WELCOME TO SYMPOSIA ON KIDNEY DISEASES

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

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OUTLINE

- BASIC -CONCEPTS ON CKD-MBD
- RECENT RECOMANDATION BY KDIGO GUIDELINE 2017

BITID is the National Institute of Tropical & Infectious Diseases FOUZDERHAT,CHITTAGONG

Chronic Kidney Disease (CKD)

- CKD is characterized by the progressive loss of the kidneys' ability to remove waste and maintain fluid and chemical balance in the body
- A CKD diagnosis is made when:

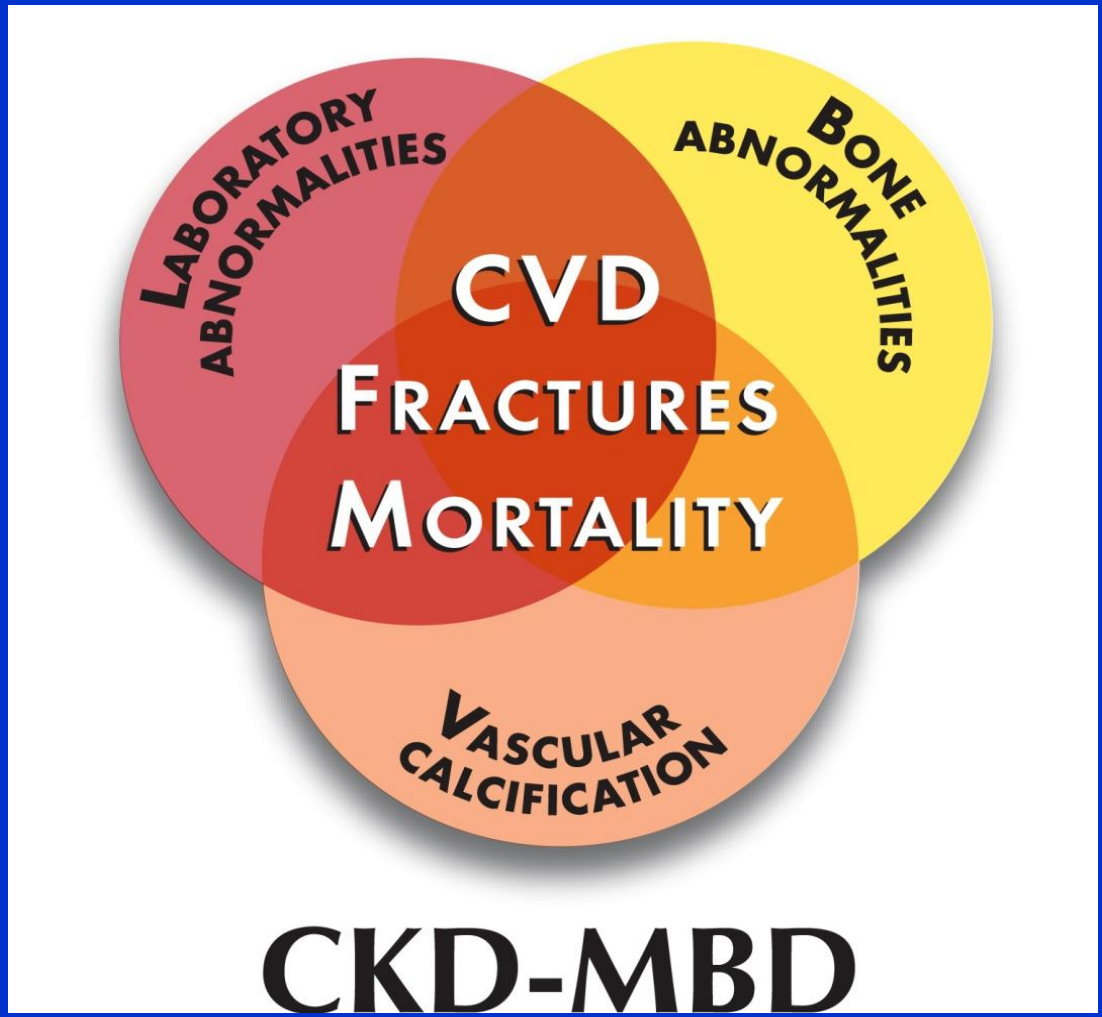
  - Kidney damage is present for >3 months, with or without decreased glomerular filtration rate (GFR), manifested by either
    - ⇨ Pathologic abnormalities, or
    - ⇨ Markers of kidney damage, including abnormalities in blood, urine or imaging tests
  - A GFR level of <60 mL/min/1.73m2 persists for >3 months, with or without kidney damage

Issues of CKD

1) Hypertension
2) Anaemia
3) CKD- Mineral & bone disorder
4) Electrolyte imbalance
5) Nutrition
6) Medication Related

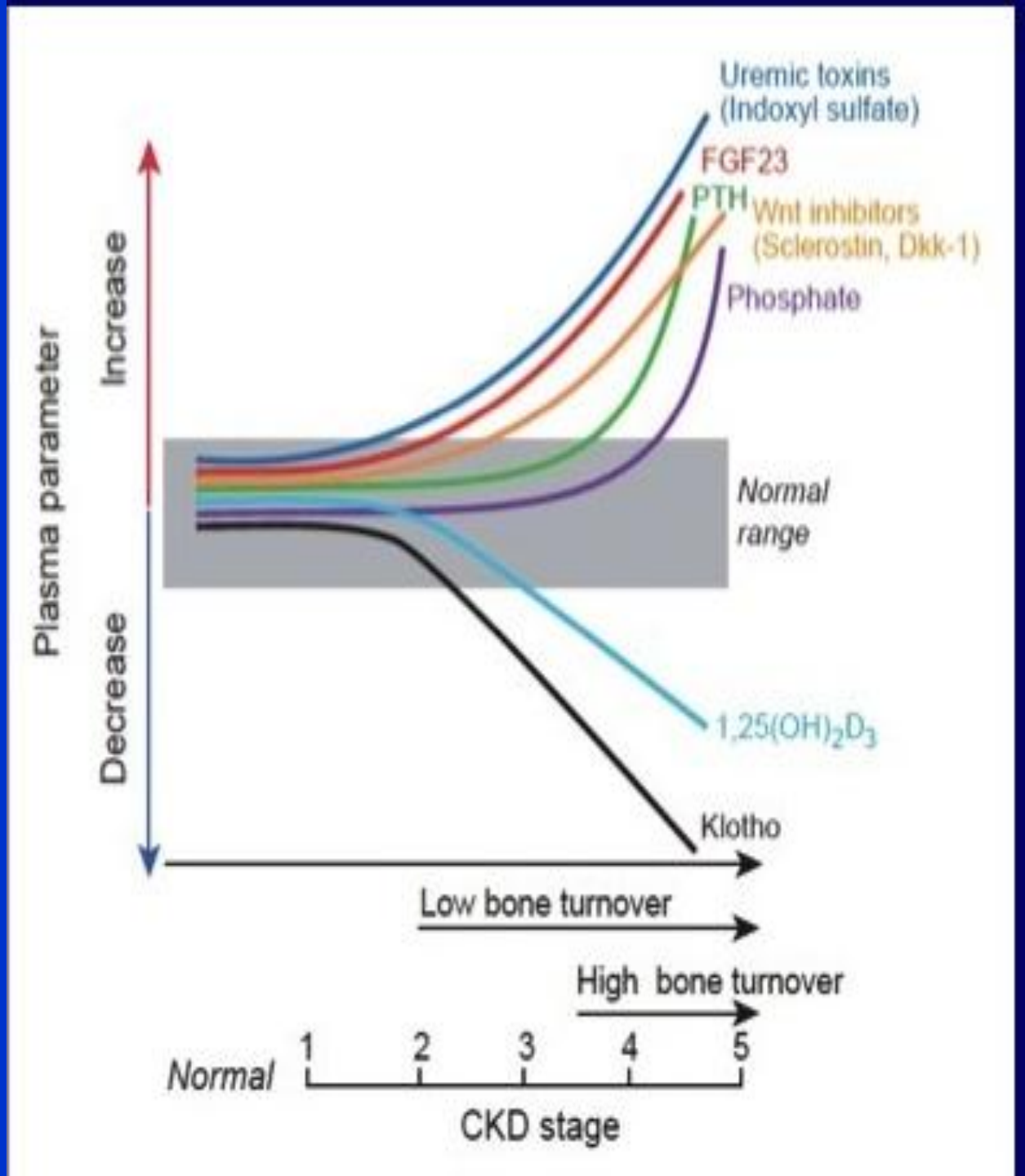
Chronic Kidney Disease – Mineral Bone Disorder (CKD – MBD)

- A systemic disorder of bone and mineral 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**



Abnormalities of MBD in CKD

- Reduced calcium
- Increased phosphorus
- Increased PTH
- Reduced calcitriol
- Increased FGF-23

