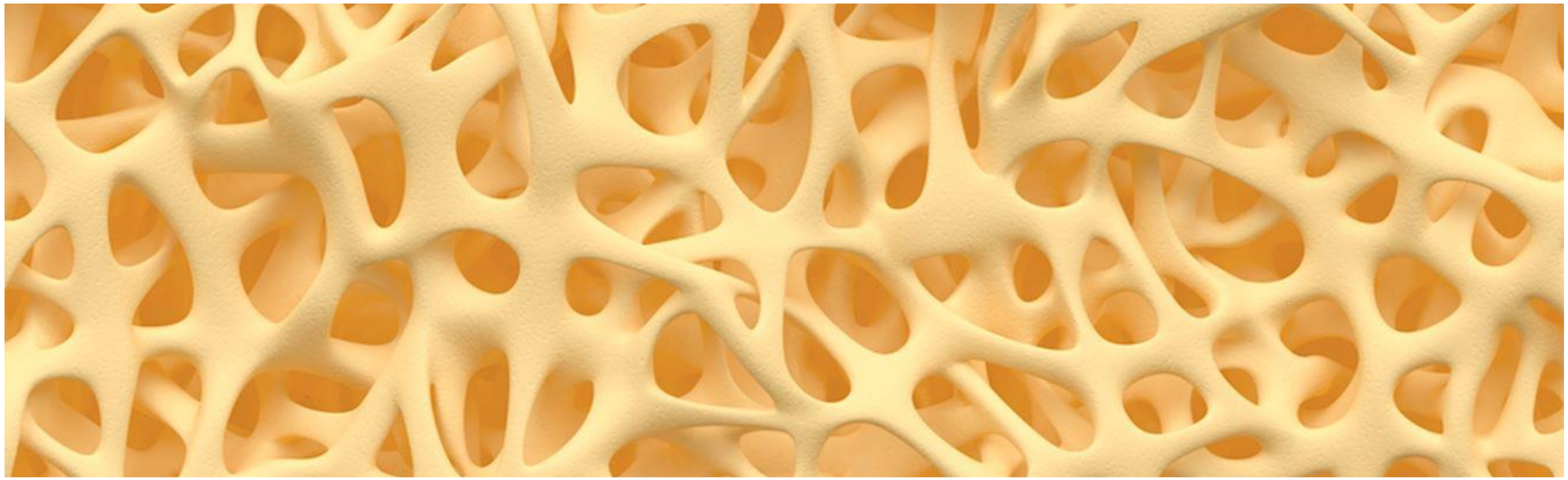
Chronic Kidney Disease Mineral Bone Disorder (CKD-MBD)



Oded Volovelsky, MD PhD

Hadassah Hebrew University Medical Center

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קווים משיקים ברפואת הילדים

7.3.2025, מרכז רפואי שמיר

האגוד הישראלי לאנדוקרינולוגיה פדיאטרית

CKD-MBD Definition

CKD-MBD

- Biochemical Abnormalities → **Ca, P, Vitamin D, PTH**
- Bone Abnormalities → **Bone Resoption**, **Minerailization**, **Linear Growth**
- Extracelluar Calcifications → **Vascular & Soft Tissue Calcifications**

