeling

Volume

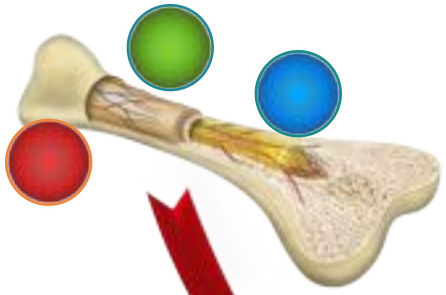
It indicates the amount of bone per unit volume of tissue

Turnover

High Turnover

PTH

PTH/PTHrP Rc.



- ↑ resorption of bone matrix
- Release of mineral in Cº

Prolonged PTH

- Peritrabecular fibrous changes

Osteitis fibrosa cystica

Osteoblast

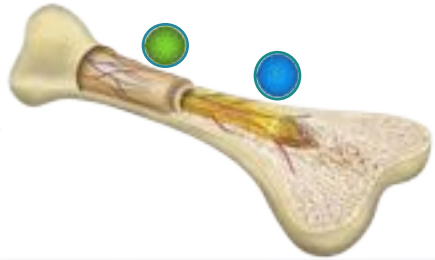
Osteocyte

Osteoclast

Low Turnover

Excess Vit. D ⟹ ⇧ Ca

?⇓ PTH



- ⇓ bone formation rate
- ⇓ cellular activity
- ⇓ osteoid accumulation

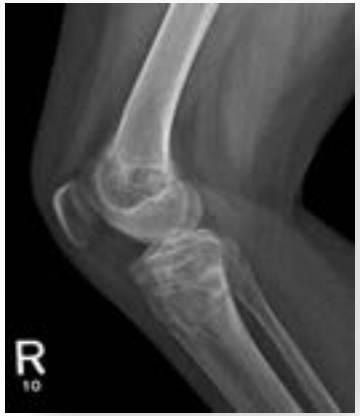
Adynamic bone disease

Pediatr Nephrol. 2015;30(9):1379-88

Turnover

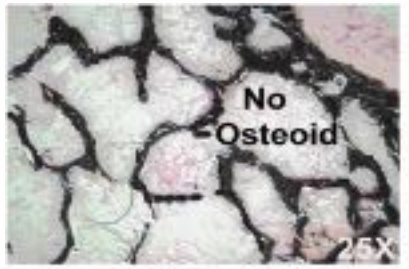
High turnover

- ⇧ PTH
- ⇧ ALP



Low turnover

- ⇧ Ca
- ⇓ ALP



Pediatr Nephrol. 2015;30(9):1379-88

Mineralization

- 25 (OH) D3 deficiency
- Altered FGF23 metabolism

Defective mineralization Normal

- Increase unmineralized bone
- Delayed rates of mineral deposition

+ High turnover

- Prolonged mineralization time
- Wide osteoid seams
- ⇧ bone formation rate
- B.M. fibrosis

Mixed uremic dystrophy

+ Low turnover

- ⇧ Number of osteoid lamellae
- Wide osteoid seams
- ⇩ bone formation rate
- NO B.M. fibrosis