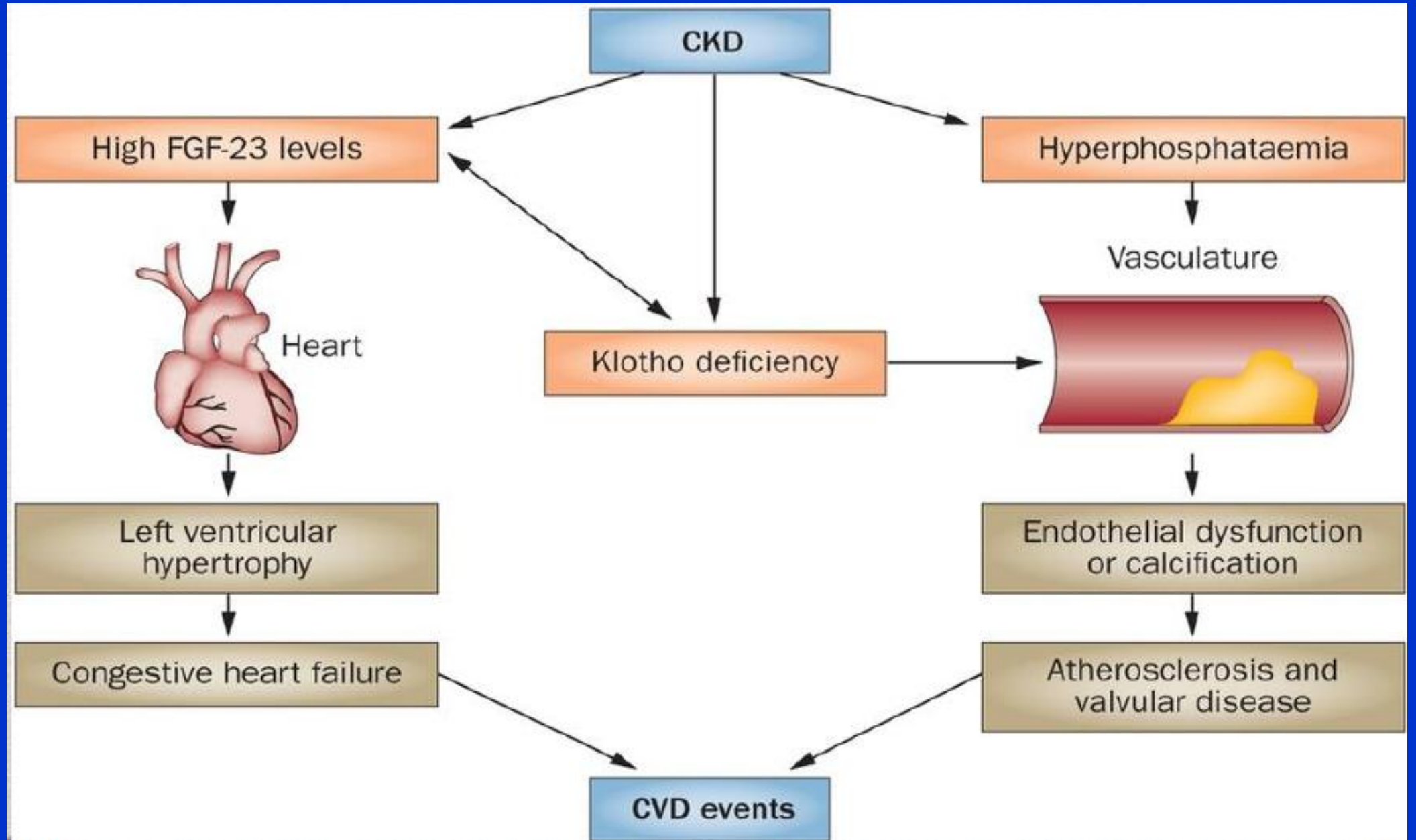


Novel CKD-BMD biomarkers

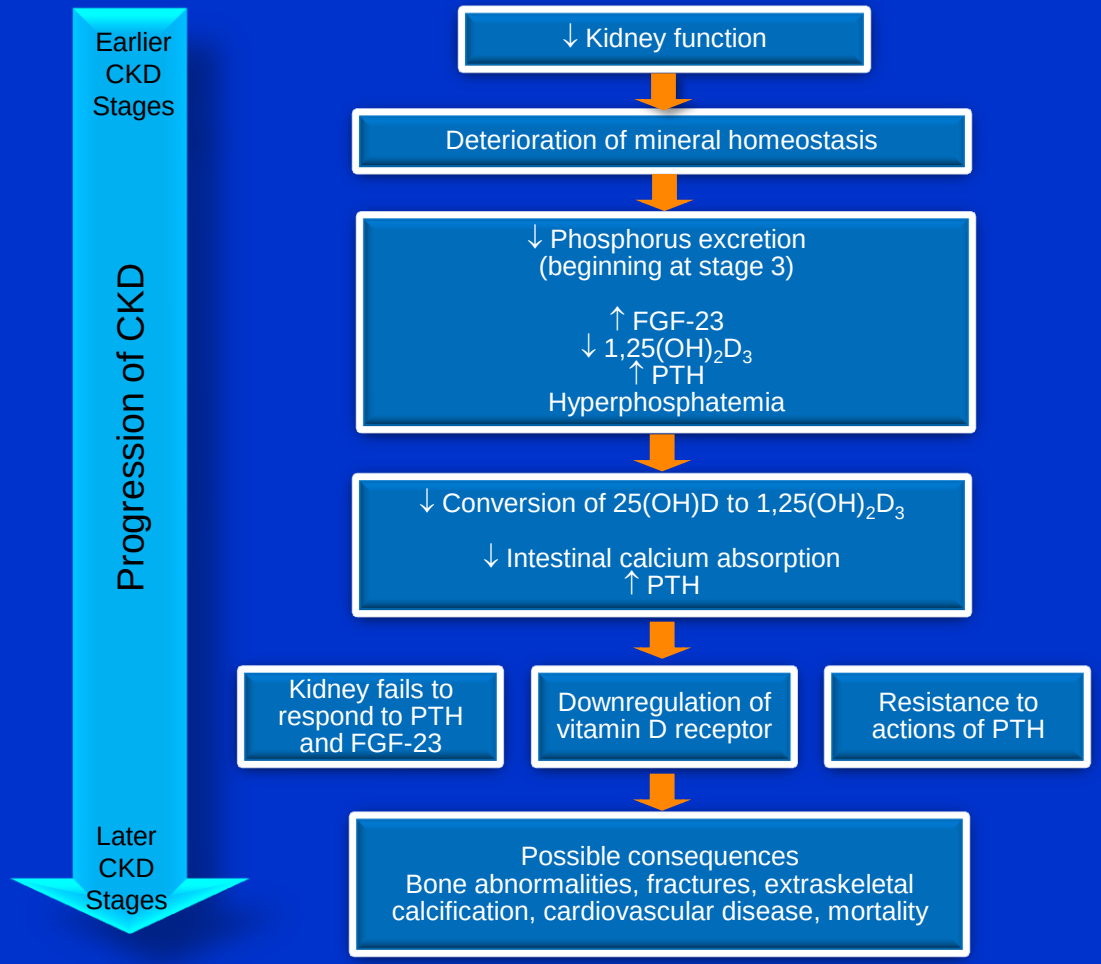
Emerging CKD-MBD biomarkers show various associations with regard to CKD-progression, cardiovascular events and death in patients with CKD

Promoter of calcification in CKD	Inhibitors of Calcification in CKD	Other/Risk Factor of CKD progression
Osteoprotegerin	Matrix-Gla protein	FGF-23
	Fetuin-A	Klotho
	Osteopontin	

Pathogenesis

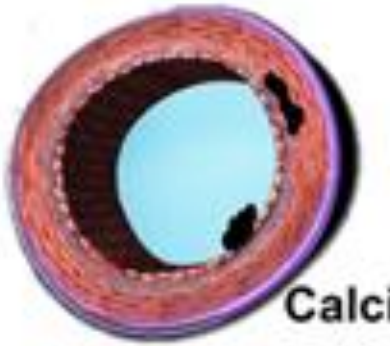


CKD-MBD: Dysregulation and Clinical Manifestations of an Increasingly Compromised System



FGF-23 = fibroblast growth factor-23; PTH = parathyroid hormone; $1,25(OH)_2D_3$ = 1,25-dihydroxyvitamin D_3; 25(OH)D = 25 hydroxyvitamin D KDIGO CKD-MBD Work Group. *Best Practices in CKD-MBD: A Focus on Phosphorus.* New York, NY: KDIGO; 2009.