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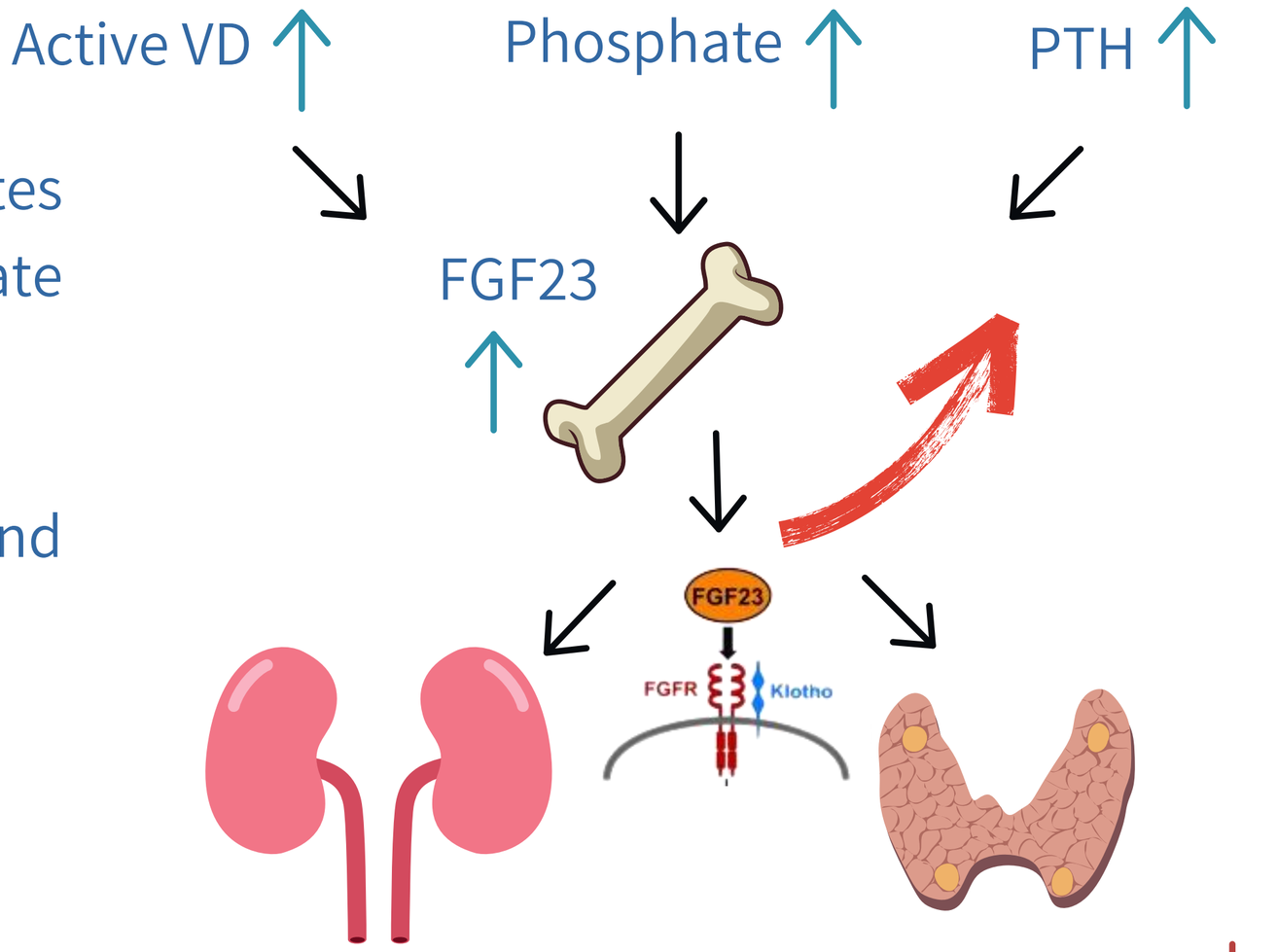
CKD-MBD Symptoms

1. Growth retardation
2. Bone Pain and Deformities
3. Muscle Weakness
4. Cardiovascular disease

Main Players - Fibroblast Growth Factor 23 (FGF23)

A hormone produced by osteocytes that plays a critical role in phosphate metabolism

