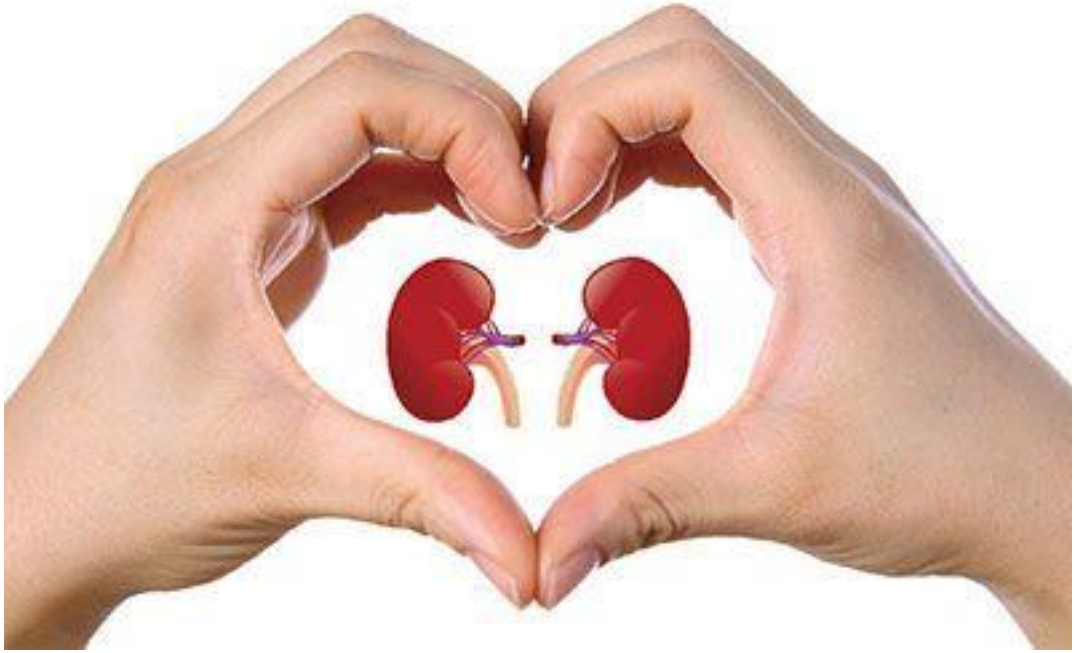
CKD-MBD



Dr mirhosseini

Assistant Professor of Nephrology

CKD-MBD

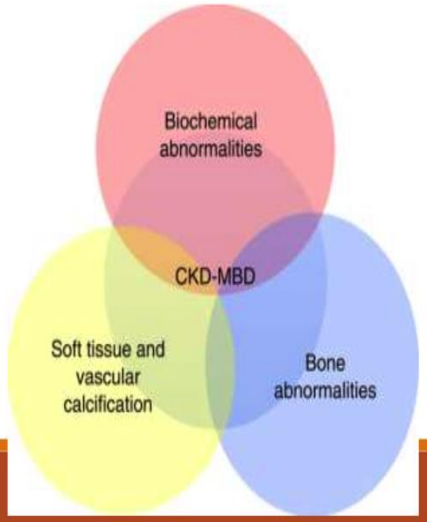
- **Chronic kidney disease–mineral and bone disorder (CKD-MBD)** is a common complication of chronic kidney disease and is a part of broad spectrum disorders of mineral metabolism.

KDIGO Classification of CKD–MBD

Definition of CKD–MBD

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

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
- Vascular or other soft-tissue calcification.



Pathogenesis of CKD MBD

Reduced glomerular filtration of phosphate leads to phosphate retention

becoming clinically evident at stage 4–5 CKD.

Reduced renal mass reduced activity of 1 –hydroxylas thus failure to increase calcitriol production

calcitriol concentrations begin to fall at stage 3 CKD

direct result of phosphate retention or as a secondary effect via FGF-23 stimulation.

Pathogenesis of CKD MBD

- Lowered calcitriol leads to reduced calcium absorption from the gut and proximal tubule

- The net effect is **secondary hyperparathyroidism** (i.e. abnormally high PTH concentrations as an appropriate response to hypocalcaemia), which further aggravates **hyperphosphataemia** (positive feedback).

Pathogenesis of CKD MBD

- Reduced expression of vitamin D receptors (VDRs),
- calcium-sensing receptors (CaSRs), FGF receptors, and klotho in the parathyroid glands.
- **FGF-23**
- is a circulating peptide, secreted by bone osteocytes and osteoblasts in response to calcitriol, increased dietary phosphate load, PTH, and calcium.
- **Klotho**
- , a transmembrane protein produced by osteocytes, is required for FGF-23 receptor activation.
- Inadequate response to PTH, which normally promotes phosphaturia and calcium reabsorption, or to FGF-23, which also enhances phosphate excretion.