Chronic Kidney Disease-Mineral Bone Disorder



Calcification

Mineral and hormonal disruption

Elevated
- FGF-23
- PTH
- Phosphorus

Decreased
- $1,25(OH)_2D_3$
- Calcium

Most associated with worsening outcomes

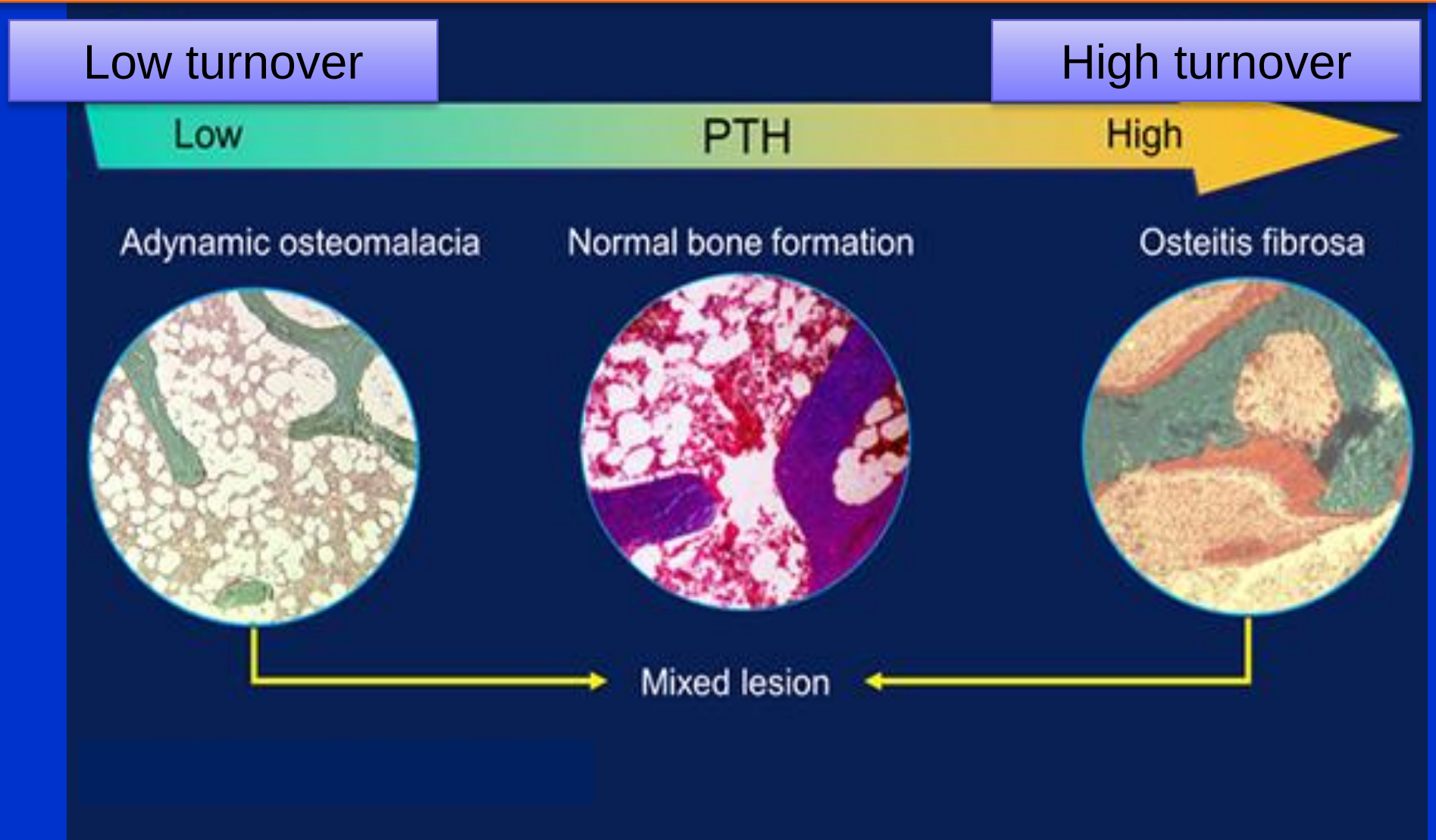
Bone disease
- Turnover
- Mineralization
- Volume
- Linear growth
- Strength
- Increased fractures

Vascular and soft-tissue calcification
- Increased pulse pressure
- Increased pulse wave velocity
- Increased coronary calcium score
- Increased mortality

Definition of Renal Osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletalcomponent of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy

Role of PTH in Development and progression of Renal Osteodystrophy



Renal Osteodystrophy Bone Disorders

Lesion	Turnover	Mineralization	Volume
Osteomalacia	↓	Abnormal	↓/Normal
ABD	↓	Normal	↓/Normal
Osteitis fibrosa	↑	Abnormal	Normal/↑
MUO	↑	Abnormal	Normal

Abbreviations: ABD, adynamic bone disease; MUO, mixed uremic osteodystrophy.

Consequences of Hyperphosphatemia

- Secondary Hyperparathyroidism
- Soft tissue Calcification
- Cardiovascular Calcification
- Increase risk of Death

Skin	Lung
Calciphylaxis	P. Fibrosis
	P. Hypertension
	RVH
	Rt sided congestive heart failure

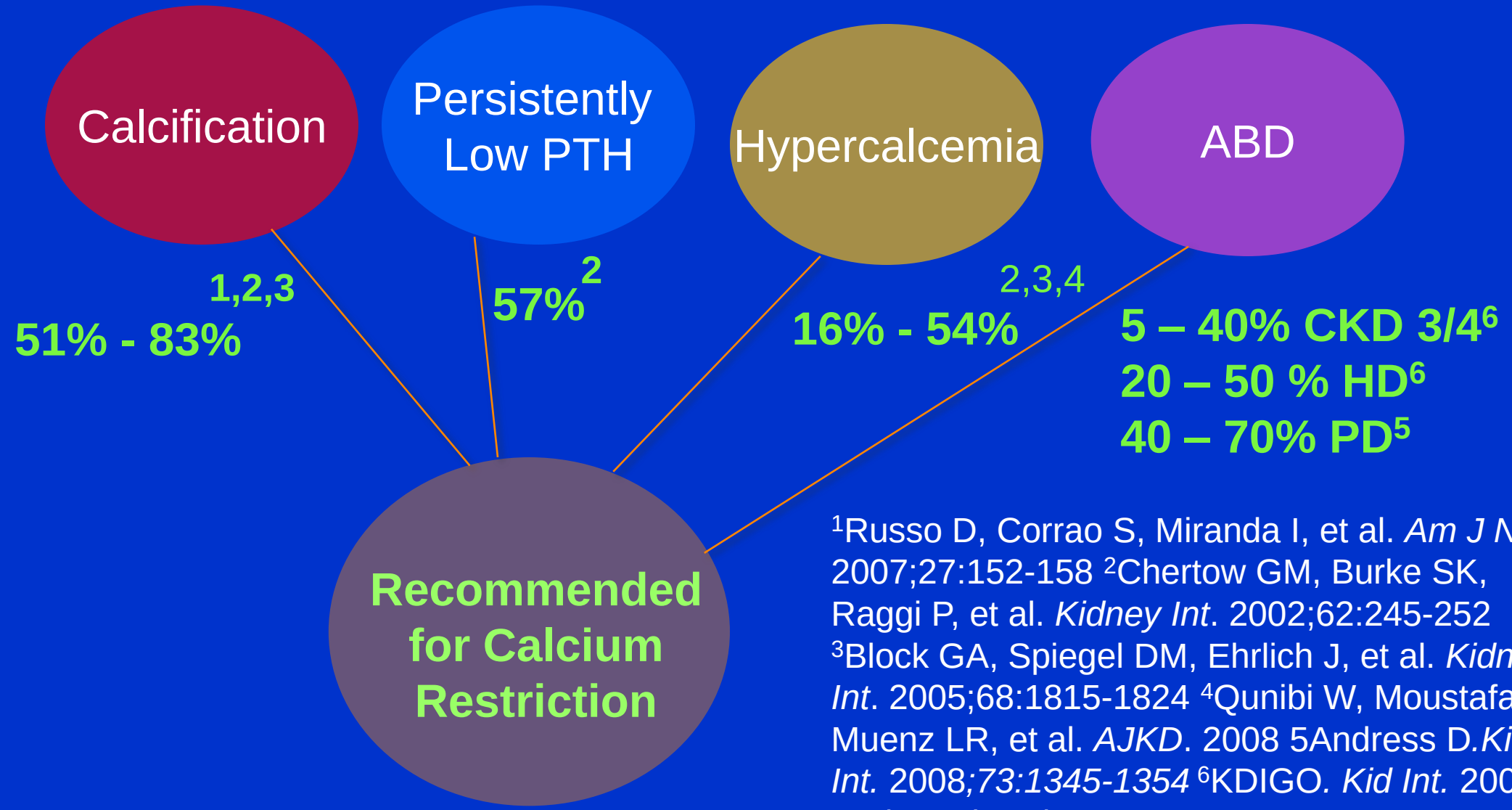
Arrhythmia	Regurgitation
Conduction abnormalities	Myocardial Ischemia
Left ventricular dysfunction	Congestive Heart Failure
Stenosis of heart valve	Death