Works with its co-receptors Klotho and FGFR to mediate effects



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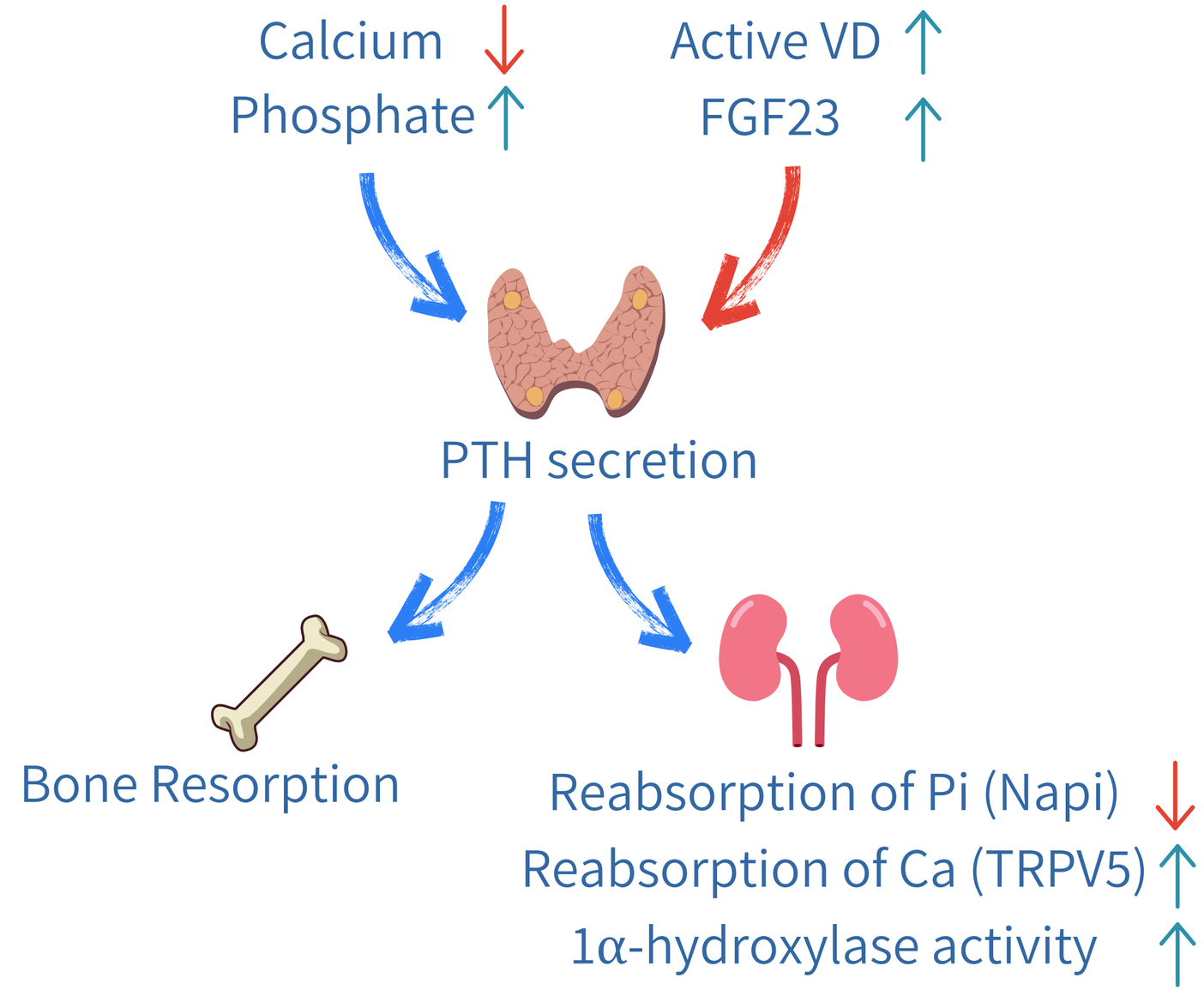
Main Players - Parathyroid Hormone (PTH)



Main Players - Vitamin D

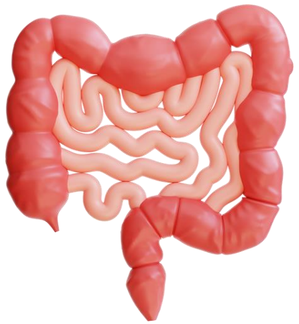
Low Ca

PTH ↑

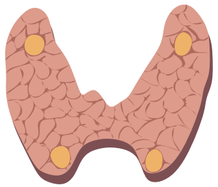
FGF23 ↑

GFR ↓

High P



1,25(OH)2 VD



Ca absorption (TPRV6 etc) ↑

P absorption (Napi2b) ↑

PTH Secretion ↓

(direct and indirect)

Mineralization ↑

Calcium release ↑

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FGF23 in CKD

FGF23 is the **earliest factor** to rise in CKD, increasing before P retention or PTH elevation

Early CKD: Increased FGF23 secretion maintains phosphate balance and reduced VD activity

