BONE MANIFESTATIONS OF CKD

Dr Reyhane Motamedifard
Nephrologist

Introduction

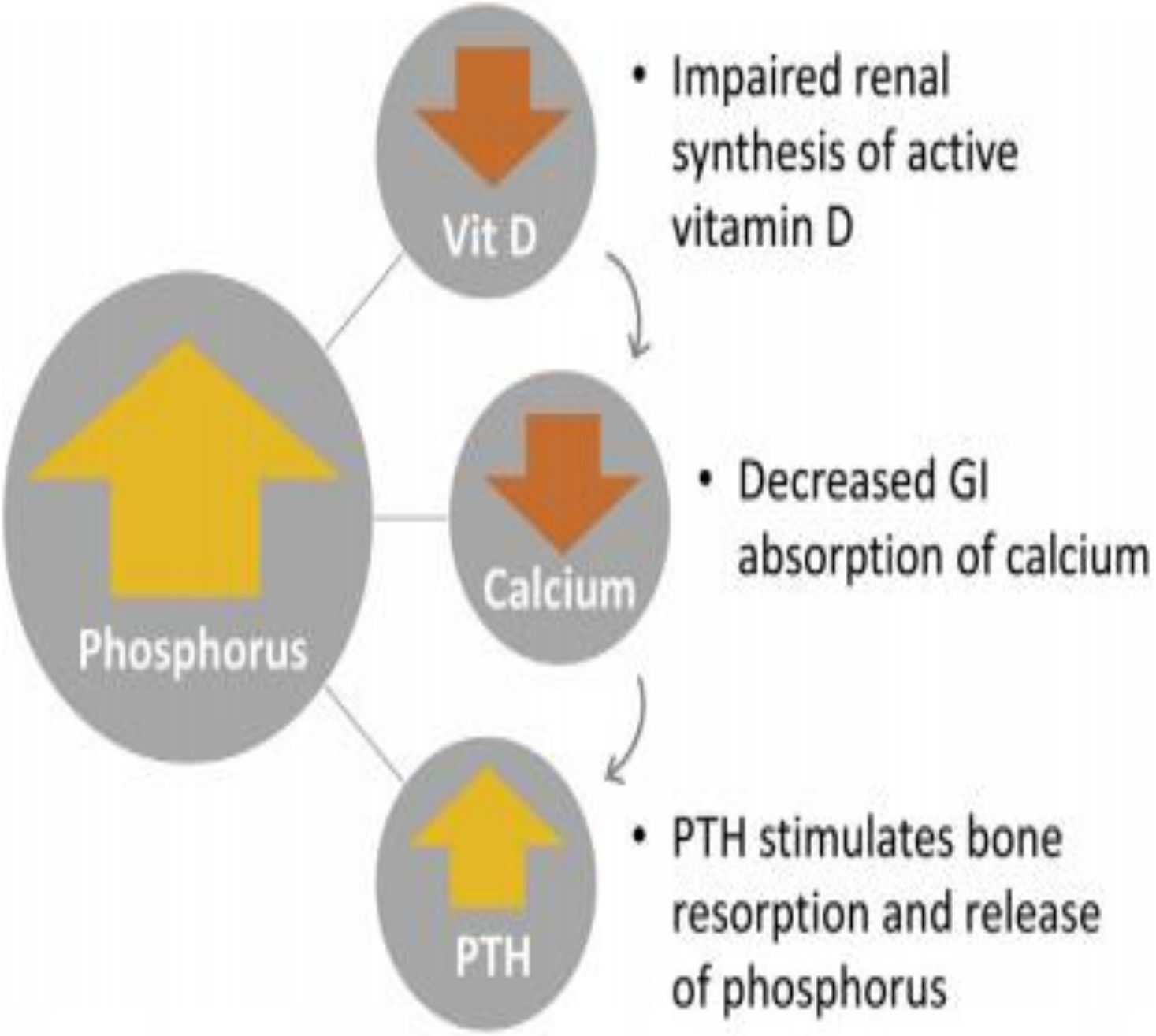
- CKD–MBD is a systemic disorder that affects multiple organs and systems and increases the risk of morbidity and mortality in patients with CKD, especially those receiving dialysis therapy

Introduction

- Among several organs involved in normal bone and mineral metabolism including kidney, bone, small intestine, soft tissues, and parathyroid glands
- The kidneys play a central role