Potential Risk of Excess Calcium

- Calcium excess may lead to vascular and soft-tissue calcification

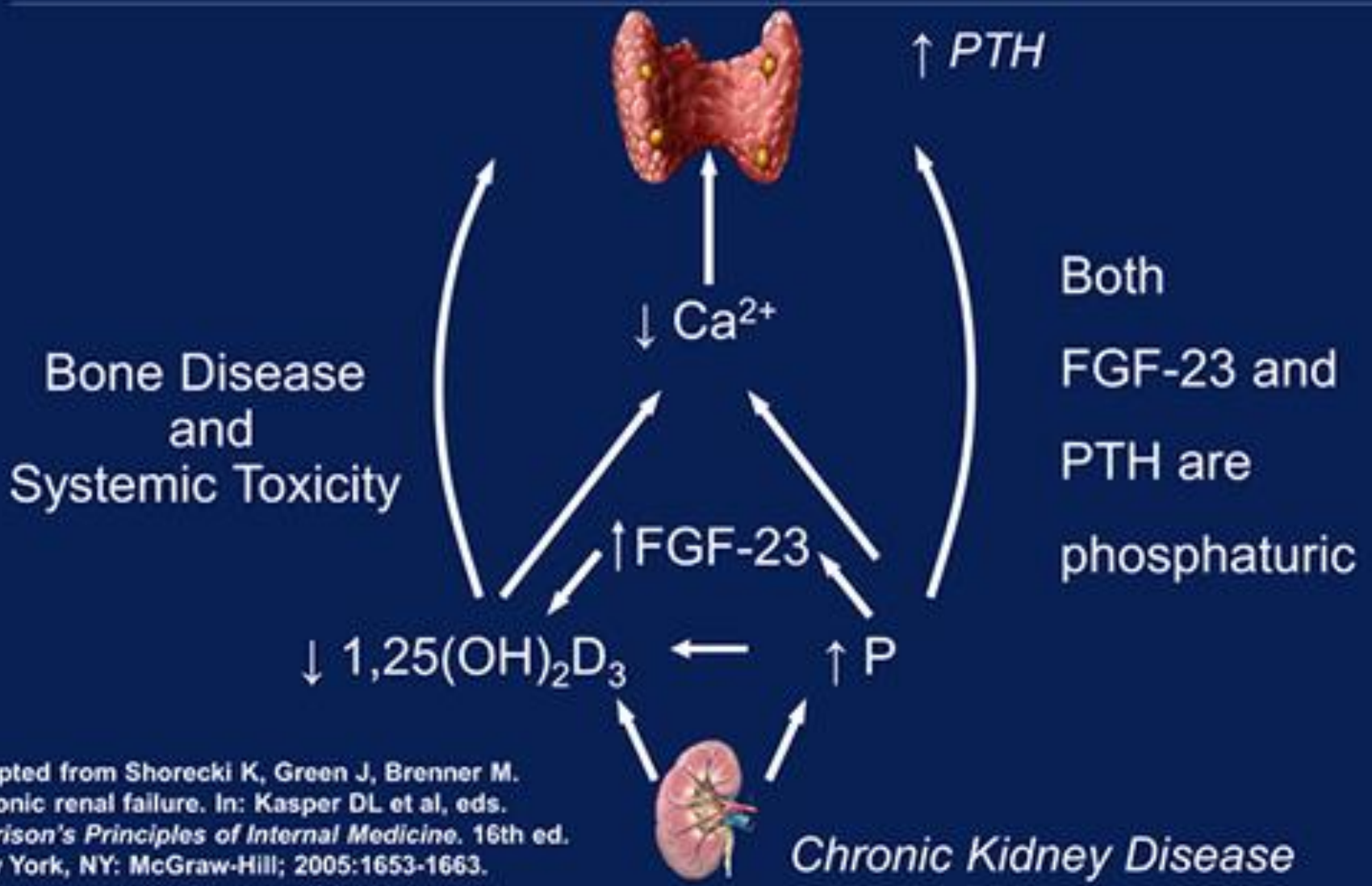
- In general population, mounting evidence linking supplemental calcium intake to vascular events

Patients In Whom it is Recommended Calcium Be Restricted



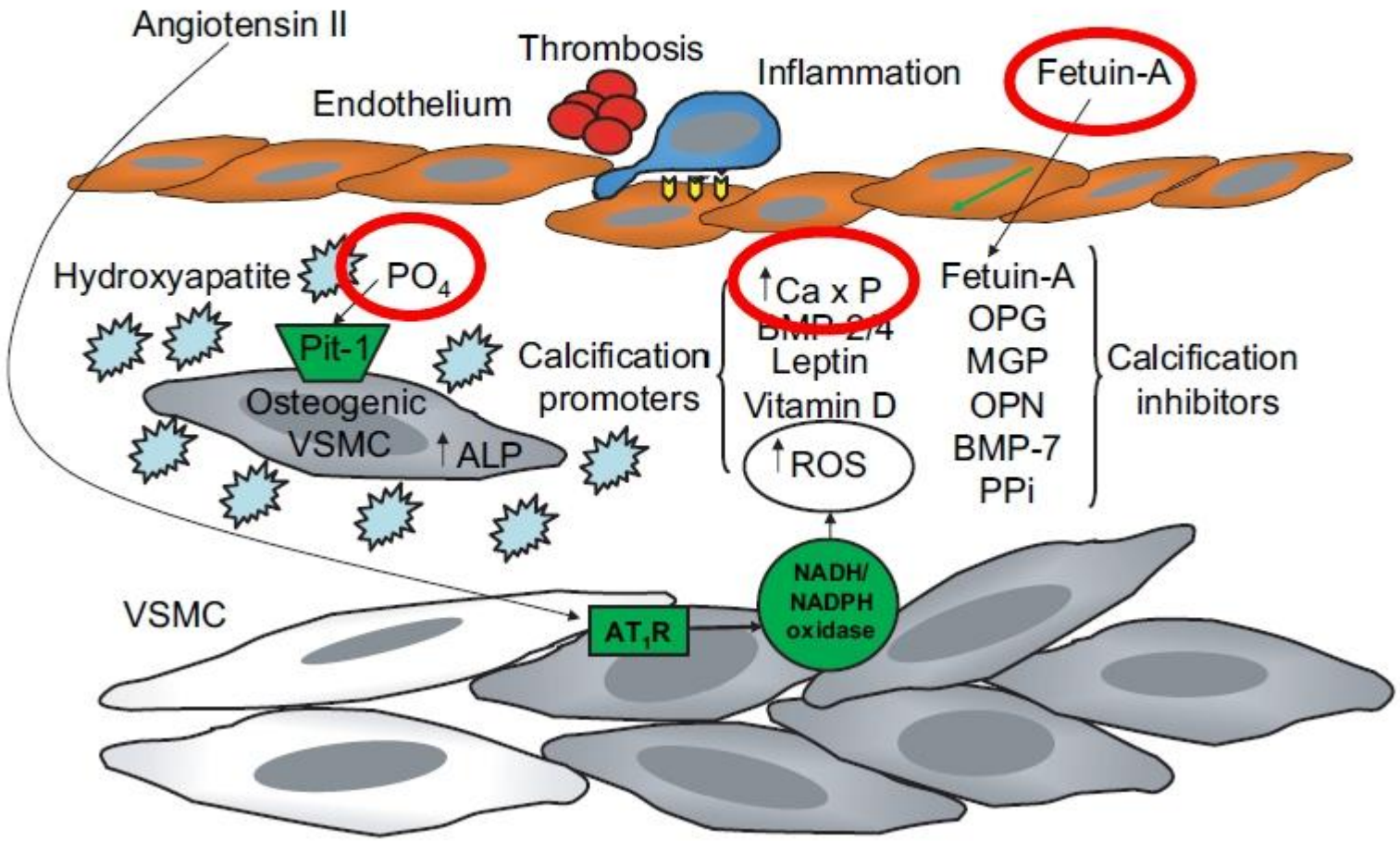
[1]Russo D, Corrao S, Miranda I, et al. *Am J Neph* 2007;27:152-158 [2]Chertow GM, Burke SK, Raggi P, et al. *Kidney Int*. 2002;62:245-252 [3]Block GA, Spiegel DM, Ehrlich J, et al. *Kidney Int*. 2005;68:1815-1824 [4]Qunibi W, Moustafa M, Muenz LR, et al. *AJKD*. 2008 5Andress D.*Kid Int. 2008;73:1345-1354* [6]KDIGO. *Kid Int.* 2009; 76 (Suppl 113):S1-S130

Pathophysiology of Secondary Hyperparathyroidism



Adapted from Shorecki K, Green J, Brenner M. Chronic renal failure. In: Kasper DL et al, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York, NY: McGraw-Hill; 2005:1653-1663.