Progression: Reduced Klotho expression leads to FGF23 resistance, impairing phosphaturia and hyperphosphatemia

Late CKD: Extremely high FGF23 levels contribute to cardiovascular disease progression

Phosphate and Calcium in CKD

Phosphorus (P):

- **Early CKD**: FGF23 enhances phosphate excretion, maintaining normal levels
- **Progression**: FGF23 resistance develops, leading to phosphate retention
- **Late CKD**: Severe hyperphosphatemia due to nephron loss and ineffective FGF23-Klotho signaling

Calcium (Ca):

- **Early CKD**: Calcium levels remain normal
- **Progression:** Hypocalcemia develops due to suppression of $1,25(OH)_2D$
- **Late CKD**: Calcium fluctuations due to phosphate binders, vitamin D therapy

Vitamin D in CKD

Vitamin D:

- **Early CKD**: FGF23 inhibits renal 1-alpha hydroxylase, reducing $1,25(OH)_2D$ production
- **Progression**: Declining renal parenchyma further reduces vitamin D synthesis
- **Late CKD**: Severe vitamin D deficiency requires high-dose active vitamin D analogs

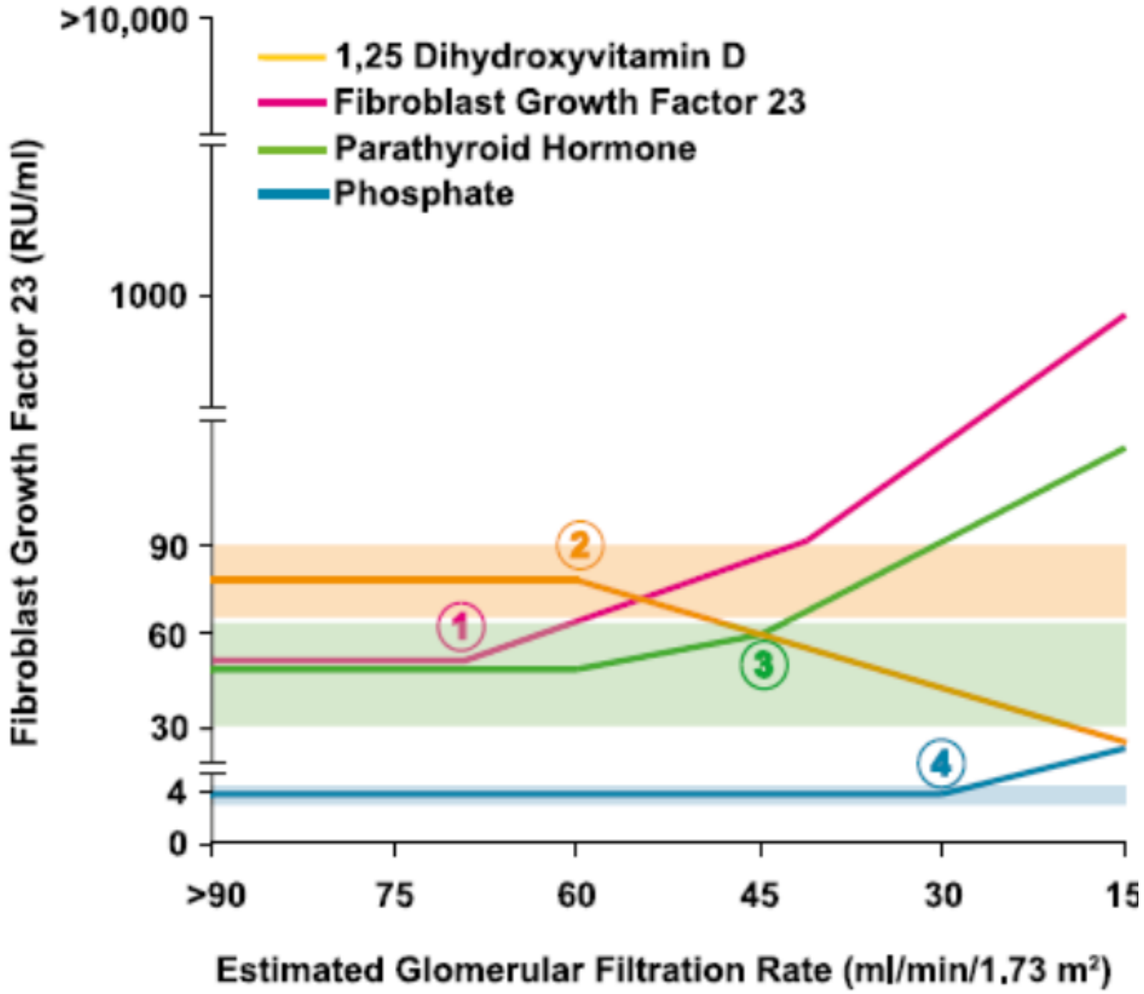
Parathyroid Hormone in CKD

Parathyroid Hormone (PTH):

- **Early CKD**: PTH rises to compensate for low calcium and high FGF23
- **Progression:** Phosphorus retention and low VD lead to persistent PTH elevation.
- **Late CKD**: Severe hyperphosphatemia and vitamin D resistance cause significant secondary hyperparathyroidism. Persistent hypocalcemia further stimulates PTH secretion

*Tertiary hyperparathyroidism may develop.

CKD-MBD Course



JASN, 26: 2328-2339, 2015

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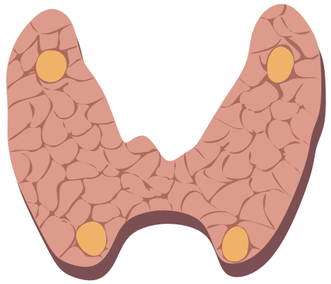