Osteomalacia

- ✓ Bone fractures
- ✓ Bone deformities
- ✓ Delayed growth

Pediatr Nephrol. 2015;30(9):1379-88

Volume

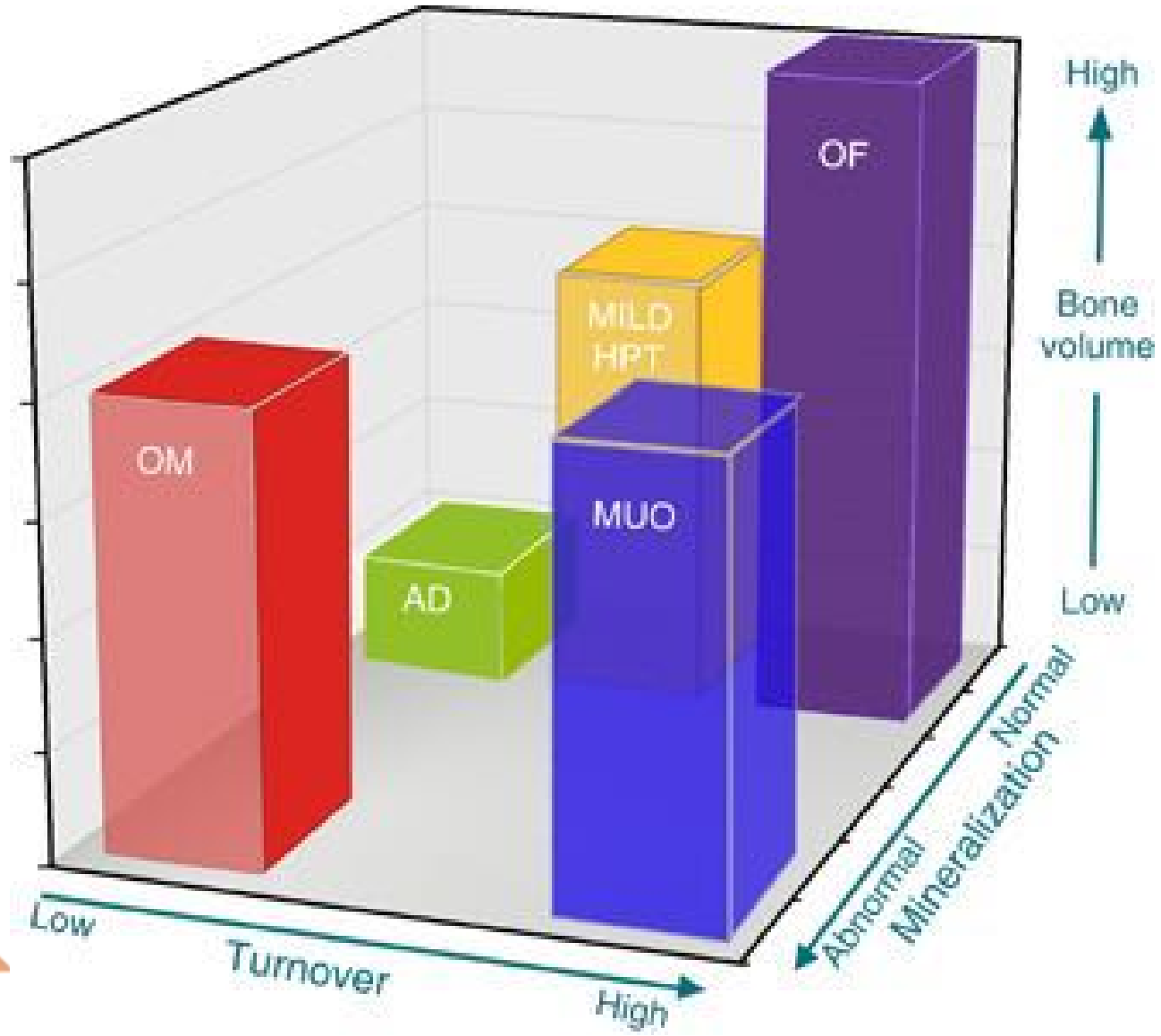
⇧ PTH

1. ⇧ Bone volume
2. ⇧ Trabecular volume
3. ⇧ Trabecular width

Patients treated with steroids

Osteoporosis

Turnover, Mineralization & Volume



Kidney Int. 2006;69:1945-1953.

Consequences

PTH

Ca

FGF23

Pi

Vitamin D

Bone diseases

Growth failure

Vascular calcification

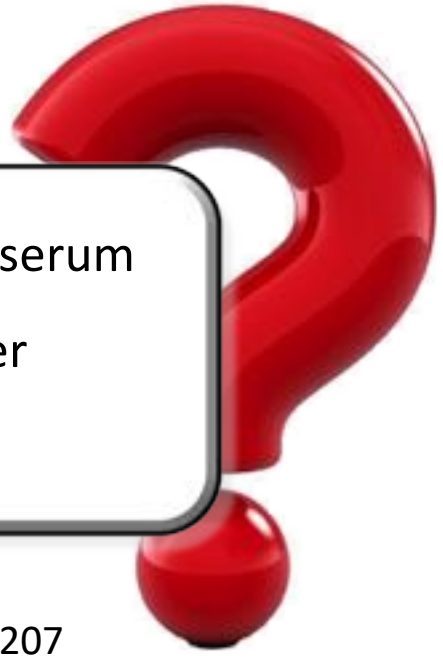
Mortality

Consequences

Growth failure is multifactorial:

- CKD-MBD
- Malnutrition
- Metabolic acidosis
- Anemia
- End-organ G.H. resistance

Despite correction of malnutrition, acidosis, and anemia; normalization of serum calcium and phosphorus levels; and vitamin D therapy, the majority of older children with CKD continue to grow poorly.