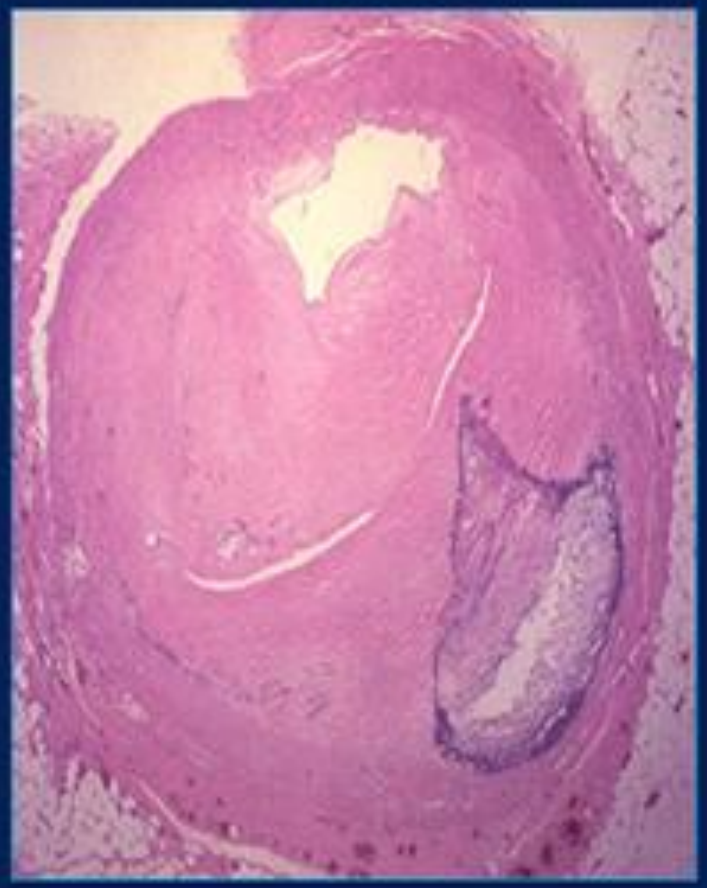
Mechanisms of Vascular Calcification in CKD



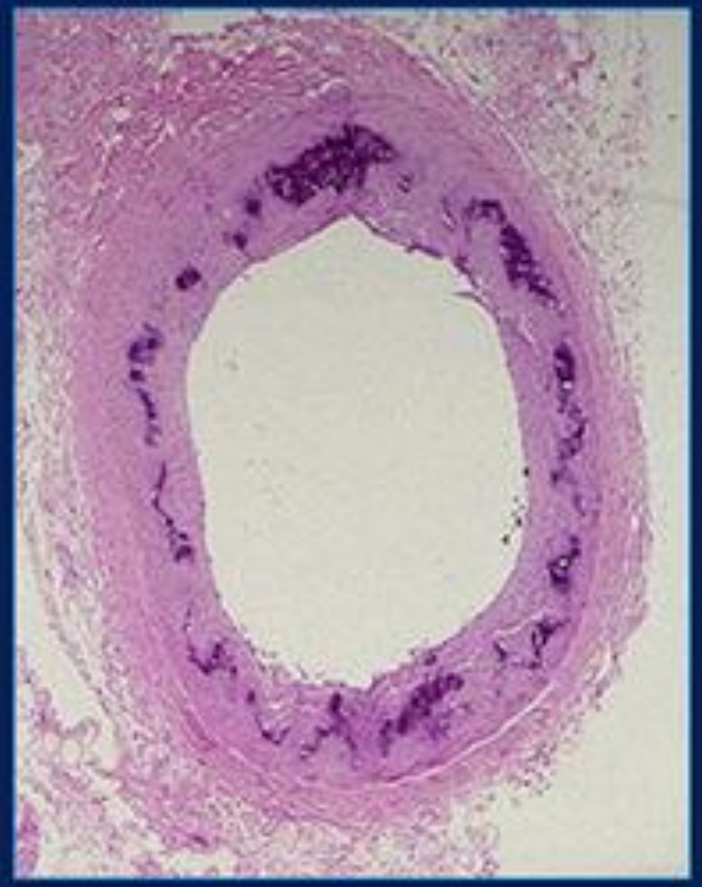
Schiffrin E et al. Circulation. 2007;116:85-97.

Vascular Calcification in CKD

Atherosclerotic
arterial intimal calcification



Mönckeberg
arterial medial calcification



CLINICAL PRESENTATION

Most with CKD and mildly elevated PTH are asymptomatic

When present classified as either

1. Musculoskeletal
2. Extra-skeletal

Musculoskeletal

- Fractures, tendon rupture and bone pain from metabolic bone disease, muscular pain and weakness.
- Most clinically significant is hip fracture, seen in CKD 53

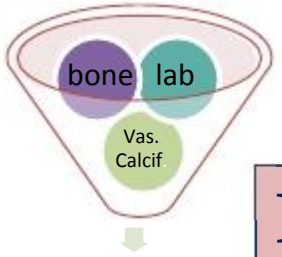
Extra-Skeletal

- Disordered bone and mineral metabolism is a system disorder affecting soft tissues, particularly vessels, heart valves and skin.
- May present with: LVH, cardiac fibrosis, extraskeletal calcification, peripheral neuropathy, importance
- CVD accounts for around half of all deaths of dialysis patients.

Diagnosis of MBD

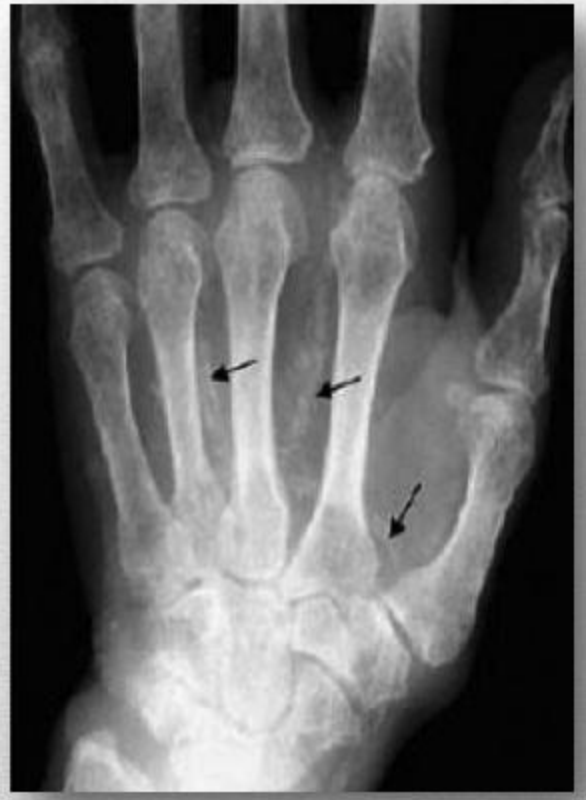
Laboratory
Calcium
Phosphorus
Alkaline phosphatase.
PTH
Vitamin D

CKD-MBD
The broad syndrome that develops as a systemic disorder of mineral and bone metabolism caused by CKD

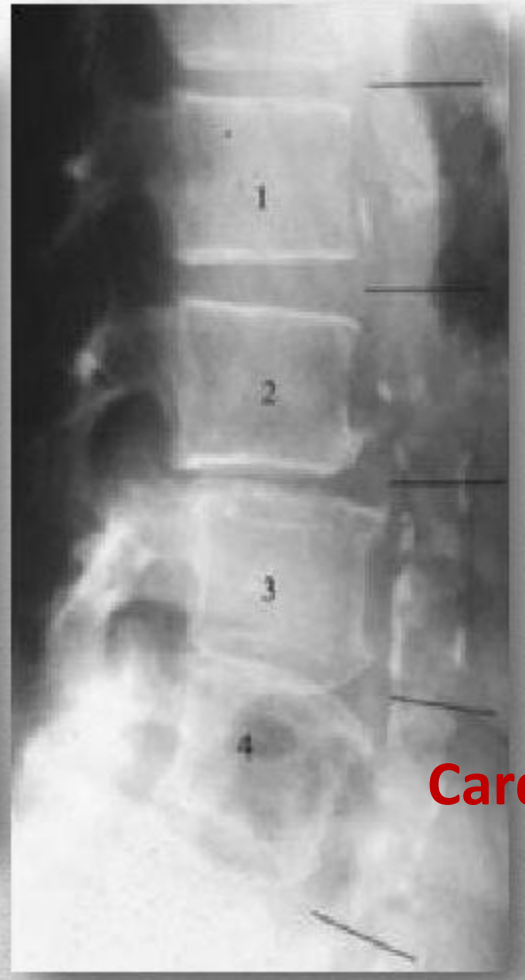


Calcification
X-ray
EBCT

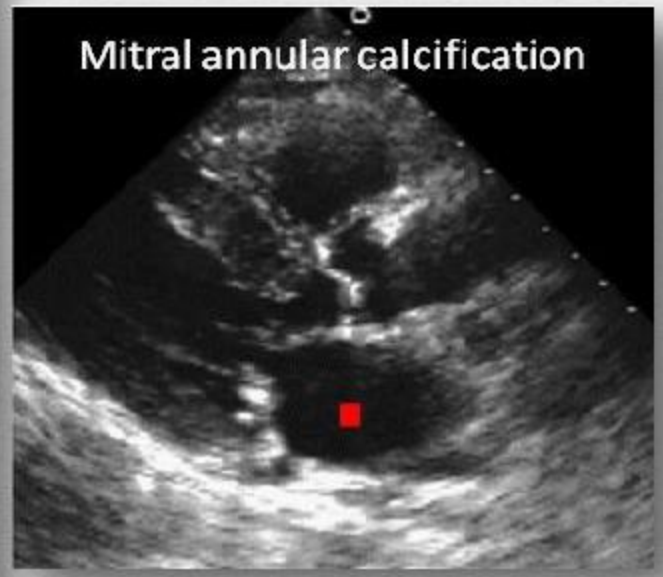
Renal Osteodysdrophy
Turnover
Mineralization
Volume
Linear Growth
Strength