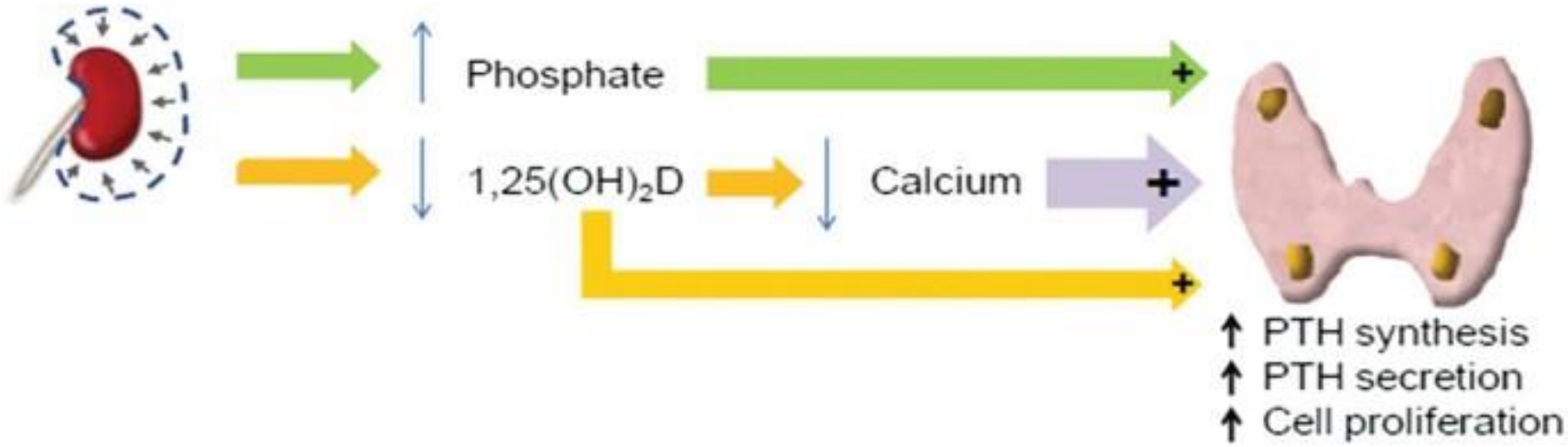
Introduction

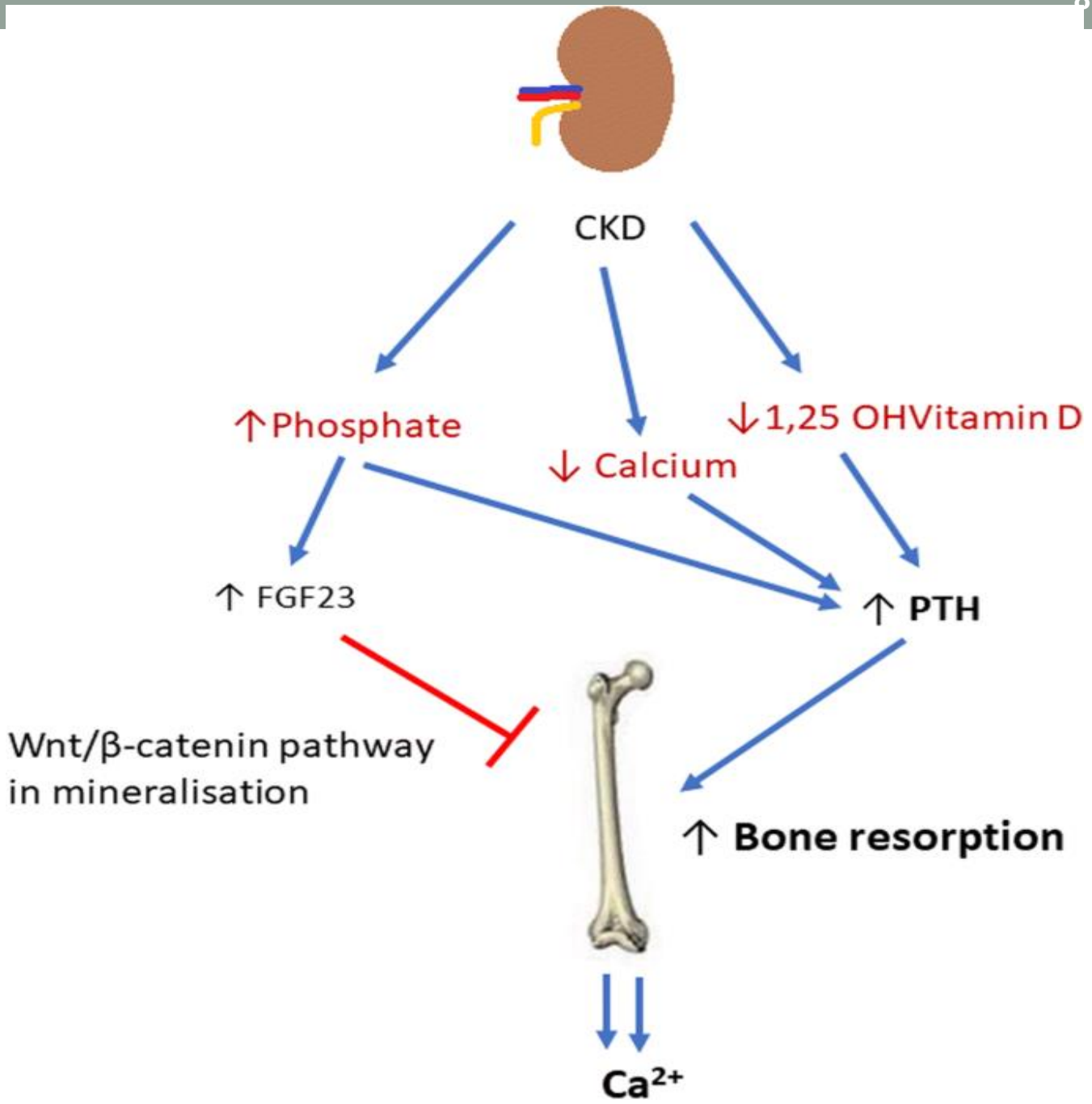
- The kidneys receive input through humoral mediators and neural networks, integrate the input, and alter the excretion and absorption of calcium and phosphate in the renal tubules to maintain a mineral balance in the whole body


Vit D
Phosphorus
Calcium
PTH
• Impaired renal synthesis of active vitamin D
• Decreased GI absorption of calcium
• PTH stimulates bone resorption and release of phosphorus

Hyperphosphatemia

- Increased risk of brain hemorrhage
- Sudden death
- Peripheral arterial diseases


Phosphate
1,25(OH)2D
Calcium
+
+
+
↑ PTH synthesis
↑ PTH secretion
↑ Cell proliferation


CKD
↑Phosphate
↓ Calcium
↓1,25 OHVitamin D
↑ FGF23
↑ PTH
Wnt/β-catenin pathway
in mineralisation
↑ Bone resorption
Ca2+

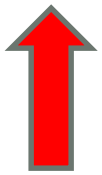
High serum phosphate

↑ serum phosphate levels ↓ in serum calcium levels

1. Circulating α-klotho levels decrease
2. Then serum fibroblast growth factor 23 (FGF23) levels increase
3. Serum calcitriol levels decrease
4. Serum PTH levels increase