Pediatr Nephrol (2008) 23:195–207

Consequences

Growth failure & PTH dilemma

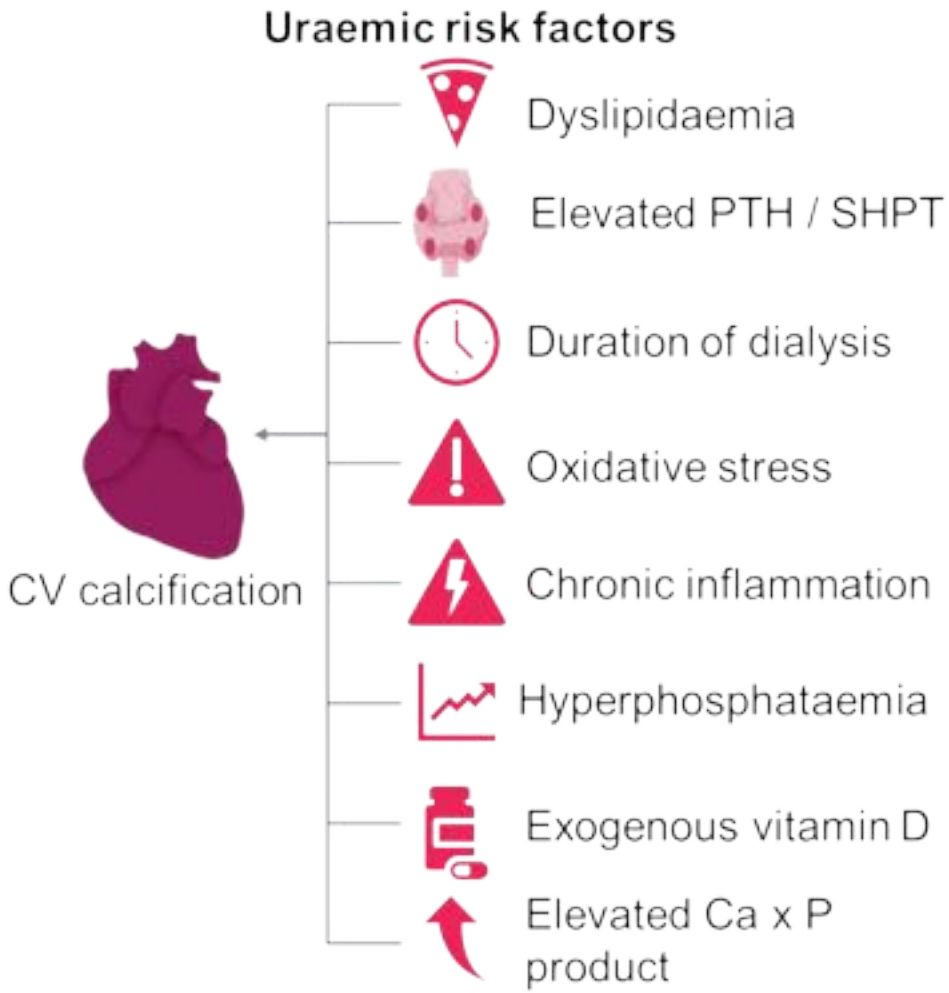
- 2°PTH contribute to growth retardation
- Some data>>> normal growth velocity with normal PTH range