Digital Arteries Calcification

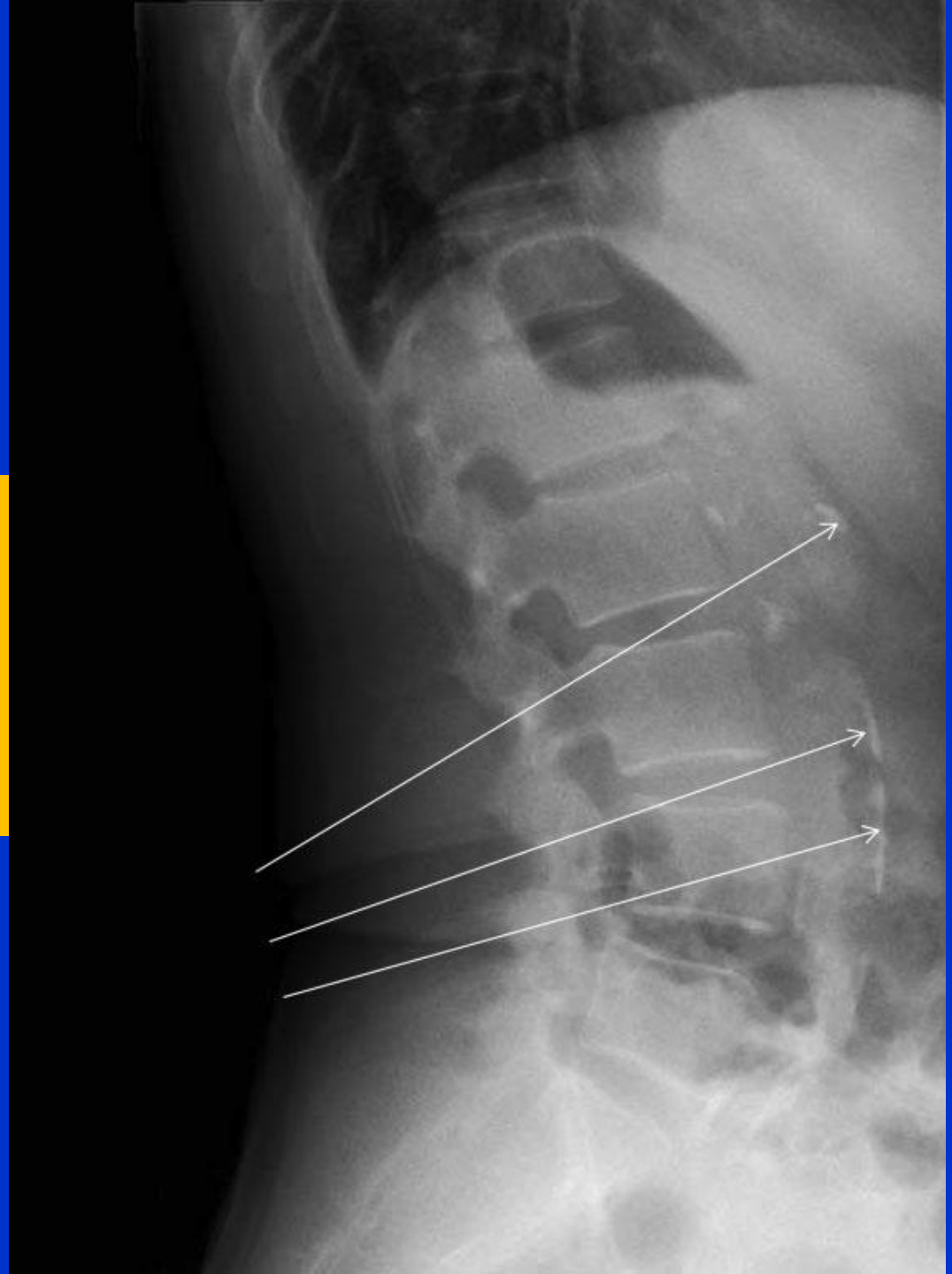


Aortic Calcifications

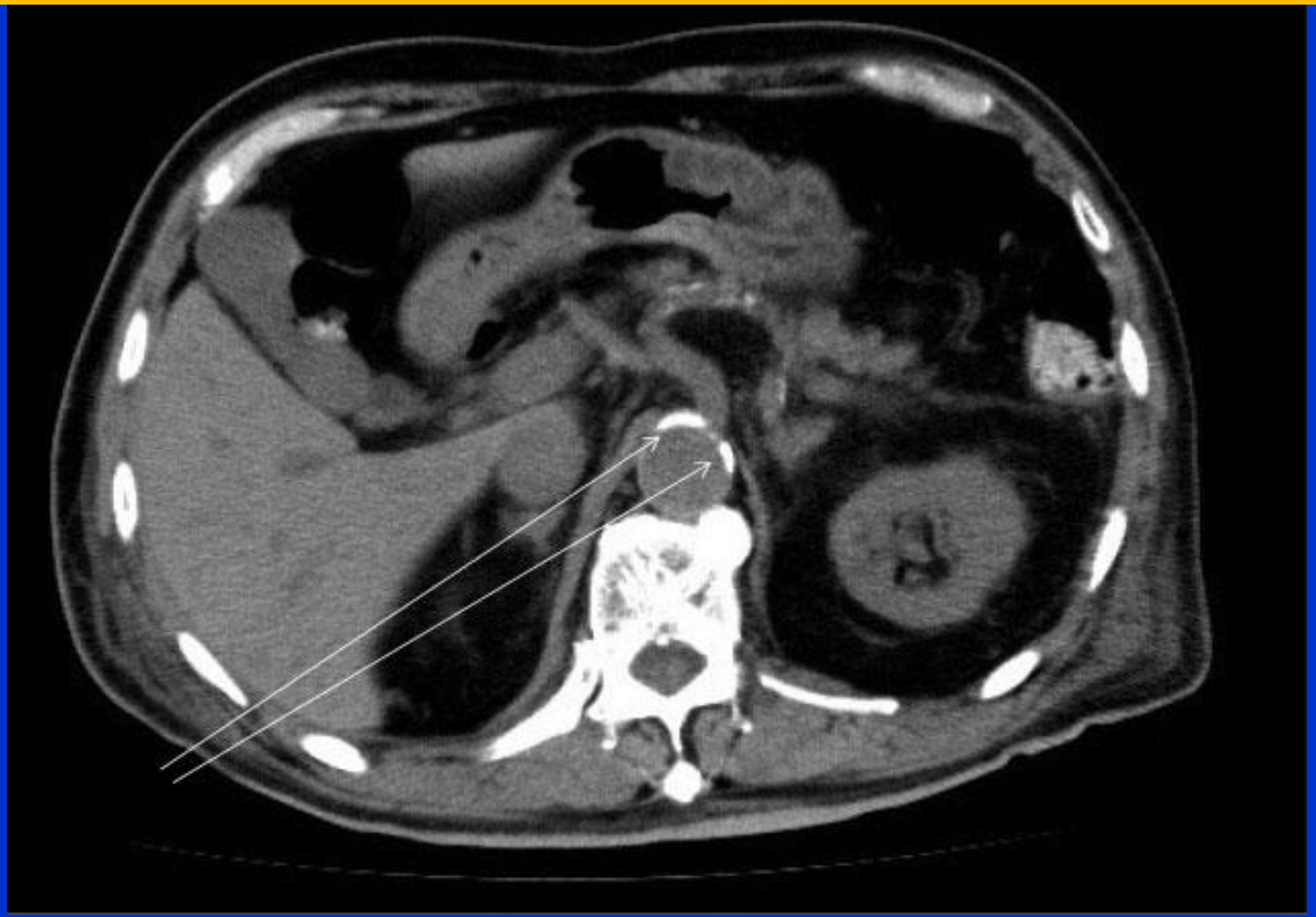


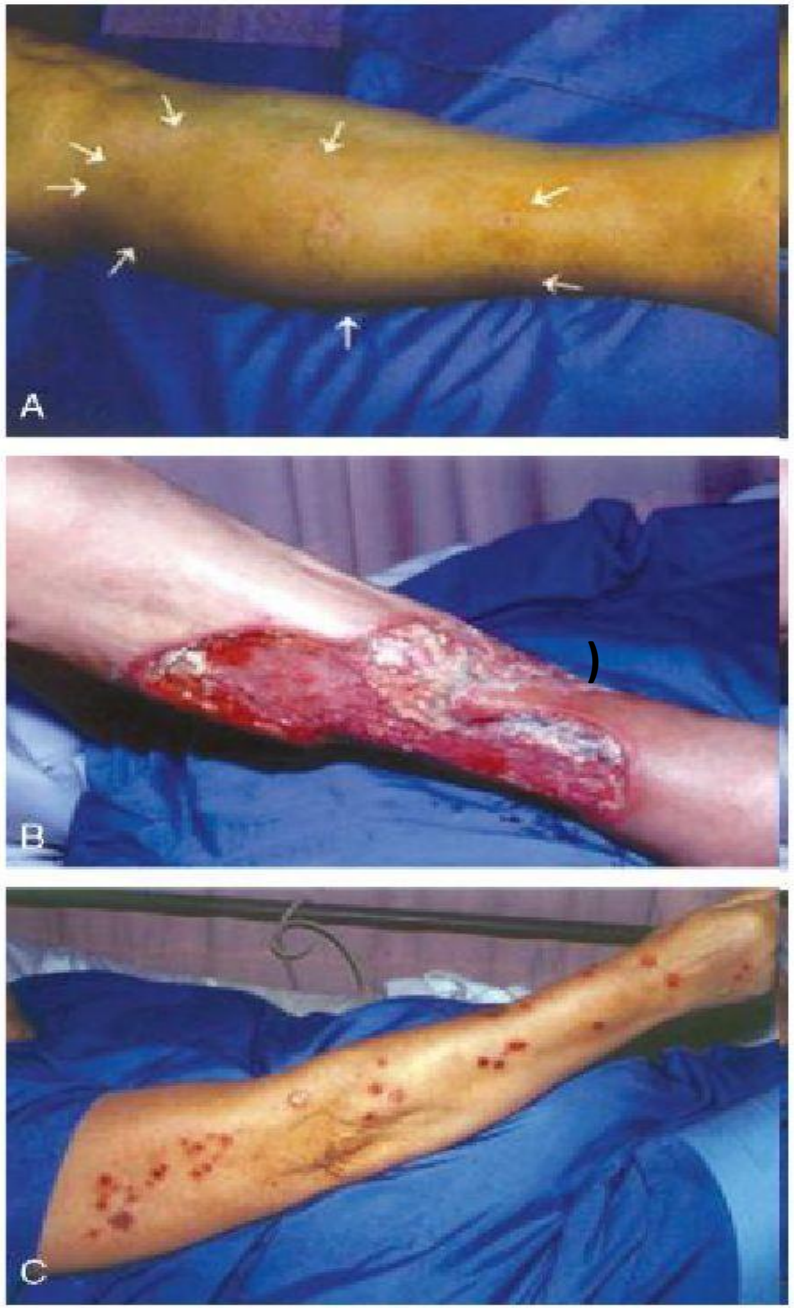
Cardiovascular calcification

Plain X-ray. The arrows show calcification show aortic calcification.



Abdominal computed tomography (CT). The arrows show aortic calcification.





Calciphylaxis(calcific uraemic arteriolopathy)

A, Confluent calf plaques (borders shown with arrows). Parts of the skin are erythematous, which is easily confused with simple cellulitis. B, Gross ulceration in the same patient 3 months later. The black Escher has been surgically debrided. C, calciphylactic plaques, a few of which are beginning to ulcerate.