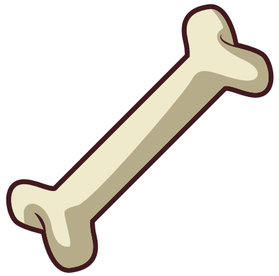
CKD-MBD Treatment

Aims

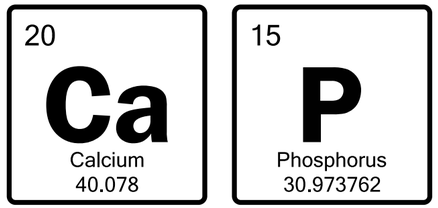


Secondary Hyperparathyroidism



Bone Disease
Adynamic Bone Disease

Inteventions



Phosphate Restrictions

Phosphate Binders

Vitamin D
Vitamin D Analogs

CKD-MBD Biochemical Monitoring

Ca, P, Alkaline phosphate, PTH, 25-VD

Table 5 Biochemical monitoring of serum biochemical variables according to chronic kidney disease (CKD) stage in pediatric patients

	GFR (ml/min/1.73 m^2)	Calcium, phosphate, alkaline phosphatase	Parathyroid hormone	25-hydroxyvitamin-D
CKD 2	60–89	Yearly	Yearly	If not on vitamin D therapy: every 6-12 months Three months after starting/modifying vitamin D treatment, if levels are normal, continue every 6 months
CKD 3	30–59	Every 6 months	Every 6 months	
CKD 4	15–29	Every 3 months	Every 3 months	
CKD 5 and 5D	< 15	Monthly	Every 1–3 months	

Calcified Tissue International, 2021

CKD-MBD Treatment - Phosphate Binders

20	15
Ca	**P**
Calcium	Phosphorus
40.078	30.973762

Age	Serum phosphate mg/dL
0–3 months	4.8–7.4
1–5 years	4.5–6.5
6–12 years	3.6–5.8
13–20 years	2.3–4.5

Age	Phosphorus DRI (mg/day)	Calcium DRI (mg/day)
0–6 months	100	210
6 months–1 year	275	270
1–3 years	460	500
4–8 years	500	800
9–19 years	1250	1300

With elevated PTH and normal P - 100% of Phosphate DRI

With elevated PTH and P levels - 80% of Phosphate DRI

Keeping an adequate protein intake

Avoid Hypophosphatemia

Up to 200% of Calcium DRI

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CKD-MBD Treatment - Phosphate Binders