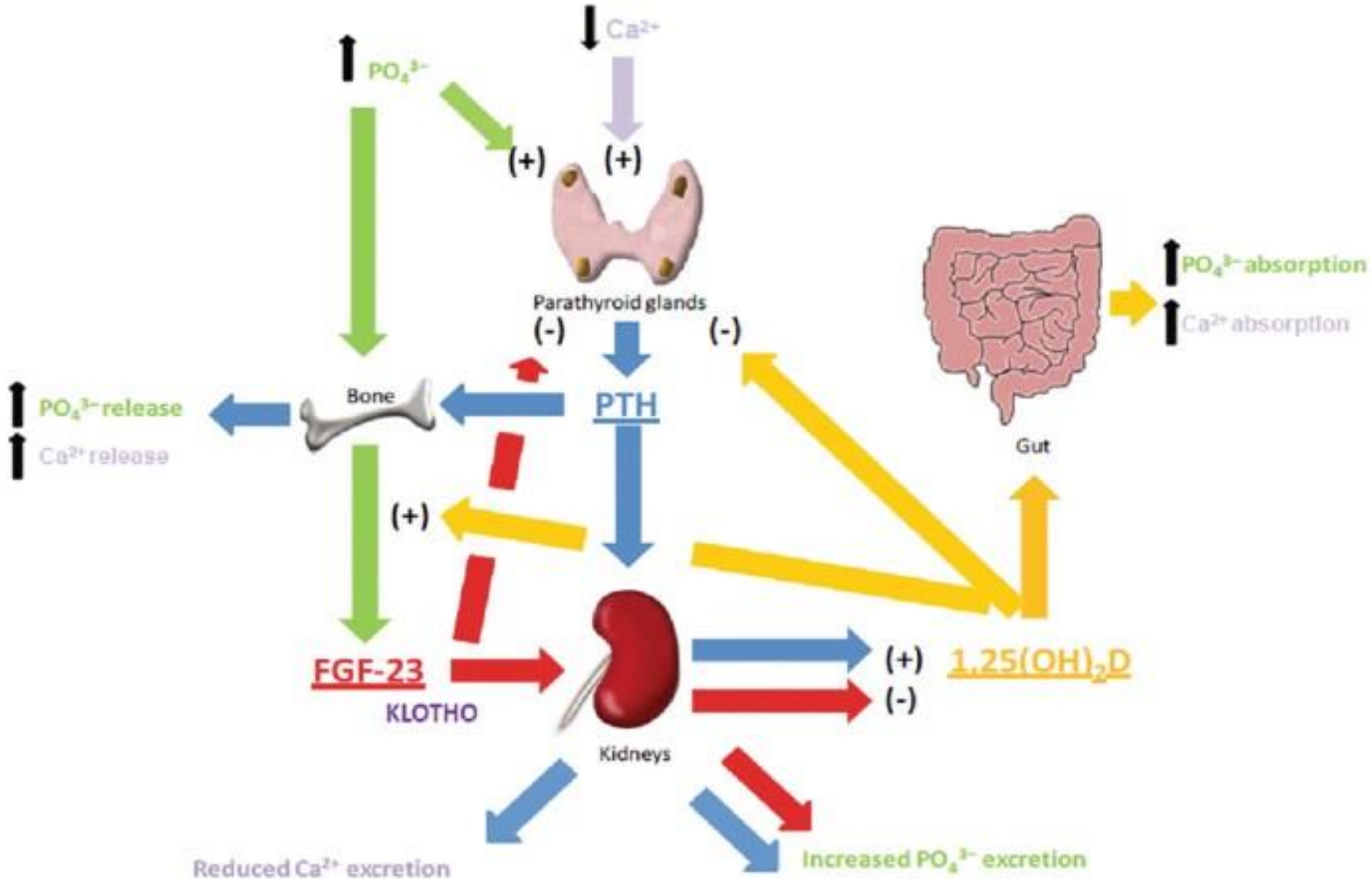
FGF23

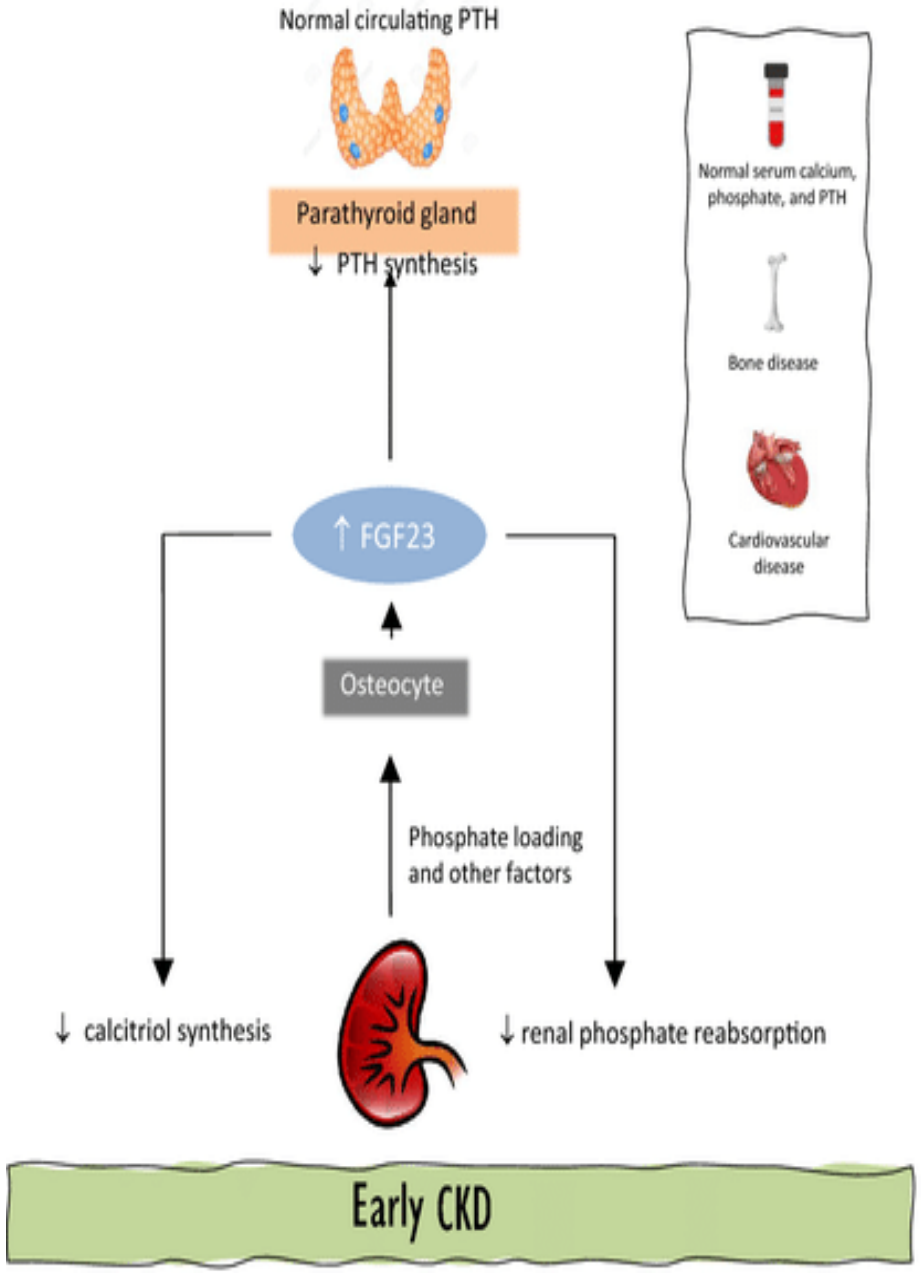
- Left ventricular hypertrophy
- Atrial fibrillation
- Vascular calcification (VC)
- Infection
- Anemia
- Inflammation
- Impaired immunity in hemodialysis patients