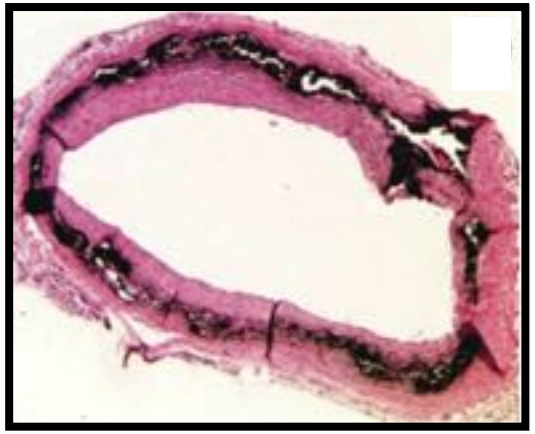
In dialysis children, adynamic bone disease & growth failure have been associated with low PTH levels

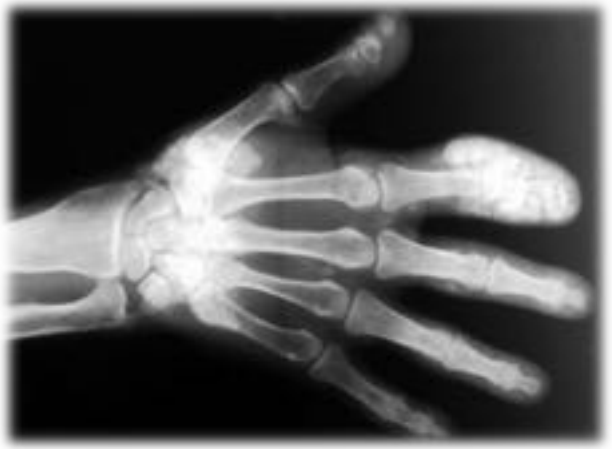
Pediatr Nephrol (2008) 23:195–207

Consequences

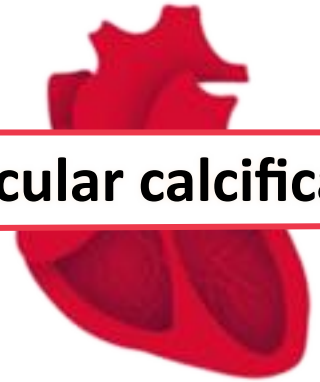
Vascular calcification



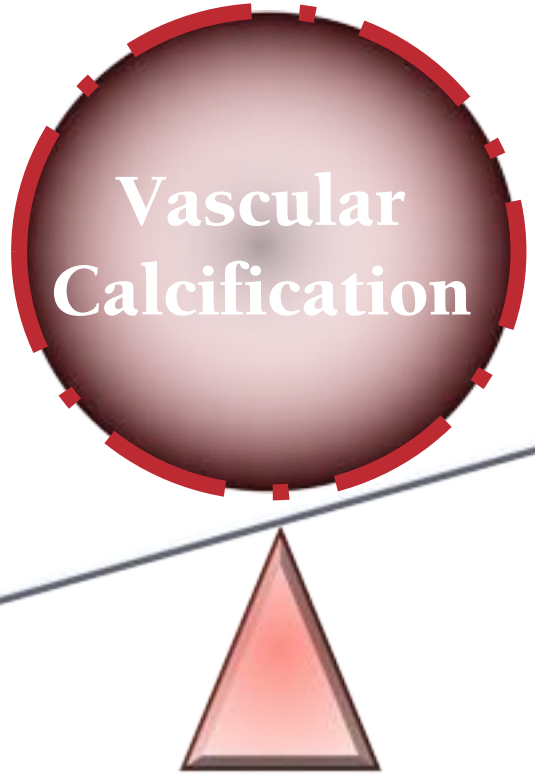




Consequences



Vascular calcification



Inhibitors of vascular mineralization