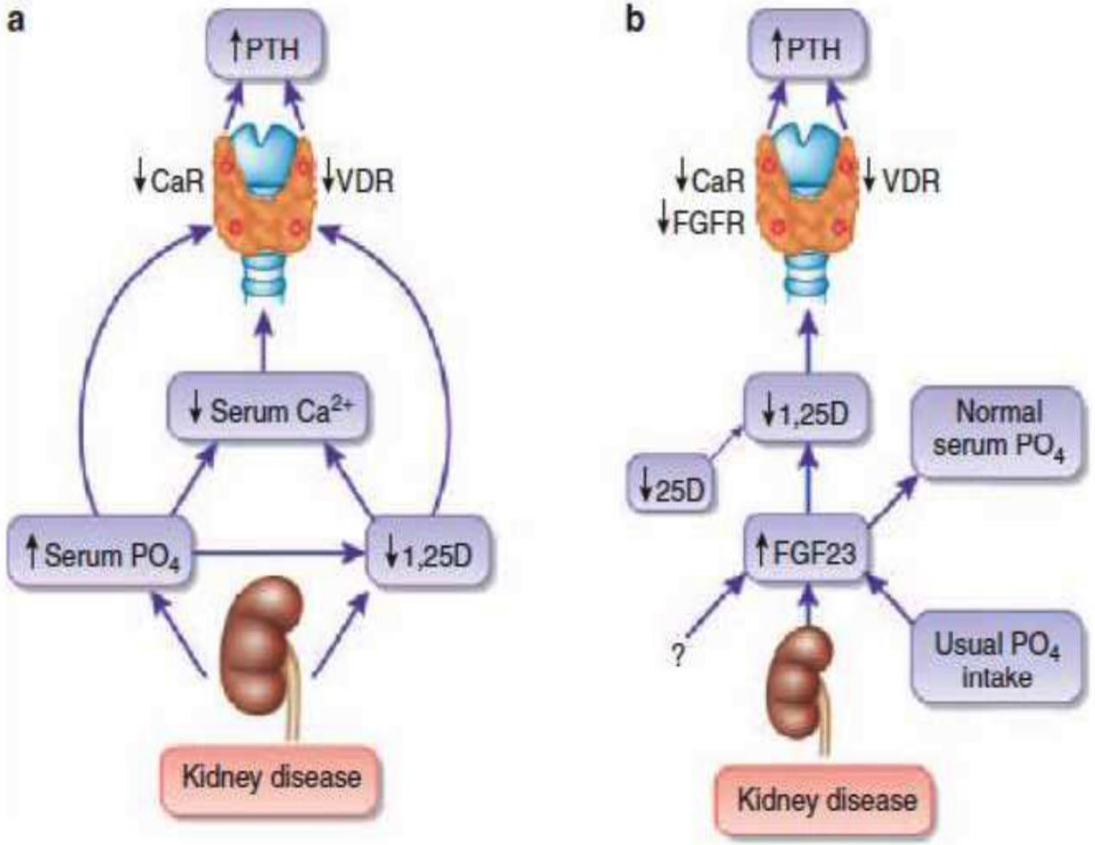


Figure 1 | Pathogenesis of disordered mineral metabolism in CKD. (**a**) Traditional view of the mechanisms that maintain secondary hyperparathyroidism in advanced chronic kidney disease. (**b**) Updated view of the mechanisms that initiate secondary hyperparathyroidism in chronic kidney disease, emphasizing the central role of FGF23. CaR, calcium sensing receptor; FGFR, fibroblast growth factor receptor; PTH, parathyroid hormone; VDR, vitamin D receptor.

Parathyroid Abnormalities in Chronic Kidney Disease

- Parathyroid gland hyperplasia: diffuse, nodular
- Decreased expression of vitamin D receptors
- Decreased expression of calcium receptors
- Increased set-point of calcium-regulated parathyroid hormone secretion

Box 85-1 Parathyroid abnormalities in chronic kidney disease.

Mechanisms Contributing to Decreased Levels of Calcitriol in CKD

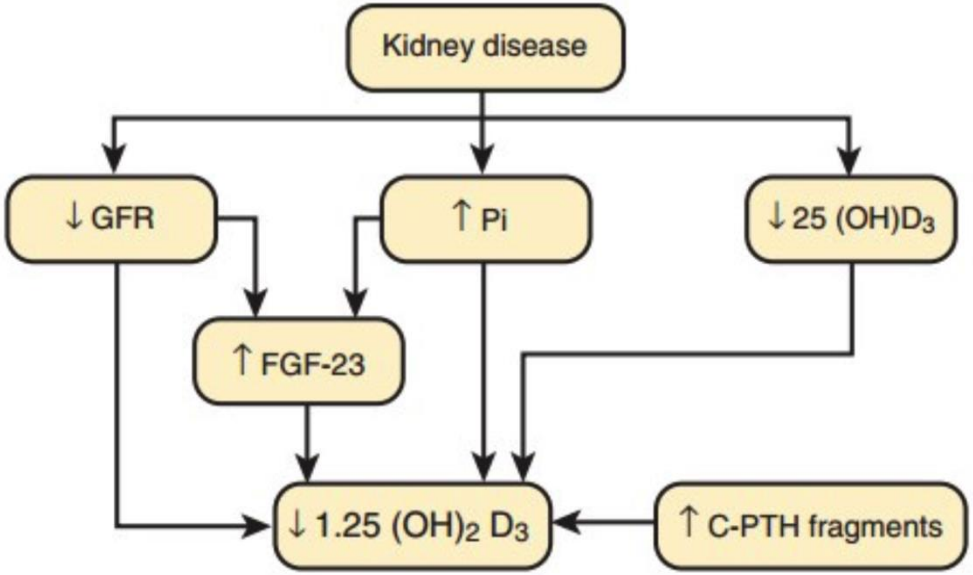


Figure 85-5 Mechanisms contributing to decreased levels of calcitriol in chronic kidney disease (CKD). *C-PTH,* Carboxyl-terminal parathyroid hormone; *FGF-23,* fibroblast growth factor 23; *GFR,* glomerular filtration rate; *Pi,* inorganic phosphate.