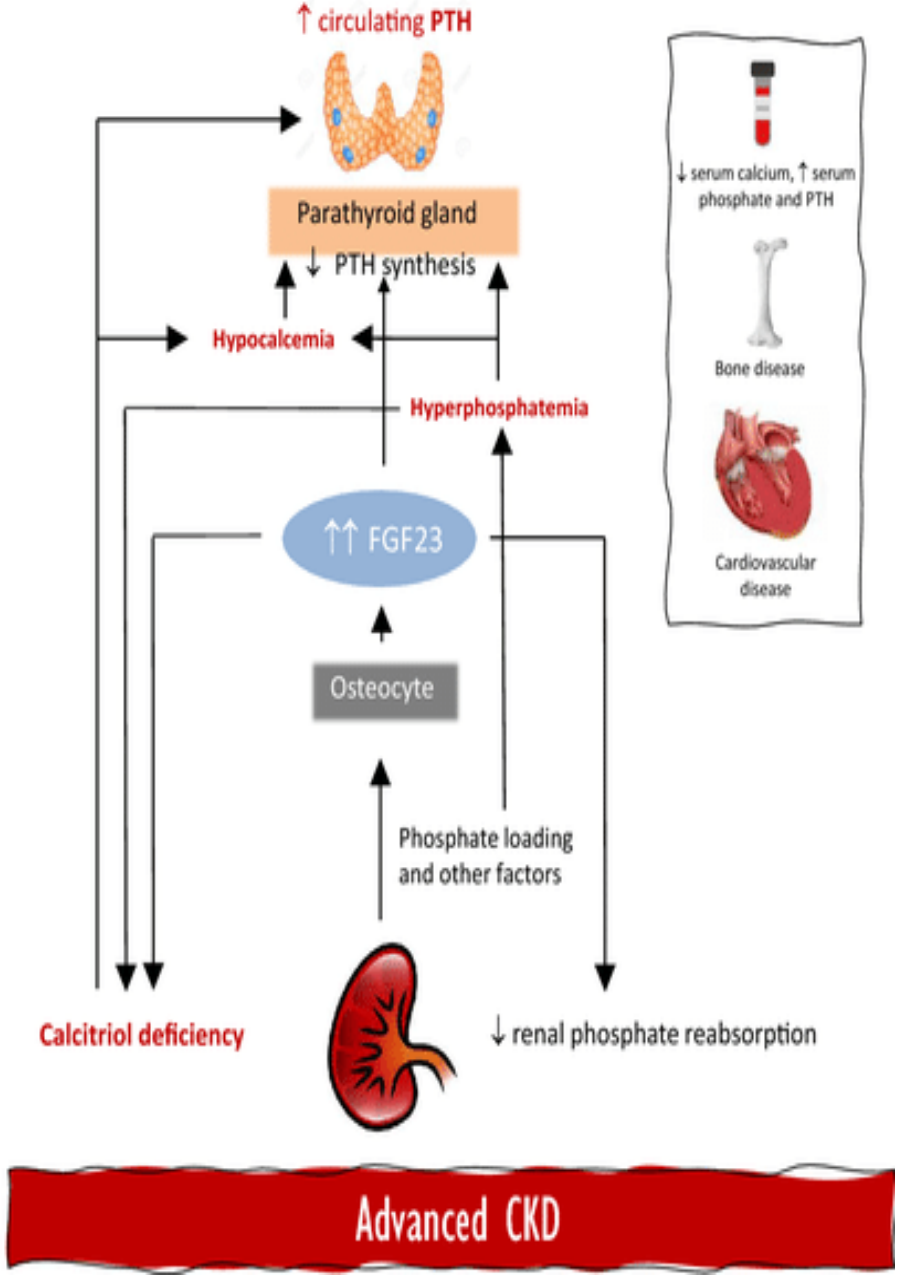


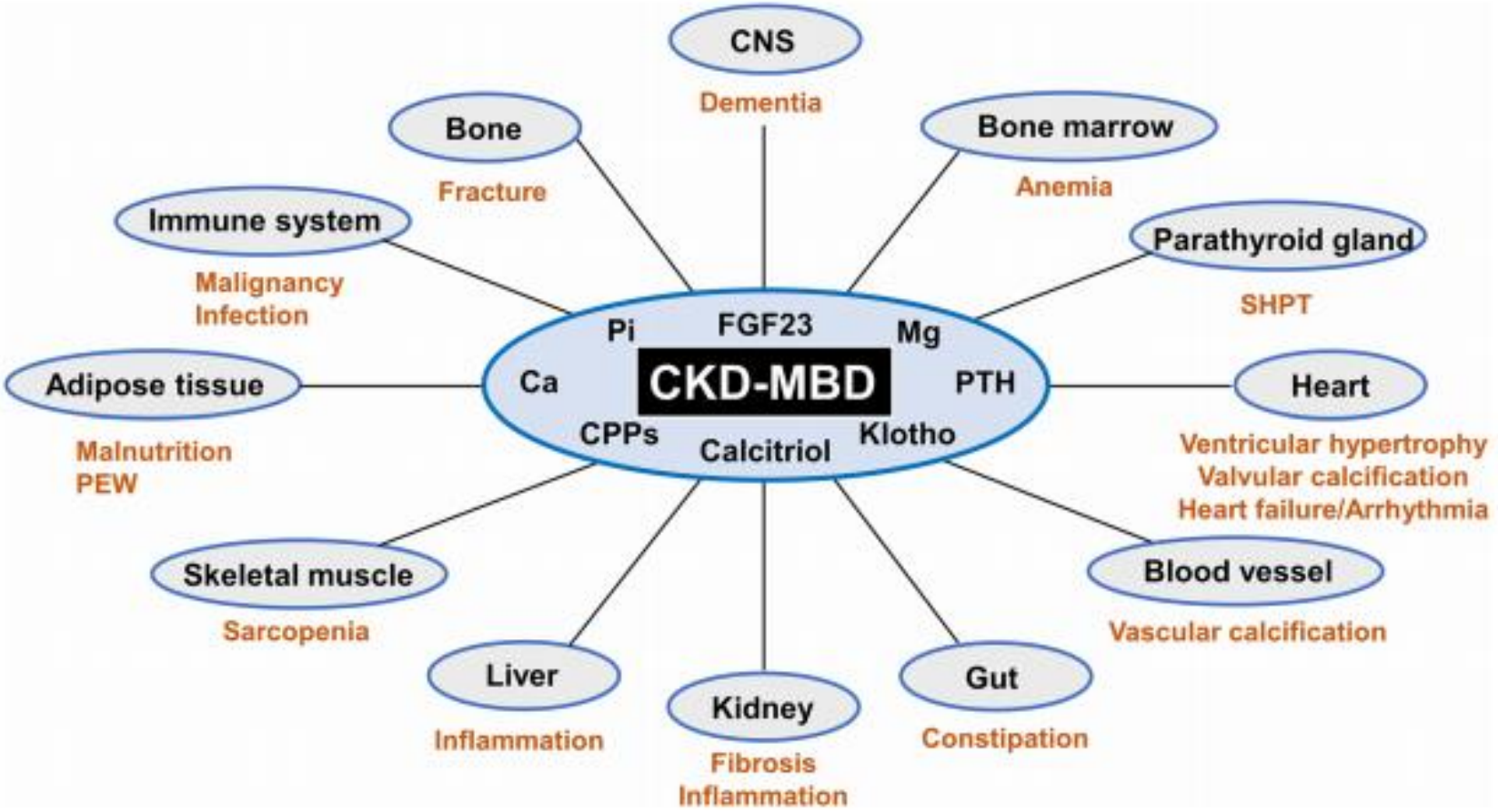
PTH

- Increase the incidence of bone fractures
- Cardiac hypertrophy
- Anemia
- Protein-energy wasting


Ca^{2+}
PO_4^{3-}
(+)
(+)
Parathyroid glands
(-)
(-)
PO_4^{3-} absorption
Ca^{2+} absorption
Gut
PO_4^{3-} release
Ca^{2+} release
Bone
PTH
(+)
FGF-23
KLOTHO
Kidneys
(+)
(-)
$1,25(OH)_2D$
Reduced Ca^{2+} excretion
Increased PO_4^{3-} excretion


Normal circulating PTH
Parathyroid gland
↓ PTH synthesis
Normal serum calcium, phosphate, and PTH
Bone disease
Cardiovascular disease
↑ FGF23
Osteocyte
Phosphate loading and other factors
↓ calcitriol synthesis
↓ renal phosphate reabsorption
Early CKD


↑ circulating PTH
Parathyroid gland
↓ PTH synthesis
Hypocalcemia
Hyperphosphatemia
↓ serum calcium, ↑ serum phosphate and PTH
Bone disease
Cardiovascular disease
↑↑ FGF23
Osteocyte
Phosphate loading and other factors
Calcitriol deficiency
↓ renal phosphate reabsorption
Advanced CKD



Abbreviations: Ca calcium, CKD–MBD chronic kidney disease-mineral and bone disorder, CNS central nervous system,CPPs calciprotein particles, FGF23 fbroblast growth factor 23, Mg
magnesium, PEW protein-energy wasting, Pi inorganic phosphate,PTH parathyroid hormone, SHPT secondary hyperparathyroidism