Calcium-Based Phosphate Binders

First-line therapy in children without hypercalcemia

Growth vs. calcification

Calcium Carbonate as - Caltrate, Calcimore, Tums, Cal Vita and others

15 mins before meals

Calcium-Free Phosphate Bunders Binders

First-line therapy in children with hypercalcemia to avoid calcifications

Sevelamer (Renvela \ Renagel) **-** Binds phosphate in the GI tract through ionic interactions may reduce cholesterol level and acidosis

Velphoro - An iron-based phosphate binder, minimally absorbed, lower number of pills

CKD-MBD Treatment - Native Vitamin D, Cholecalciferol)

Vitamin D

Low 1,25-VD due to retention of P & high FGF23 levels

Leads together with high P to low Ca and SHPT

Age	25 (OH)D serum concentration	Vitamin D supplementation dose (IU/day)
Intensive replacement phase (3 months)		
< 1 year		600
> 1 year		
50–75 nmol/l (20–30 ng/ml)		2000
12–50 nmol/l (5–20 ng/ml)		4000
< 12 nmol/l (5 ng/ml)		8000
Maintenance phase		
< 1 year		400
> 1 year		1000–2000 based on CKD stage

25(OH)D 25-hydroxy Vitamin D

Check after 3 months

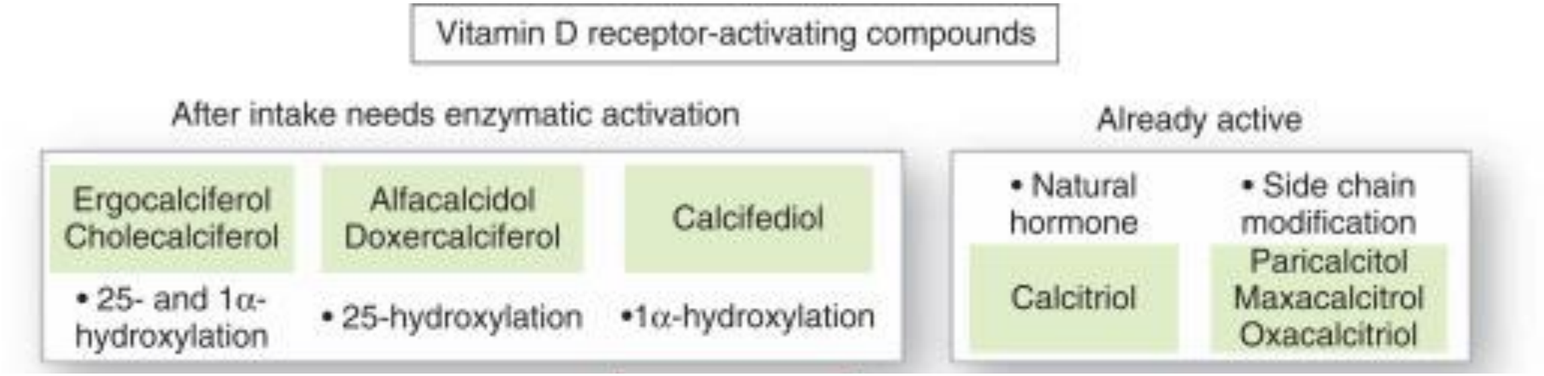
CKD-MBD Treatment - Active Vitamin D Analog