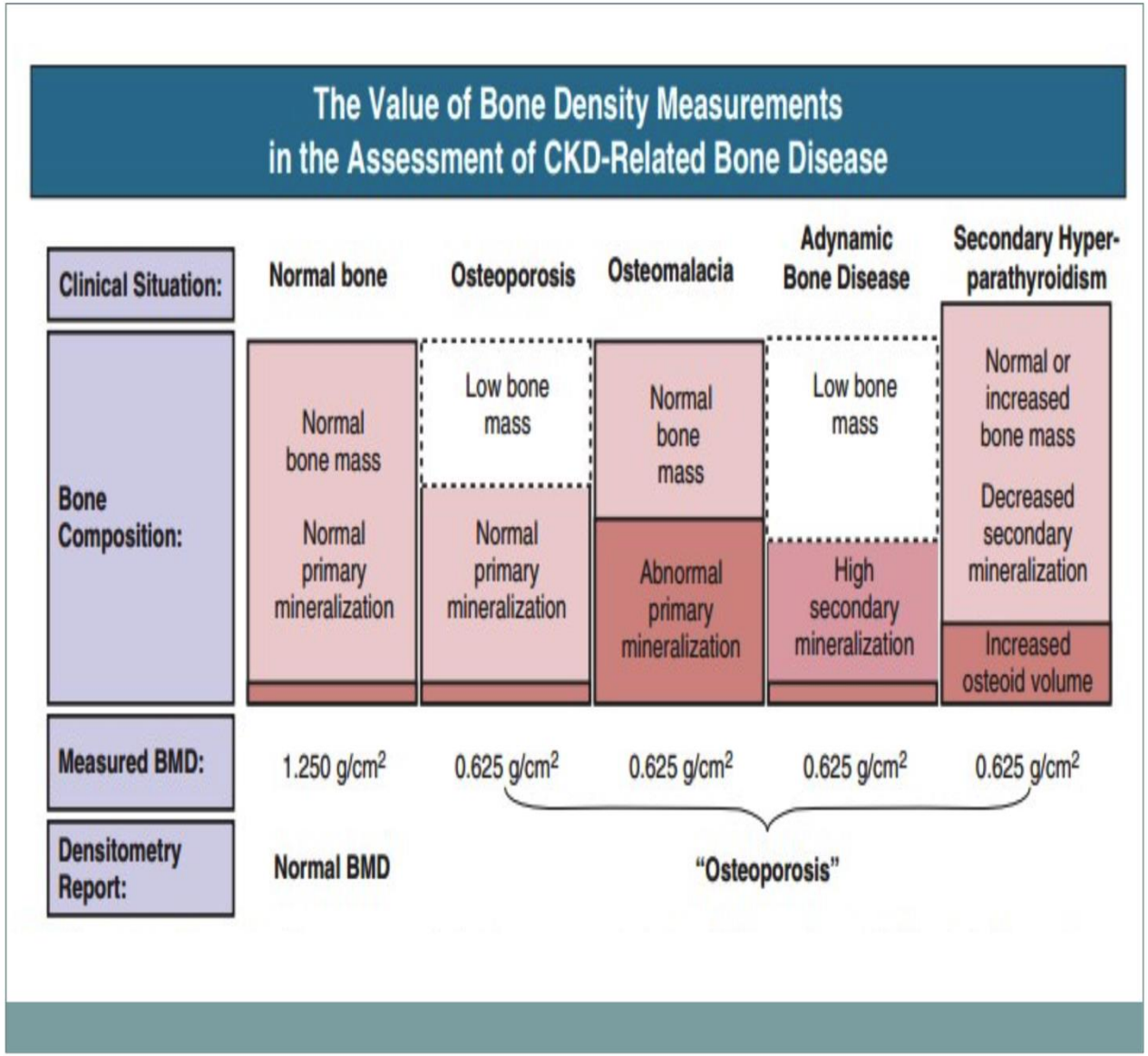
BONE DISEASE DUE TO CKD

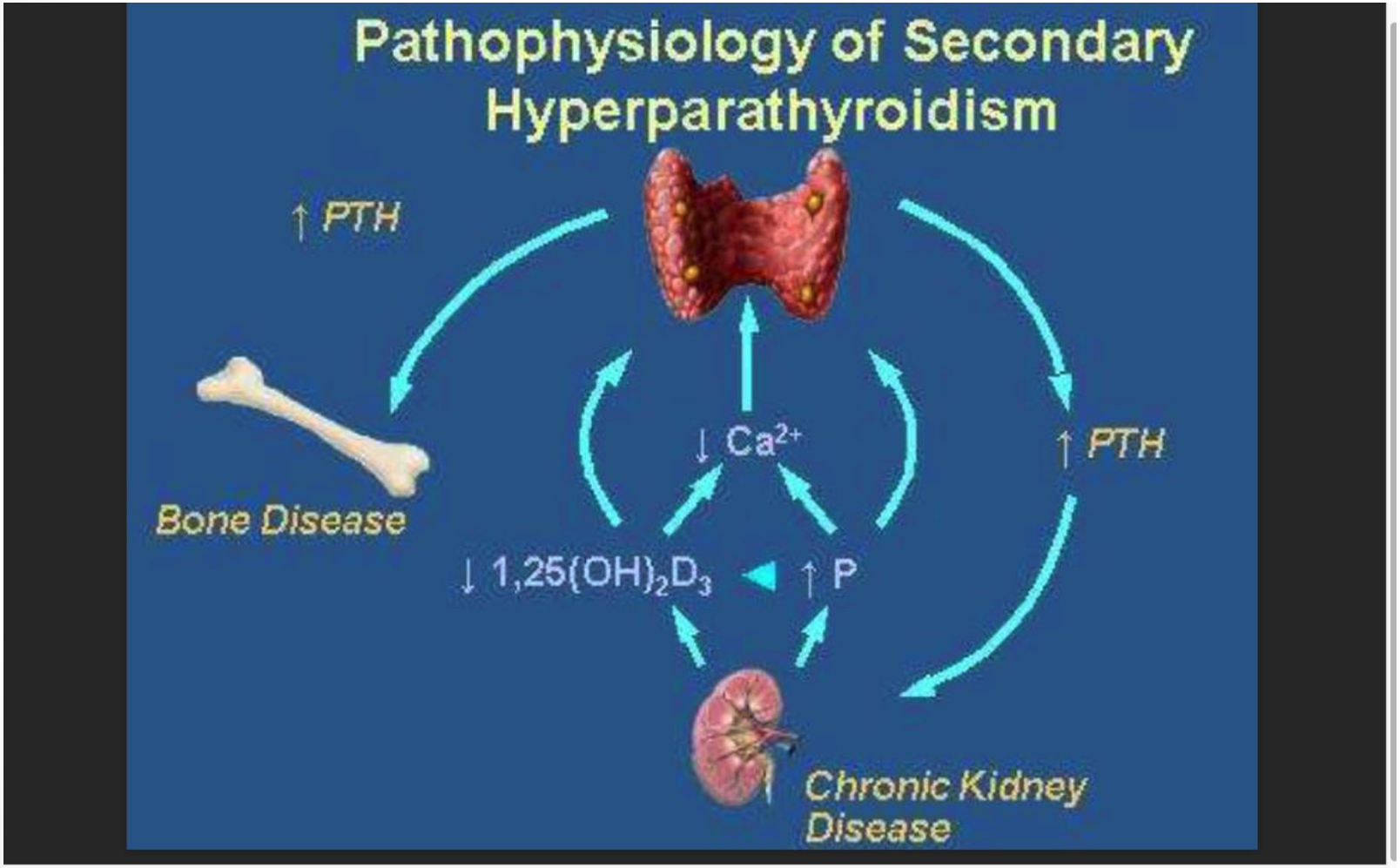
- **Osteitis fibrosa:** increased osteoclast & osteoblast activity, peritrabecular fibrosis, and increased bone turnover.

- **Osteomalacia:** defective mineralization of newly formed osteoid most often caused by aluminum deposition; bone turnover is decreased.
-
- **Adynamic bone disease :** abnormally low bone turnover.
- **Osteopenia** or **osteoporosis**