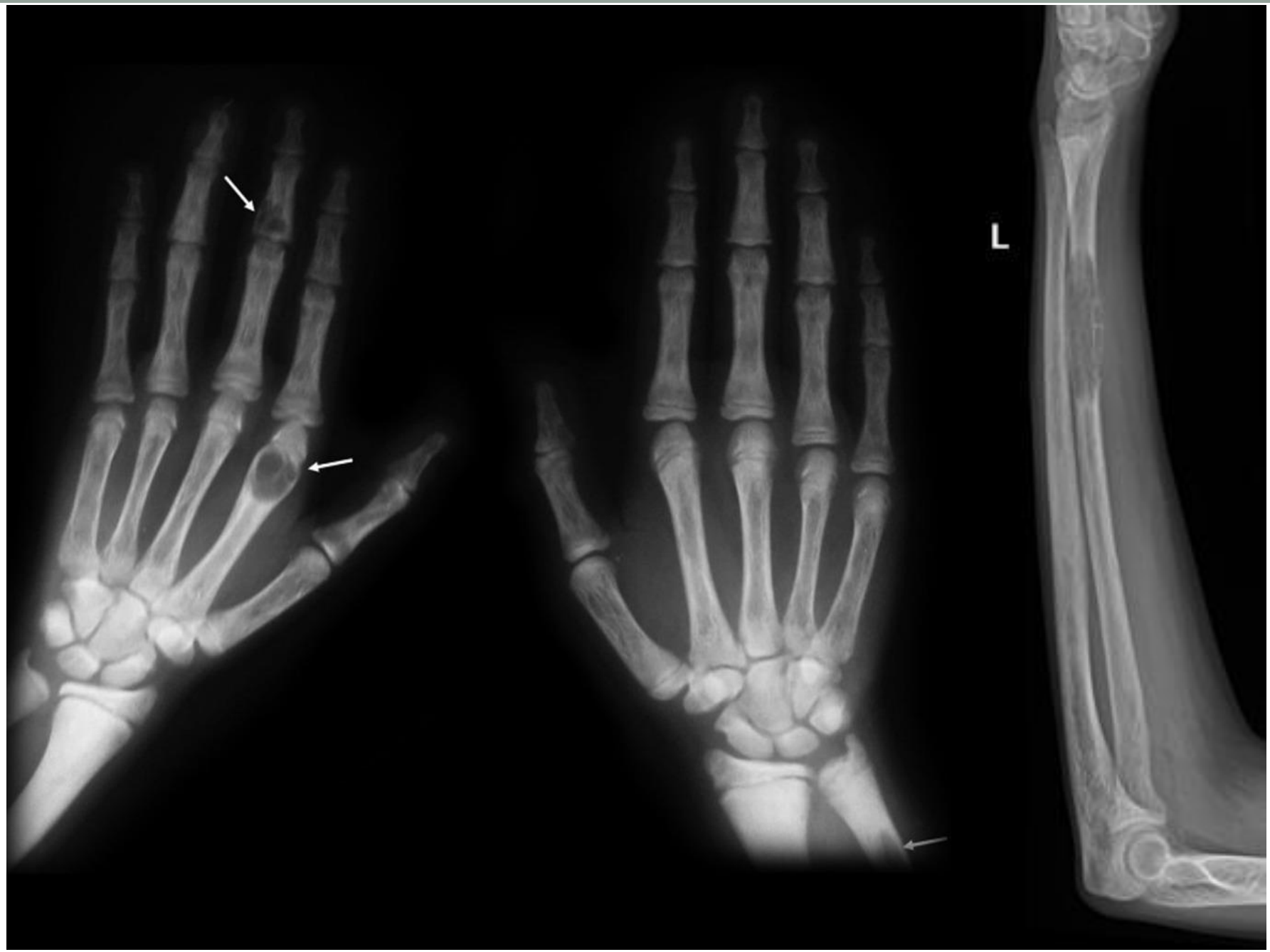
Manifestation

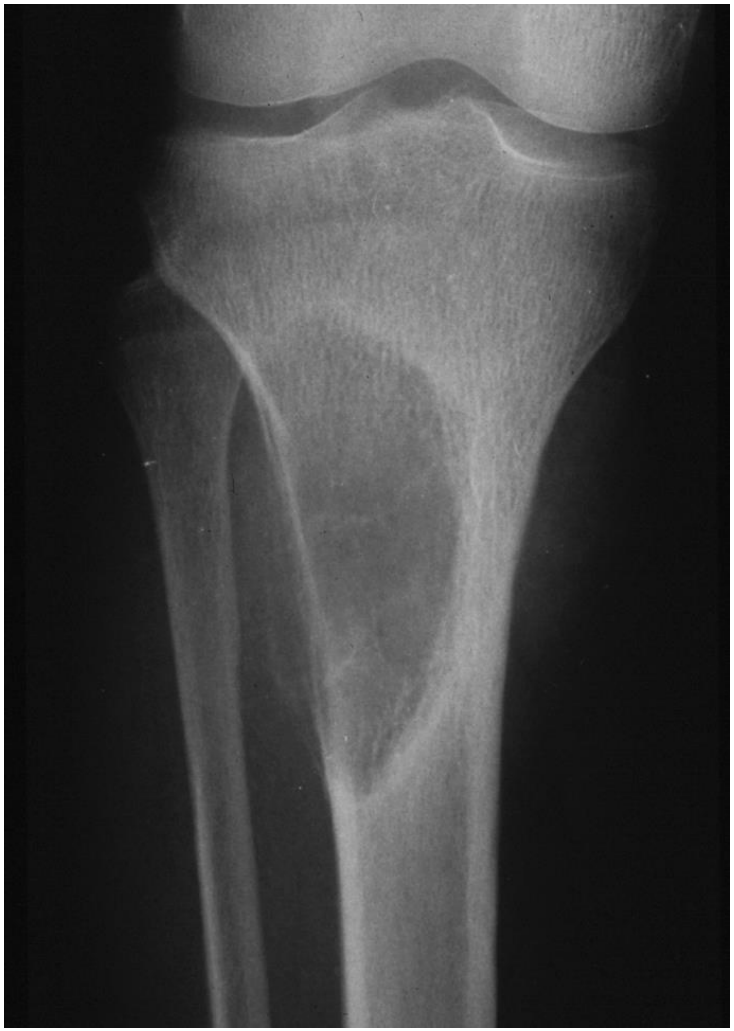
- Secondary hyperparathyroidism
- Adynamic bone disease

Hyperparathyroidism

Manifestations of severe hyperparathyroidism

- Bone pain and fragility
- Brown tumors
- Compression syndromes
- Erythropoietin resistance related to the bone marrow fibrosis


L

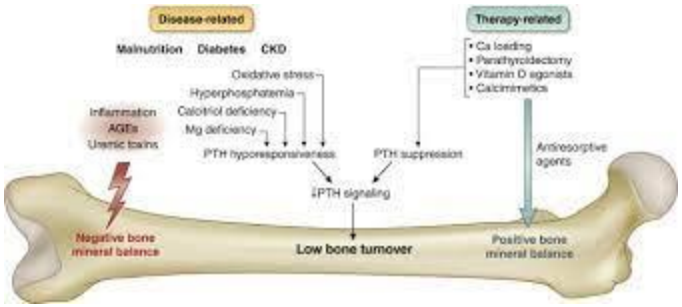


Adynamic bone disease

Characterized by reduced bone volume and mineralization and may result from excessive suppression of PTH production, chronic inflammation, or both

Adynamic bone disease

- Suppression of PTH can result from the use of vitamin D preparations or from excessive calcium exposure in the form of calcium-containing phosphate binders or high-calcium dialysis solutions



TREATMENT

The optimal management of secondary hyperparathyroidism and osteitis fibrosa is prevention

- Low-phosphate diet
- Phosphate-binding agents.
- Calcitriol
- Calcimimetic agents

management of CKD–MBD

Because serum levels of PTH and FGF23 increase in response to phosphate loading, lowering serum phosphate and reducing phosphate loading is of primary importance for the management of CKD–MBD

management of CKD–MBD

- Targeted at lowering high serum phosphate and maintaining serum calcium
- Treatments of CKD-MBD should be based on serial assessments of phosphate ,calcium , and PTH levels

Management of Hyperphosphatemia

- As a first-line approach, dietary phosphorus control
- Restricting phosphorus in the diet to 800 to 1,200 mg per day is the key to controlling serum phosphorus

Control of Hyperphosphatemia

- The normal range for serum phosphorus is 2.7 to 4.6 mg/dL (0.9–1.5mmol/L)
- In dialysis patients, the KDIGO bone guidelines recommend attempting to maintain predialysis phosphorus in the normal range

Source:	Plant	Animal	Inorganic Additives
Common Foods:	Grains Legumes Nuts	Meat Cheese Fish	Soda Prepared Foods Canned Foods
Bioavailability:	30-50%	60-90%	**90-100%**

Management of Hyperphosphatemia

- Phosphorus can be further managed through dialysis treatment and the use of drugs that include phosphate binders, active/analog vitamin D, and calcimimetics