Vitamin D

Indications -

1. High PTH level
2. Normal Vitamin D
3. No hypercalcemia
4. Preferably no hyperphosphatemia

Check monthly after start and then every 3 months



Cunningham, John et al. Kl, Volume 79, Issue 7, 702 - 707

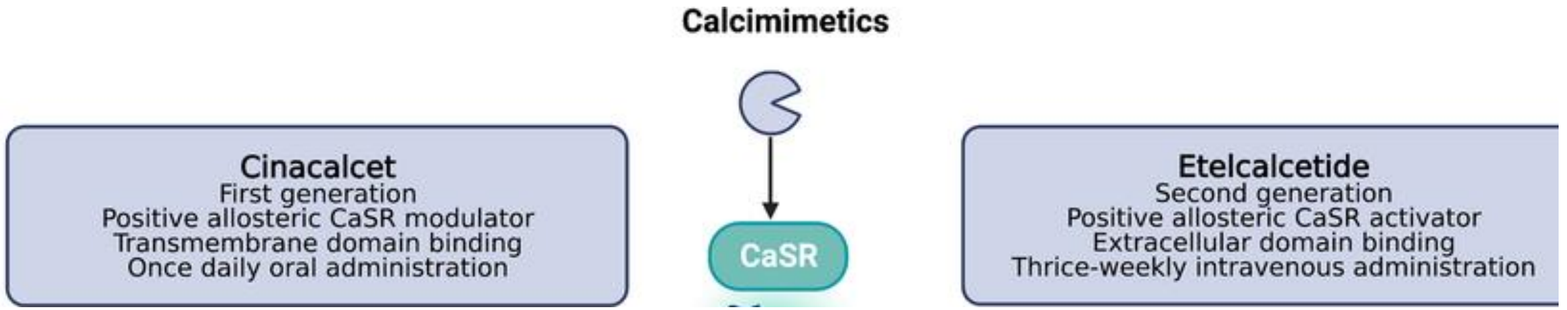
CKD-MBD Treatment - Calcimimetics

Suppresses PTH secretion by enhancing calcium receptor sensitivity without hypercalcemia

Limited pediatric studies; effective in refractory hyperparathyroidism

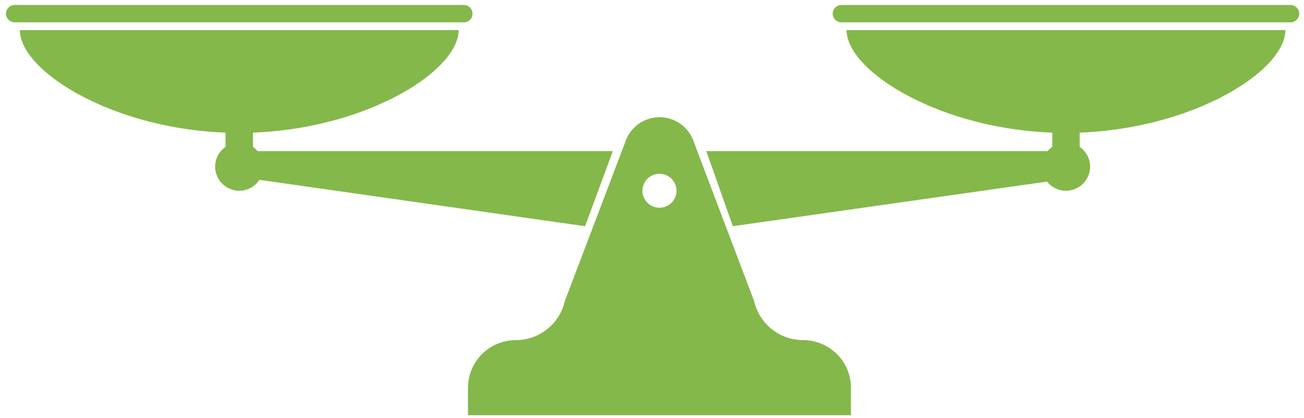
Adverse Effects: Hypocalcemia (10.7%), mortality (0.2%)