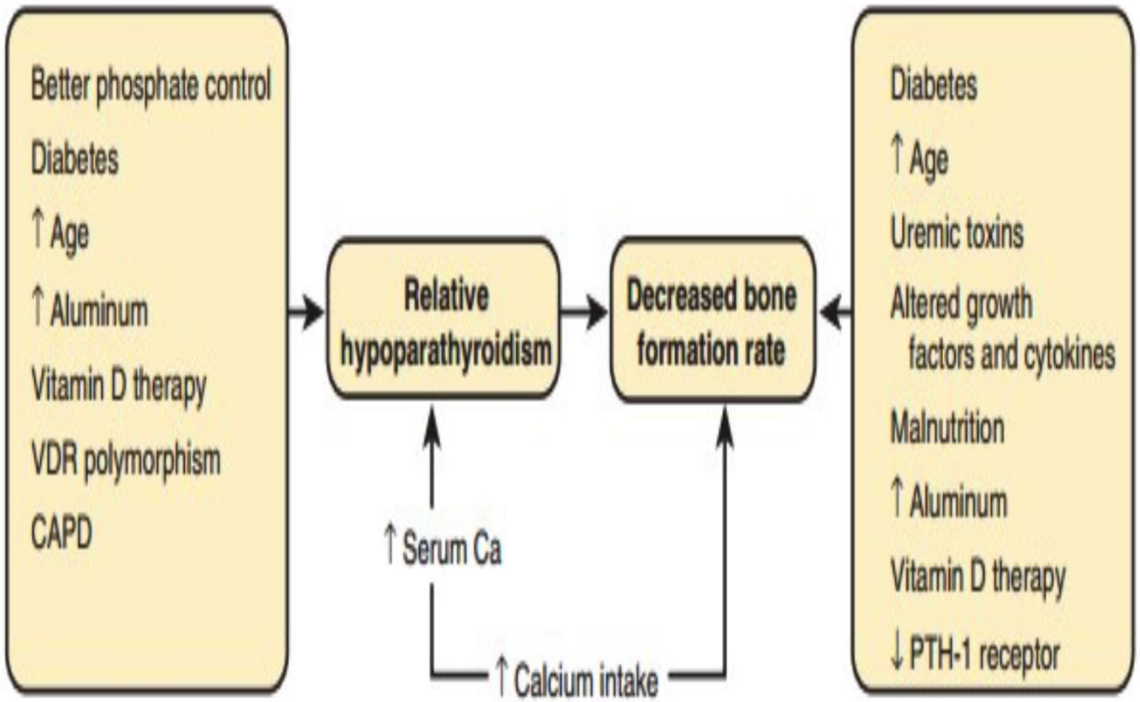
- **Mixed renalosteodystrophy**

- **Others** (e.g., chronic acidosis, β2-microglobulin amyloidosis).


The Value of Bone Density Measurements
in the Assessment of CKD-Related Bone Disease
Clinical Situation:
Normal bone
Osteoporosis
Osteomalacia
Adynamic Bone Disease
Secondary Hyper-parathyroidism
Bone Composition:
Normal bone mass
Normal primary mineralization
Low bone mass
Normal primary mineralization
Normal bone mass
Abnormal primary mineralization
Low bone mass
High secondary mineralization
Normal or increased bone mass
Decreased secondary mineralization
Increased osteoid volume
Measured BMD:
1.250 g/cm2
0.625 g/cm2
0.625 g/cm2
0.625 g/cm2
0.625 g/cm2
Densitometry Report:
Normal BMD
"Osteoporosis"


Pathophysiology of Secondary Hyperparathyroidism
↑ PTH
↓ Ca2+
↑ PTH
Bone Disease
↓ 1,25(OH)2D3
↑ P
Chronic Kidney Disease

Pathogenesis of Adynamic Bone Disease

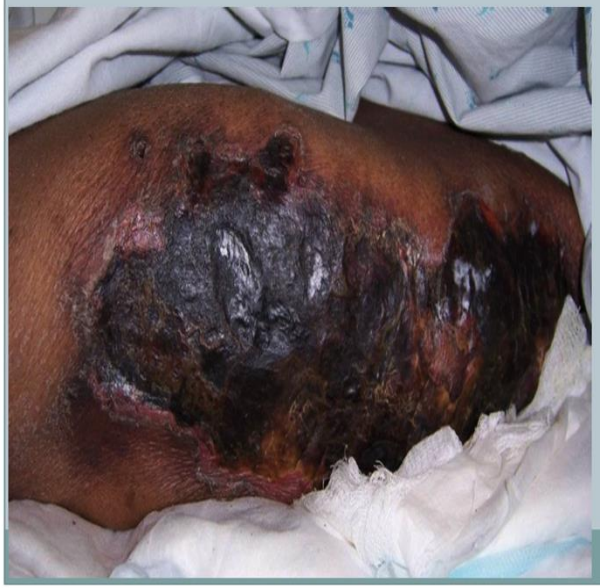


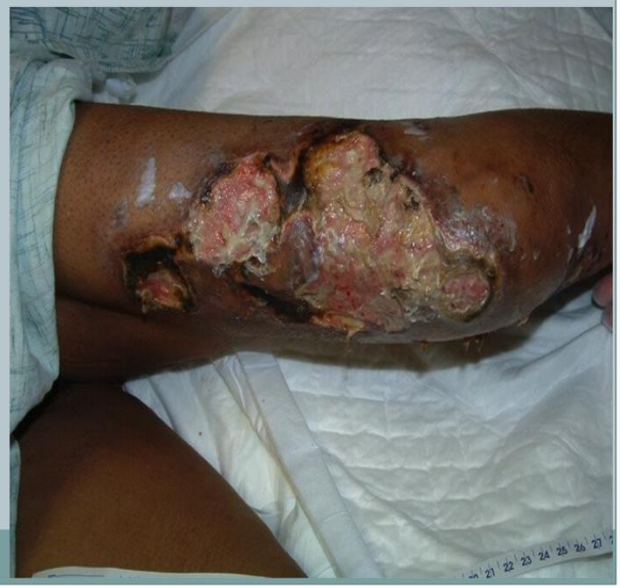
VASCULAR CALCIFICATIONS

- In CKD-MBD, there is a greater proportion of calcification in the arterial media which causes **vascular stiffness and hypertension.**
- **Calciphylaxis** is a condition where small cutaneous blood vessels become calcified, leading to acute, painful necrosis and ulceration of the skin. It is strongly associated with the presence of CKD-MBD

PATHOGENESIS

- **Calciphylaxis** (Calcific uremic arteriolopathy) is a rare and serious disorder characterized by systemic medial calcification of the arterioles that leads to ischemia and subcutaneous necrosis.





manifestation

- **Bone Disease:**
- Most cases are asymptomatic
  Weakness, fractures, bone and muscle pain. Tendon rupture
  Avascular necrosis (especially in dialysis). **Extra skeletal Calcifications:**
- Vascular calcification: systolic hypertension, left ventricular hypertrophy , and impaired coronary artery perfusion.
- Soft tissue calcification.