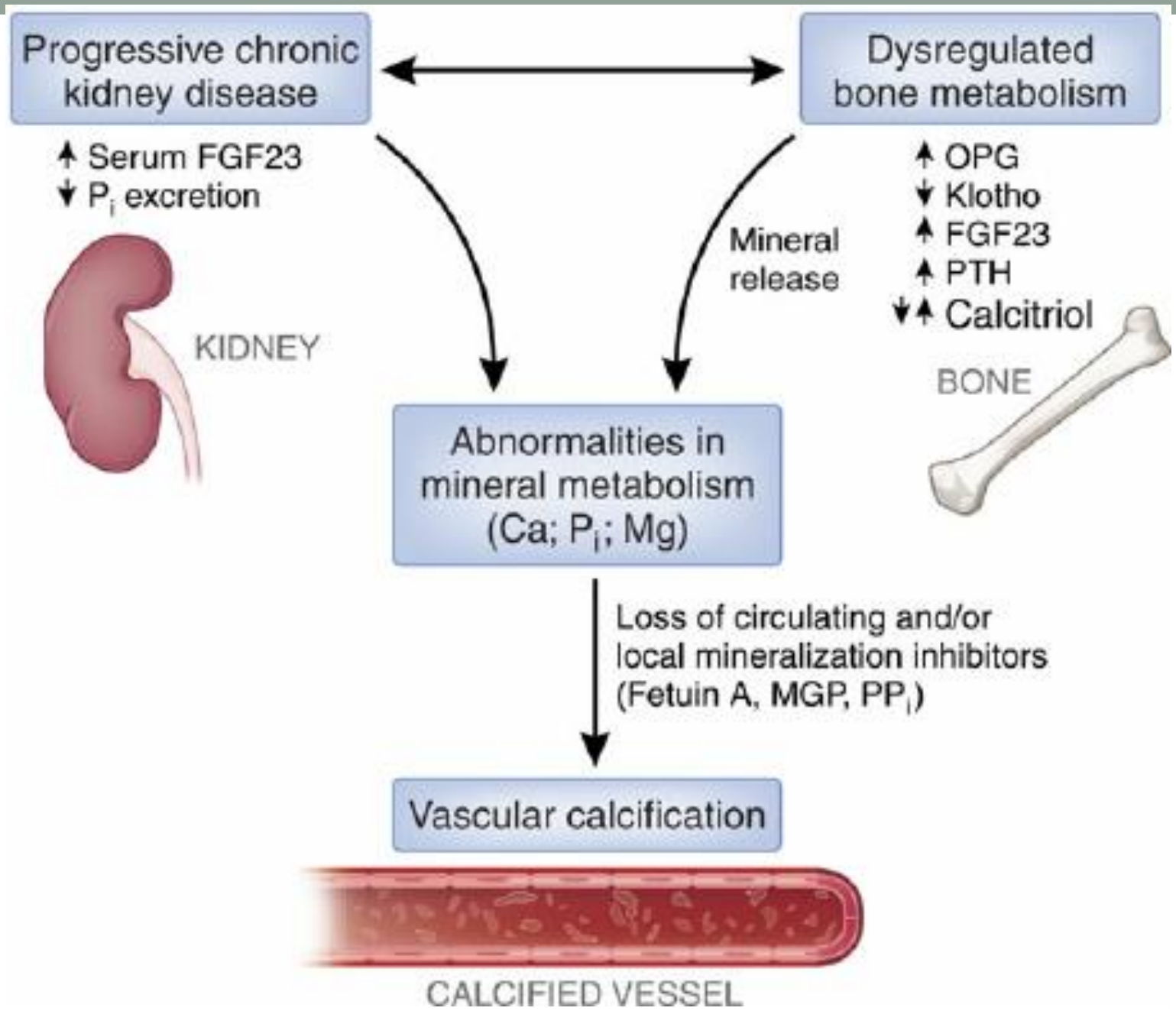
Management of Hyperphosphatemia

In patients with CKD G3a–G5D

- Lowering elevated phosphate levels toward the normal range
- Avoiding hypercalcemia
- Restricting the dose of calcium-based phosphate binders

The pathogenesis and mechanisms of VC in CKD

- VC is associated with increased cardiovascular morbidity and mortality
- In CKD, calcification inducers such as phosphate and calcium loading are accumulated, while calcifcation inhibitors such as fetuin-A, pyrophosphate, and magnesium in the circulation are decreased


Progressive chronic kidney disease
Dysregulated bone metabolism
↑ Serum FGF23
↓ P_i excretion
KIDNEY
Mineral release
↑ OPG
↓ Klotho
↑ FGF23
↑ PTH
↓↑ Calcitriol
BONE
Abnormalities in mineral metabolism (Ca; P_i; Mg)
Loss of circulating and/or local mineralization inhibitors (Fetuin A, MGP, PP_i)
Vascular calcification
CALCIFIED VESSEL

Diagnosis of calcification

In patients with CKD G3a–G5D

- Lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification
- An echocardiogram can be used to detect the presence or absence of valvular calcification

Conventional Approach

- Dietary intervention
- Phosphate binders
- Active/analog vitamin D
- Calcimimetics

All 3 key labs should be taken into account before making changes to the treatment plan, and first-line drug treatment may include a combination of phosphate binders, vitamin D, and calcimimetics.

2017 KDIGO Guide for Key CKD-MBD Labs	
Lab	**Goal**
Calcium	Avoid hypercalcemia
Phosphorus	Reduce toward the normal range
PTH	2x – 9x the upper limit of normal

Treatment of abnormal PTH levels in CKD-MBD

In patients with CKD G3a–G5 not on dialysis

- The optimal PTH level is not known
- Patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including:
  - Hyperphosphatemia
  - Hypocalcemia
  - High phosphate intake
  - Vitamin D deficiency

Treatment of abnormal PTH levels in CKD-MBD

In adult patients with CKD G3a–G5 not on dialysis

- Calcitriol and vitamin D analogs not be routinely used
- It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism

Treatment of abnormal PTH levels in CKD-MBD

In patients with CKD G5D

- Maintaining iPTH levels in the range of approximately 2 to 9 times the upper normal
- Calcimimetics , calcitriol , or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs
- Severe hyperparathyroidism (HPT) who fail to respond to medical or pharmacological therapy ⇒ parathyroidectomy

Phosphate Binders

- Phosphate binders are designed to be taken with meals to reduce the amount of phosphorus available for absorption in the GI tract
- Phosphate binders should be used in combination with diet and calcimimetics to control phosphorus from all sources

Phosphorus binders

Phosphorus binders in two broad categories:

- Those that contain calcium (calcium carbonate and calcium acetate)
- Those that do not (sevelamer, lanthanum, magnesium carbonate ,sucroferric oxyhydroxide, ferric citrate, and aluminum-containing compounds)