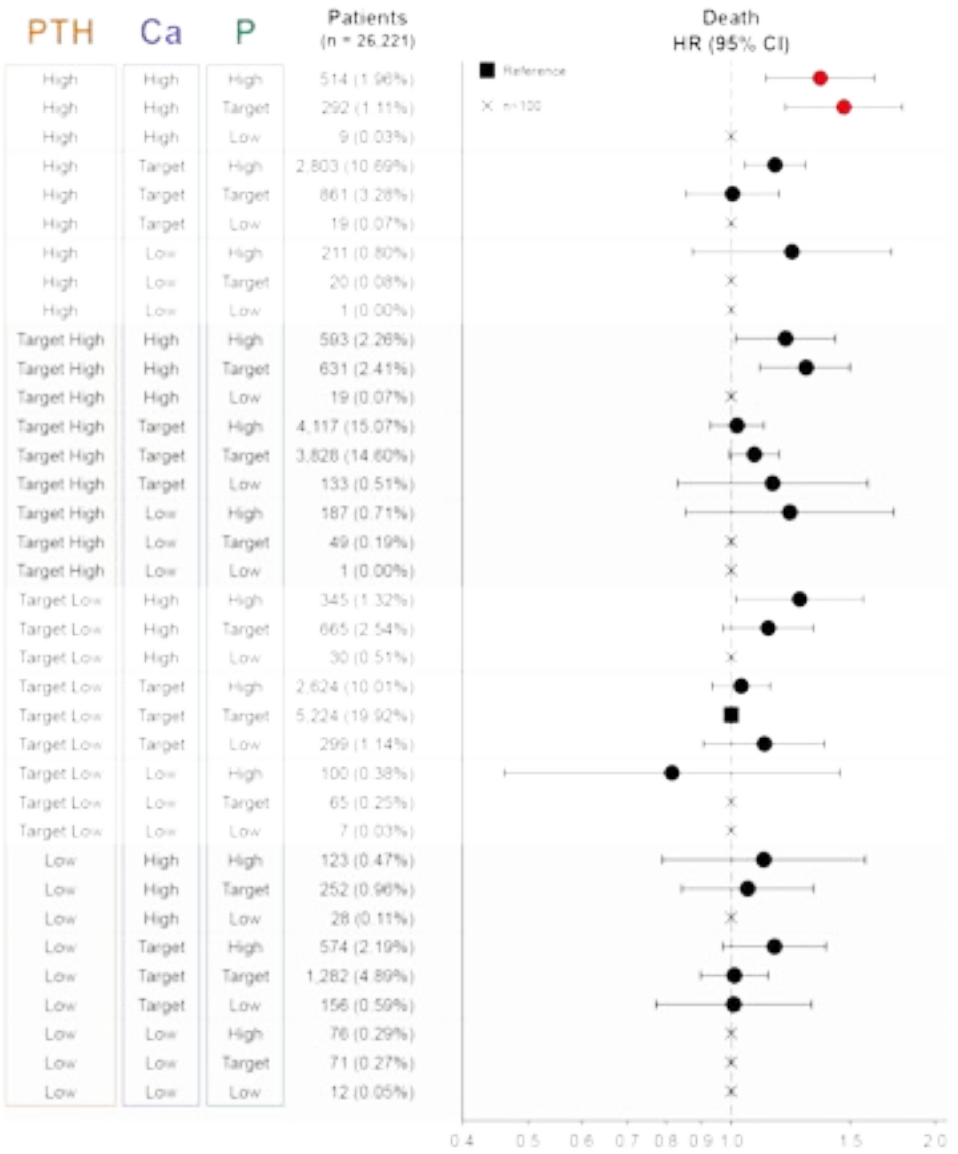
- Pyrophosphate
- Matrix gla protein (MGP)
- Fetuin/2-HS-glycoprotein

Inducers of vascular mineralization

- Disordered Ca/P
- ↑ intracellular P → apoptosis→ phospholipid rich membranous debris.
- Core binding factor-1
- Na dependent phosphate transporter (PIT-1)
- Osteopontin, bone sialoprotein, osteonectin, etc…

Consequences

A combination of ⇧ Ca, PTH and ⇧ or target P puts patients at greatest risk of death