DIAGNOSIS OF CKD-MBD

Biochemistry

Serum calcium, phosphorus, alkaline phosphatase (ALP)

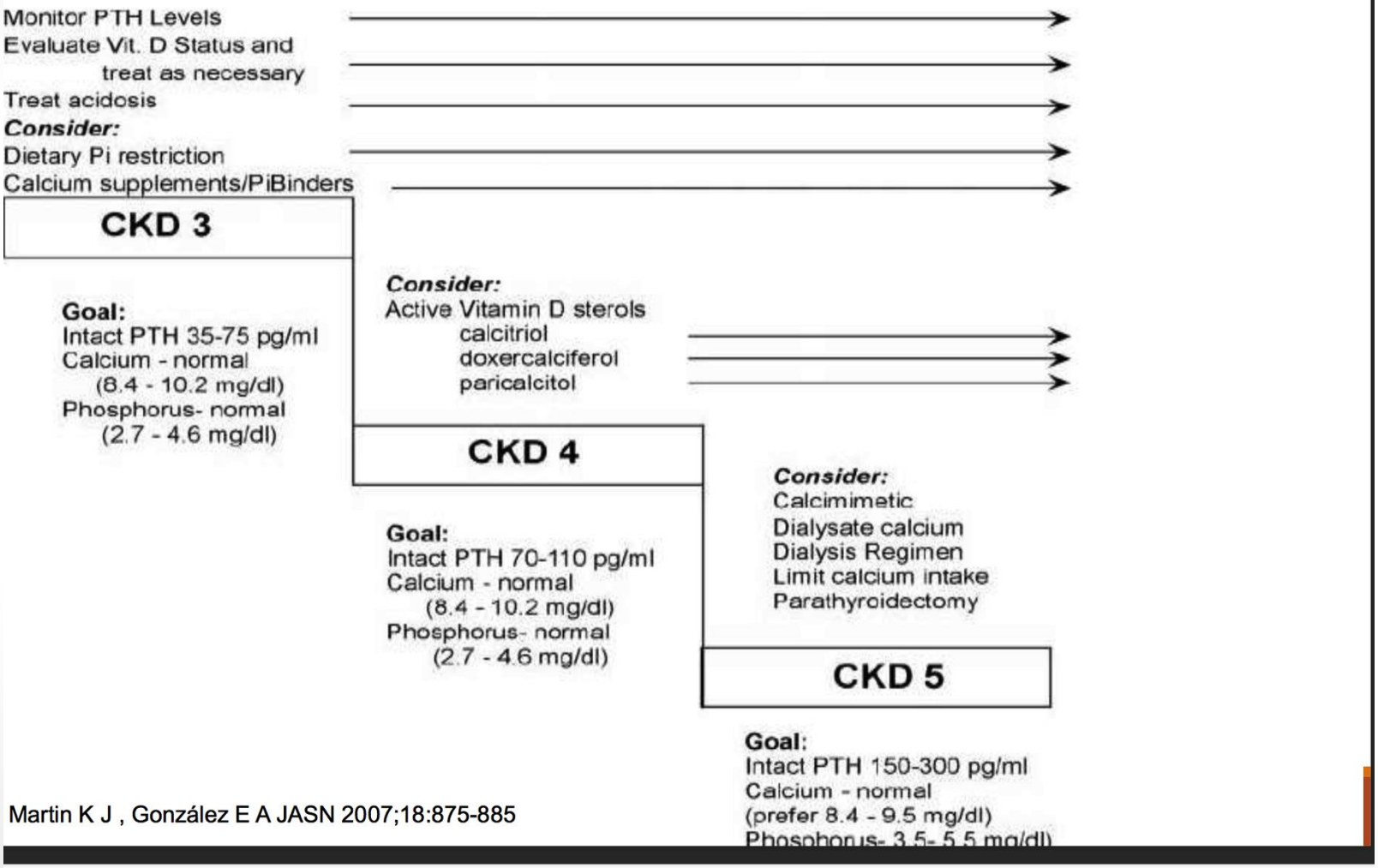
Bone biopsy

Radiology – x ray

Table Schedule for monitoring biochemical markers of CKD-MBD (KDIGO)

Test in serum	Frequency	Target
Calcium and phosphate	CKD3: 6–12 months CKD4: 3–6 months CKD5: 1–3 months	Normal
PTH	CKD3: not required CKD4: 6–12 months CKD5: 3–6 months	Within 2–9 times upper limit of normal for assay. Trend significant
Alkaline phosphatase	Annually, or more frequently in presence of elevated PTH	Normal

A "stepped-care" approach to the prevention and treatment of secondary hyperparathyroidism in CKD.