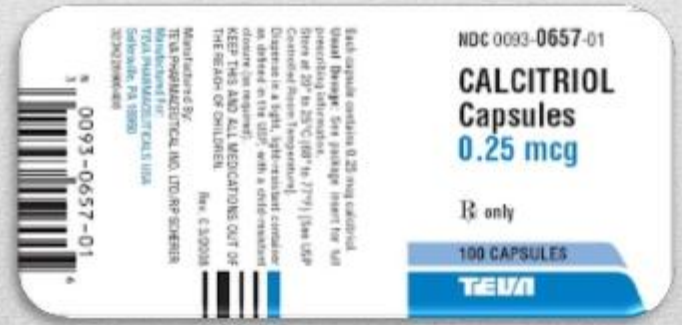
Treatment of CKD-MBD

- **A) Medical:**
  - Dietary phosphate restriction
  - Calcitriol or other Vit D analogues
  - Phosphate binders
  - Calcimimetics
- **B) Surgical:**
  - Parathyroidectomy

Treatment

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

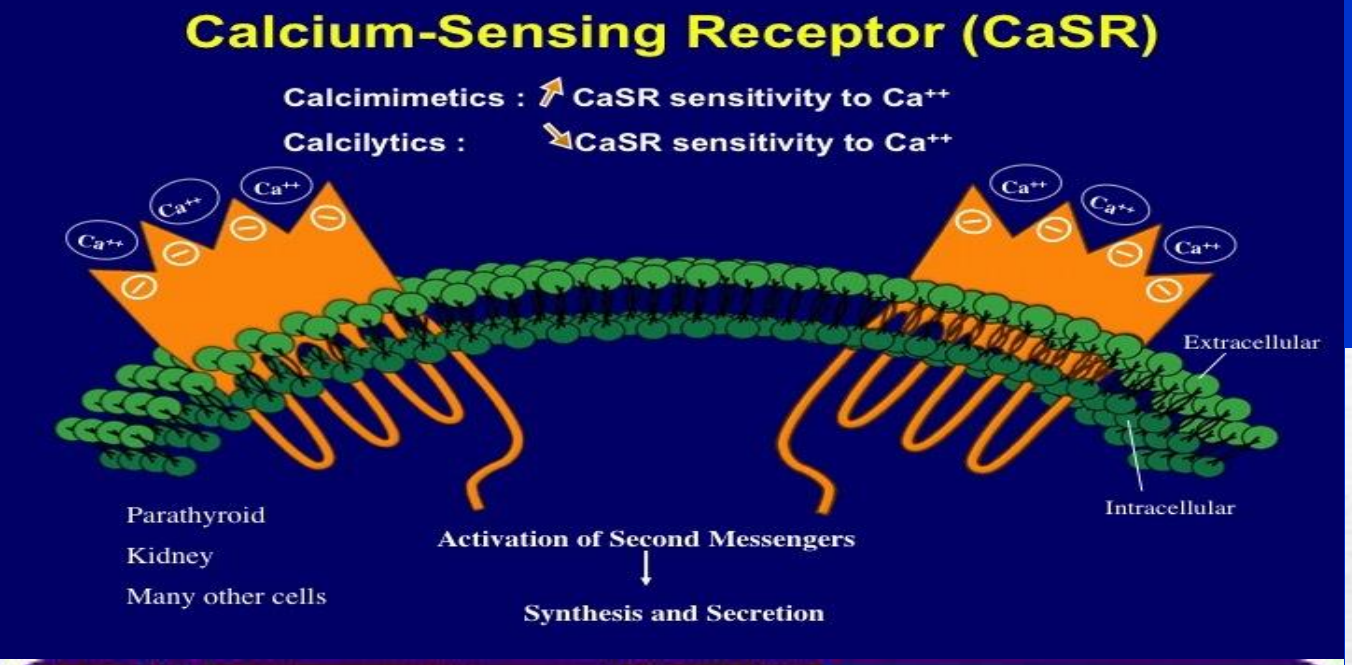
There is no convincing evidence, including the result from the one large, prospective, randomized comparative trial, supporting the use of a specific derivative of the six analogs currently available over another.