Comparison of Common Phosphate Binding Oral Agents in CKD

Phosphate Binder	Pros	Cons
Calcium-based: calcium acetate calcium carbonate calcium citrate	• Increases calcium and can correct hypocalcemia • Low cost • Moderate pill burden	• Hypercalcemia and/or positive calcium balance • Cardiovascular calcification
Sevelamer-based: sevelamer carbonate sevelamer hydrochloride	• No systemic absorption • Potentially less vascular calcification (calcium-free) • Lowers LDL cholesterol • Improvement in metabolic acidosis with carbonate variant	• Adverse GI effects • High pill burden • High cost • Binds fat-soluble vitamins • Metabolic acidosis with the hydrochloride variant
Iron-based: sucroferric oxyhydroxide	• Lower pill burden • Minimal systemic absorption, no iron overload • Greater efficacy • Increased GI motility which might be beneficial in constipated and PD patients	• High cost
Iron-based: ferric citrate	• Noninferior to sevelamer, well tolerated, beneficial effect on renal anemia	• Systemic absorption with potential for iron overload
Lanthanum carbonate	• Twice as potent as calcium and sevelamer	• High cost • Systemic absorption and potential tissue deposition/toxicity • GI intolerance, nausea • Difficult to chew

Aluminum hydroxide

- Aluminum hydroxide, the first phosphate binder used on mass scale, has a high ionic binding affinity, low pill burden, and is relatively inexpensive
- The potential for serious toxicity limits it use

Calcium-based binders

They are some of the most commonly used binders and available as generic/over-the-counter formulations (e.g., calcium carbonate),can improve hypocalcemia but also can contribute to increased calcium loading (hypercalcemia), a risk factor for CV calcification and mortality

Iron-based agent

- Improve anemia but can result in iron overload and associated toxicity
- Sucroferric oxyhydroxide also tends to have a favorable side effect profile on the GI system and is one of the most efficacious binders currently on the market

Sevelamer

- Resin-based ion exchange binders (e.g., sevelamer) have no systemic absorption, can lower cholesterol, and have beneficial effects on vascular calcification
- Sevelamer can have adverse GI effects with a high pill burden and binds to fat-soluble vitamins, thereby reducing its bioavailability

Lanthanum carbonate

- Non-calcium-based binder
- High phosphate-binding affinity
- Low pill burden
- Expensive
- Can produce adverse GI effects
- Has uncertain long-term effects on the liver and nervous tissues because of systemic absorption and is difficult to chew

Comparison of Phosphorus Removal Between Dialysis Modalities

Modality	Frequency	Phosphorus Removal (mg/wk)
Conventional HD	3 × 4 h	1,572 ± 366
Extended HD	3 × 5 h	3,400 ± 647
Short daily HD	6 × 3 h	2,452 ± 720
Nocturnal daily HD	6 × 6-8 h	8,000 ± 2,800
CAPD	24.0 h*	2,790 ± 1,022
APD, CCPD	18.5 ± 7.3 h*	2,739 ± 1,042

Vitamin D

- Abnormal vitamin D metabolism plays a key role in the development of SHPT
- Low levels of vitamin D are common in patients with CKD
  - ✓Poor nutrition
  - ✓Limited sun exposure
  - ✓Reduced ability of the kidney to convert vitamin D into its biologically active form

Vitamin D

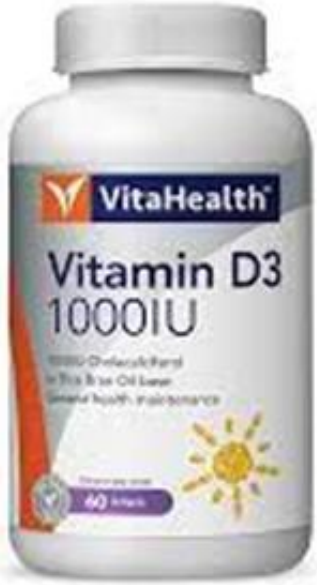
Vitamin D regulates PTH:

- Directly by binding to the vitamin D receptor in the parathyroid gland to suppress synthesis of PTH
- Indirectly by increasing calcium absorption from the gut

Different forms of vitamin D

Calcitriol , paricalcitol , and doxercalciferol

- ✓Decreasing PTH
- ✓Hypercalcemia
- ✓Hyperphosphatemia



Calcimimetics

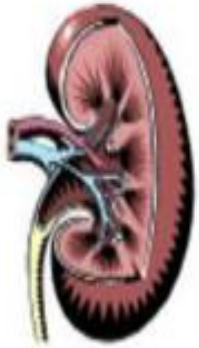
- Calcimimetics activate the calcium-sensing receptor to inhibit calcium-regulated PTH secretion, effectively mimicking or potentiating the effects of extracellular calcium calcimimetics also decrease bone resorption and thus decrease the contribution of serum phosphorus from bone

Table 3. Effect of Various Classes of Drugs on Key CKD-MBD Biomarkers

Class of Drugs	Calcium	Phosphorus	PTH	FGF-23
Phosphate binders	–/↑*	↓	↓	↑↓†
Active/analog vitamin D	↑	↑	↓	↑
Calcimimetics	↓	↓	↓	↓

Calcimimetics

- Calcimimetics offer minimal (cinacalcet) to no (etelcalcetide) pill burden.
- Etelcalcetide shows some advantages over cinacalcet, including a stronger efficacy profile, longer half-life, and intravenous mode of administration
- Potential limitations of calcimimetics include hypocalcemia and nausea/vomiting



	KIDNEY	GUT	BONE
Source of High Phosphorus	Loss of kidney function and impaired renal excretion of phosphorus	Dietary phosphorus absorption	Bone resorption releases stored phosphorus
Treatments and Limitations	Regular dialysis: Dialyzer removes phosphorus from the blood ▪ Dialysis removal not sufficient to reach target range	Dietary changes: Reduce intake of phosphorus and phosphate additives ▪ Increased protein requirement necessitates dietary phosphorus Phosphate binders: Reduce phosphorus absorption ▪ High pill burden and adverse GI effects	Vitamin D: Increases calcium and suppresses PTH ▪ Can increase phosphorus absorption from gut Calcimimetics: Suppress PTH-induced bone turnover and phosphorus release ▪ Possible hypocalcemia and GI symptoms

kidney transplant

In patients in the first 12 months after kidney transplant with GFR>30 ml/min/1.73 m2 and low BMD:

- Treatment with vitamin D, calcitriol/alfacalcidol
- Treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D
- There are insufficient data to guide treatment after the first 12 months


THANK you
HEALTH HISTORY FORM 2
Symptoms/ Illness
YES, Explain
NO