Martin K J , González E A JASN 2007;18:875-885

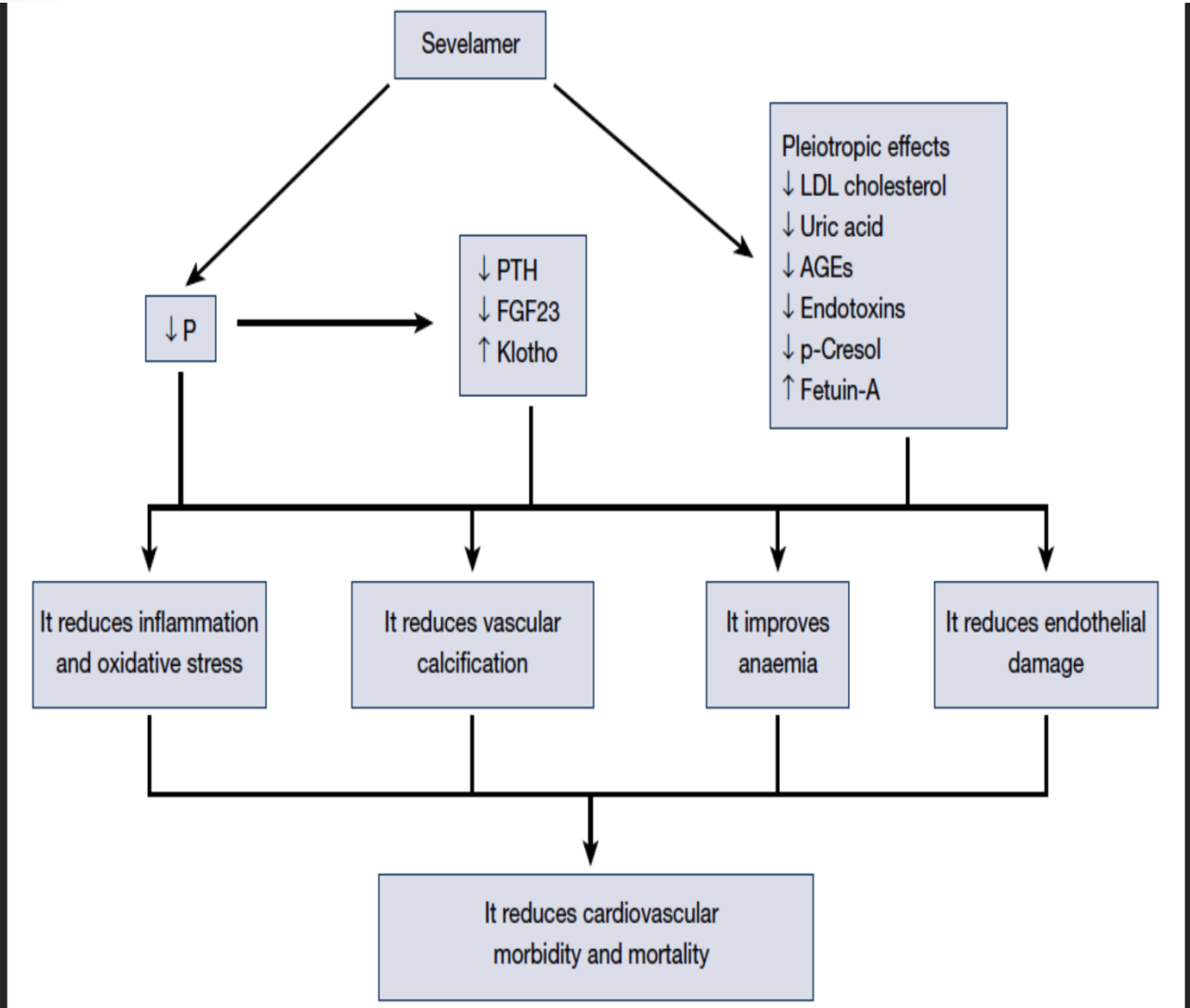
Treatment

- **2nd hyperPTH and hyperphosphataemia**
- **1.Dietary phosphorous restriction dietary phosphate intake to 900 mg/day**
- **2. Phosphate binders**
- **3. Calcitriol or other Vit D analogues.**
- **4. Calcimimetics**
- **5. Parathyroidectomy**

PHOSPHATE BINDERS

- Agents containing calcium are inexpensive and well tolerated, but these may contribute to vascular calcification.

- Non-calcium-containing phosphate binders (lanthanum and sevelamer) have the advantage of reducing calcium intake and thus slowing vascular calcification.



NEFROLOGIA 2015; 35(2):207-217

- **Sevelamer: Calcium-free, aluminium-free phosphate binders**

- Sevelamer was approved by the US Food and Drug Administration (FDA) in 1998.

- Sevelamer not absorbed from the GI tract.

- Reduces total and LDL, while increasing HDL, cholesterol.

- Sevelamer is commonly initially used over lanthanum, although equally effective in lowering Phosphate, as the long-term data on safety of Lanthanum are more limited.

	Sevelamer HCL(Renagel) Carbonate(Renvela)	Lanthanum carbonate hydrate(fosrenol)
Type	Non absorbed polymer, trends dietary phosphate in exchange for CL,CO2	Heavy metal(like AL),effective at binding dietary phosphate
Dose:	Usual initial dose:800-1600mg TID Max:12-13g Swallow whole	Usual initial dose:500-1000mg TID 250,500,750,1000 mg chewable tablets
Disadvantage/ side effect	more expensive than other products GI:Constipation,bloating Metabolic:acidosis(sevelamer HCL)	Similar to sevelamer GI: Diarrehea, Neurologic effect
Advantage	Less vascular calcification than ca-ph binders,lower all-cause mortality ↓LDL	Less vascular calcification than ca-ph binders

CALCINOMIMETIC AGENTS

- Calcium-sensing receptor (CaSR) is a G protein–coupled receptor identified as an essential molecule for the regulation of PTH secretion by extracellular calcium (Ca).