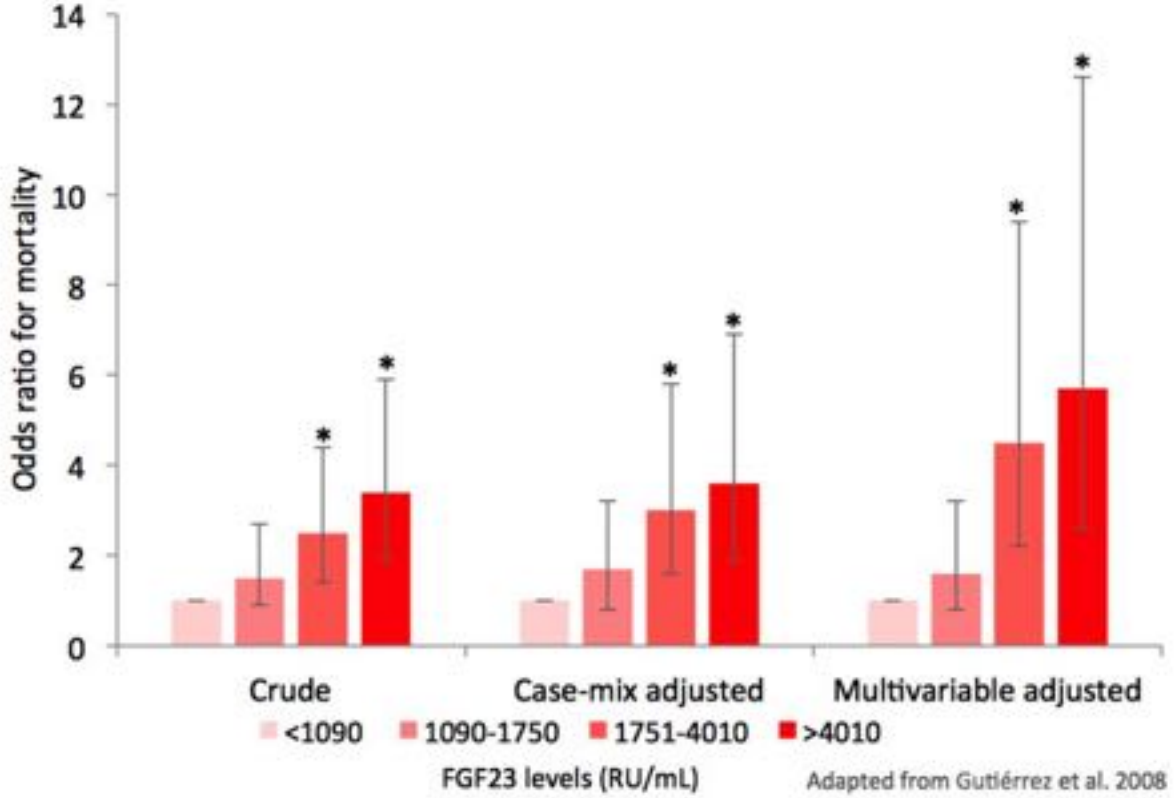
Block G et al. Clin J Am Soc Nephrol 2013;8:2132–40.

Consequences

Mortality

FGF23 levels appear to be independently associated with mortality in patients starting HD

Odds ratio for mortality according to quartile of FGF23 levels[1]



Odds ratio and 95% CI for mortality according to FGF23 levels.
Quartile 1 (<1090 RU/mL) was the reference group. * = P<0.05.

GuBérrez OM et al. N Engl J Med 2008;359:584–92.

SUMMARY

- CKD-MBD is a systemic disorder with abnormalities in:
  - a. Abnormalities in Ca, P, PTH and vit. D
  - b. Abnormalities in bone T – M – V
  - c. Vascular & other soft tissue calcification
- FGF-23 plays a major role in pathogenesis of CKD-MBD
- Osteitis fibrosa cystica happens with prolonged 2°PTH while adynamic bone disease happens due to ⇧Ca & ⇩PTH mostly in dialysis patients
- CKD-MBD is associated with growth failure, vascular calcification and higher mortality


THANK
YOU!

MCQ 1

❖2°PTH in CKD patients could be explained by all of the following EXCEPT:

a. Decrease in VDR responsiveness
b. Decrease in CaR responsiveness
c. Increase klotho expression in PTH gland
d. Increase FGF-23 production

MCQ 2

❖ Defective bone mineralization in CKD patients when associated with high turnover results in:

a. Osteitis fibrosa cystica
b. Adynamic bone disease
c. Osteomalacia
d. Mixed uremic dystrophy

MCQ 3

❖ Which of the following happens in absence of 2°PTH:

a. Adynamic bone disease

b. Vascular calcification

c. Osteoporosis

d. Adequate growth