Requires close monitoring; more research needed



Current Osteoporosis Reports
27 February 2023

Target PTH level



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Target PTH level

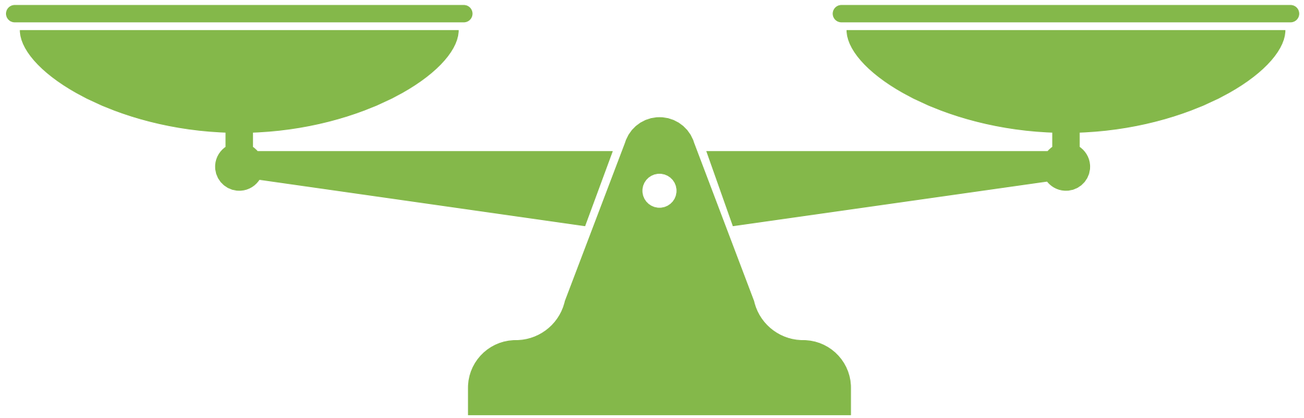
Renal osedodystrophy

Growth failure

Anemia

Cardiovascular disease

(LVH & calcification)



Target PTH level

Lower P and improve Ca

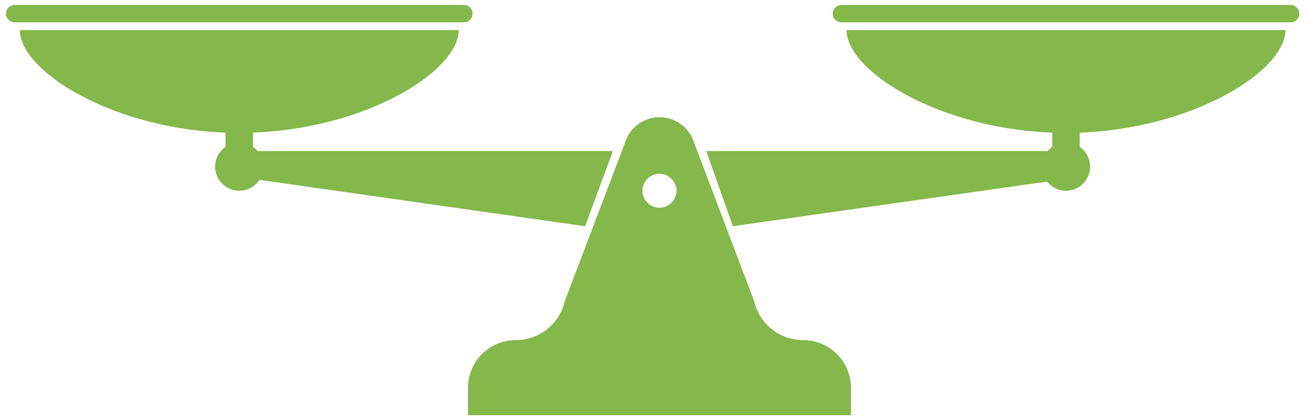
Calcitriol stimulating

Side effects of treatment

U-curve mortality shape

PTH unresponsiveness

Adynamic bone disease



Target PTH level

Table 1 Recommended PTH target range according to CKD stage

Reference	CKD stage	GFR (ml/min/1.73m^2)	iPTH (fold UNL)
K/DOQI [12]	2	60–89	1×
	3	30–59	1×
	4	15–29	1–2×
	5	< 15, dialysis	3–5×
KDIGO [13]	5	< 15, dialysis	2–9×
ESPN [14]	2	60–89	1×
	3	30–59	1×
	4	15–29	2–3×
	5	< 15, dialysis	2–3×
IPPN [15]	5	Peritoneal dialysis	1.7–3×
Present article	2	60–89	1–2×
	3	30–59	1–2×
	4	15–29	1.7–5×
	5	< 15, dialysis	1.7–5×

CKD, chronic kidney disease; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; K/DOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease: Improving Global Outcomes; ESPN, European Society for Paediatric Nephrology; IPPN, International Pediatric Dialysis Network

None were validated in a large pediatric CKD cohort study

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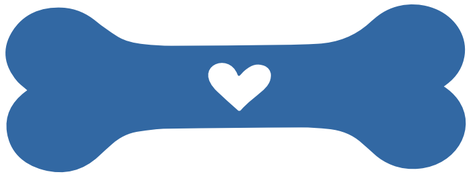
Summary

Early Detection



Protect Growth Bone and Heart Health

Balanced Treatment

Multidisciplinary Care

Summary

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