- Binding of extracellular Ca inhibits PTH secretion

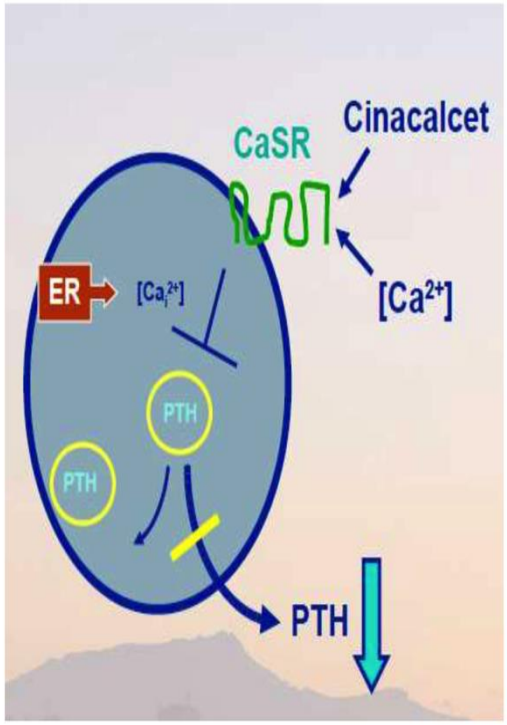
- Calcimimetics are agents that increase the sensitivity of the calcium- sensing receptor (CaSR) in the parathyroid gland to calcium, regulating PTH secretion and the gland hyperplasia.

Cinacalcet: mechanism of action

The calcium-sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion.

Cinacalcet directly lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor(CaSR) to extracellular calcium.

The reduction in PTH is associated with a concomitant decrease in serum calcium levels.



DOSAGE AND ADMINISTRATION

- 30 mg once daily with food or shortly after a meal.
- Serum calcium and phosphorus should be measured within 1 week and PTH measured 1 to 4 weeks after initiation
- Cinacalcet should be titrated no more frequently than every 2 to 4 weeks through sequential doses of 60, 90, 120, and 180 mg once daily to target iPTH
- PTH levels should be assessed no earlier than 12 hours after dosing with Cinacalcet.

ADJUVANT WITH VITAMIN D ANALOGUES

- Treatment is associated with hypocalcaemia, hyperphosphataemia and an increased requirement for calcium supplements.

- The long-term consequences of these effects are unknown, thus the use of cinacalcet is recommended only in patients with CKD stage 5.

- They generally used to adjunct treatment with vitamin D analogues where the latter have not sufficiently suppressed PTH production

Treatment

2) Vitamin D, calcitriol, and vitamin D analogs:

Terminology

- **Vitamin D** includes both vitamin **D2** (ergocalciferol) and vitamin **D3** (cholecalciferol).

- **Vitamin D derivatives** include:

1. the **naturally** occurring vitamin D metabolite, **calcitriol** (1,25-dihydroxycholecalciferol [$1,25(OH)_2D$]), and

2. **synthetic vitamin D analogs** such as **doxercalciferol, paricalcitol, alfacalcidol, falecalcitriol,** and **22-oxacalcitriol** (or maxacalcitol [1,25 dihydroxy-22-oxavitamin D3]).

- **Vitamin D, calcitriol, and vitamin D analogs**

- •Most dialysis patients with increased plasma iPTH levels (>300 pg /mL) require treatment with calcitriol or vitamin D analogs.

- • Because calcitriol increases gastrointestinal absorption of calcium and phosphate, more selective vitamin D analogs have been developed that may reduce the risk of hypercalcemia and hyperphosphatemia.

Vitamin D, calcitriol, and vitamin D analogs

- The continued up-titration with active vitamin D to supraphysiologic levels, if necessary to suppress PTH, is often successful in lowering PTH, but frequently achieves this one goal at the expense of hypercalcemia and hyperphosphatemia.

- The effect of oral pulse alfacalcidol is superior to its daily use in the treatment of 2nd hyperparathyroidism

- The efficacy of oral alfacalcidol is similar to that of IV in managing 2nd hyperparathyroidism**.**

- Calcitriol or the synthetic analog should be discontinued for frank hypercalcemia (>10.2 mg/dL).

Vitamin D, calcitriol, and vitamin D analogs

- **Contraindications**

- Calcitriol or synthetic vitamin D analogs should not be given until the serum phosphorus concentration has been

- controlled (<5.5 mg/dL) and the serum calcium is <9.5 mg/dL.

- Low plasma PTH concentration, possibly <150pg/mL, because of the association with adynamic bone d sease.

Adynamic Bone Disease (ABD)

- 1. Decreasing the doses of calcium-based phosphate Binders.
-
- 2. Using non-calcium-based phosphate binders.
-
  3. Decreasing or stopping active vitamin D analogs.

- 4. For patients on dialysis, possibly by using a low dialysate calcium concentration.

Indications for Parathyroidectomy

- Severe hyperparathyroidism
  - With persistent hyperphosphatemia
  - Unresponsive to calcitriol and calcium
  - With hypercalcemia
  - With intolerance or unresponsiveness to calcimimetics
  - In renal transplantation candidate
  - With evidence of metastatic calcification
- Calciphylaxis with evidence of hyperparathyroidism
- Severe pruritus, only if additional evidence of hyperparathyroidism

Thank you for being awake