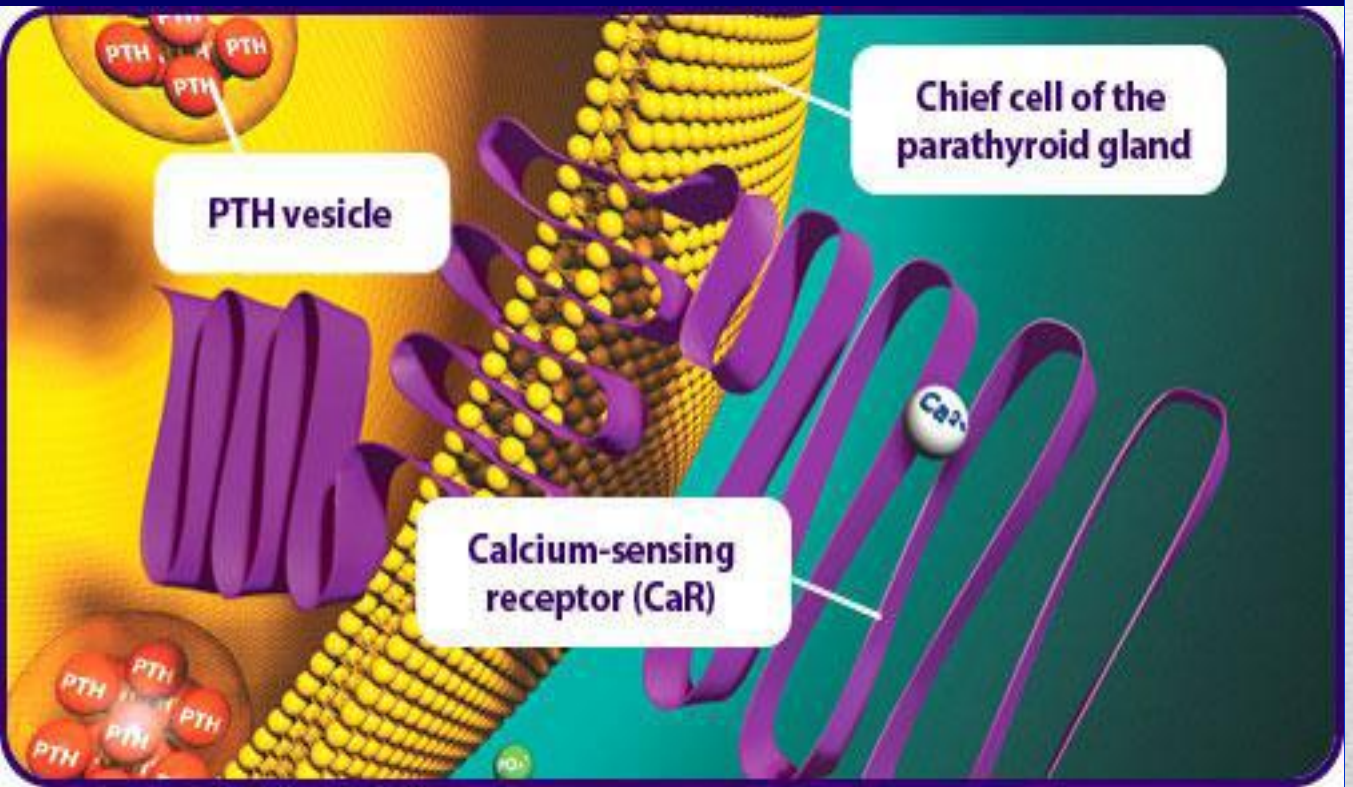


VITAMIN D STEROLS AND ANALOGS

Compound	Chemical Name	Source
Pro-vitamin D2	Ergosterol	Diet
Pro-vitamin D3	7-Dehydrocholesterol	Cholesterol
Vitamin D2 (Calciferol®, Drisdol®)	Ergocalciferol	UV light → ergosterol
Vitamin D3	Cholecalciferol	UV light → 7-dehydrocholesterol
Calcidiol	25(OH)-cholecalciferol; 25(OH)D3	25-OH'n → D3 (liver)
Calcitriol (Rocaltrol®)*	1,25$(OH)_2$-cholecalciferol; 1α-25$(OH)_2$-D3	1α-OH'n → 25(OH)D3 (kidney)
Doxercalciferol (Hectorol®)*	1α-(OH)D2	Synthetic D2 prohormone
Paricalcitol (Zemplar®)*	19-nor-1α-25$(OH)_2$-D2	Synthetic D2 analog

*Active vitamin D sterol





Treatment

3) Calcimimetics:

Pharmacotherapeutic Options for Management of hyperparathyroidism

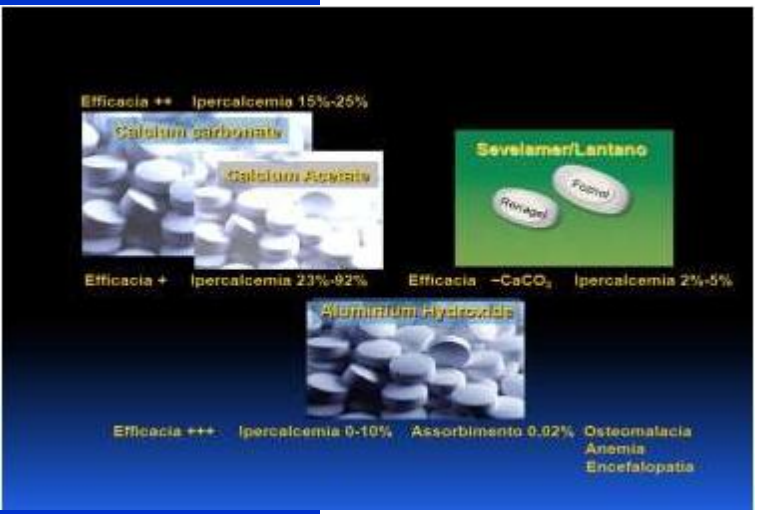
Drugs Based on 1,25(OH)2D3

- Increase calcium absorption
- Decrease PTH secretion

Calcimimetics

- Act through calcium-sensing receptor present in parathyroid gland
- Sensitize gland to the presence of calcium
- Direct action on PTH
- Does not increase calcium and phosphate absorption
- Decrease PTH in a pulsatile fashion
  - Where kidney function is present, this increases bone turnover markers

Phosphate binders



1)Calcium Based
- Calcium acetate
- Calcium Carbonate
- Calcium citrate
- Calcium Ketoglutarate
- Calcium Gluconate

2) Non Calcium Based
- Sevelamer Hcl
- Sevelamer carbonate
- Lanthanum Carbonate

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kidney INTERNATIONAL supplements

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m^2), description and range				Persistent albuminuria categories, description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

KDIGO Grading of Recommendations

Strength of Recommendation	Implications
Level 1	"We recommend …" "Most patients should receive the recommended course of action."
Level 2	"We suggest …" "Different choices will be appropriate for different patients."

Grade for Quality of Evidence	Quality of Evidence
A	High
B	Moderate
C	Low
D	Very Low

Not Graded

"The strength of a recommendation is determined not just by the quality of evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs."

KDIGO: Diagnosis of CKD-MBD Biochemical Abnormalities

Diagnosis of CKD-MBD:
Biochemical Abnormalities

- In the initial CKD stage[a], the recommendation is to monitor serum levels of:
  - Phosphorus
  - Calcium
  - PTH
  - Alkaline phosphatase
- In CKD stages 3-5D[b], frequency of monitoring serum calcium, phosphorus, and PTH should be based:
  - On the presence and magnitude of abnormalities
  - The rate of progression of CKD
- In children[c], the suggestion is to begin monitoring in CKD stage 2

Diagnosis of CKD-MBD: Biochemical Abnormalities

⇨ In patients with CKD stages 3-5D, the suggestions[a] are to:

- ➢ Measure 25(OH)D (calcidiol) levels
- ➢ Repeat testing on the basis of:
  - Baseline values
  - Therapeutic interventions
- ➢ Correct vitamin D deficiency and insufficiency in accordance to treatment strategies recommended for the general population
- ➢ In patients with CKD G3a-G5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD- MBD assessments (1C).

Diagnosis of CKD-MBD: Biochemical Abnormalities

In patients with CKD stages 3-5D,

The suggestion is that medical practice should be guided by:

- The evaluation of individual values of serum calcium and phosphorus together
- Rather than the calcium–phosphorus product (Ca x P) In reports of laboratory tests for patients with CKD G3a-G5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), or handling specifications of facilitate the appropriate interpretation of biochemistry data (1D).

Diagnosis of CKD-MBD : Bone

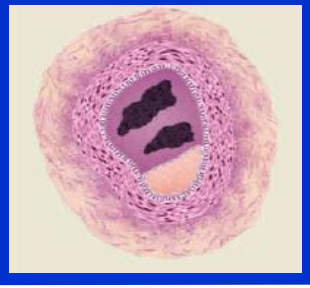
1. In patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (2B).

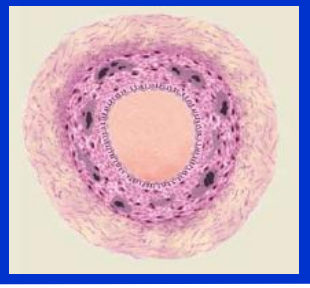
2. In patients with CKD G3a-G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (No graded).

KDIGO: Diagnosis of CKD-MBD Vascular Calcification

Arterial Media Calcification in ESRD: Impact on All-Cause and Cardiovascular Mortality

Arterial Intimal Calcification*





Arterial Medial Calcification*

- usually observed in…
  - older patients with a clinical history of atherosclerosis before starting HD
  - those with typical risk factors associated with atherosclerotic disease

- usually observed in…
  - young and middle-aged patients without conventional atherosclerotic risk factors
  - associated with
    - duration of HD
    - calcium-phosphate disorders
    - oral dose of elemental calcium prescribed as a phosphate binder ($CaCO_3$)

n=202
ESRD=end-stage renal disease
HD=hemodialysis

For illustration purposes only

London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. *Nephrol Dial Transplant*. 2003;18:1731-1740.

Diagnosis of CKD-MBD: Vascular Calcification

- In CKD stages 3-5D, the suggestions[a] indicate that:
  - It is reasonable to use alternatives to computed tomography-based imaging to detect the presence or absence of vascular calcification, including:
    - Lateral abdominal radiograph
    - Echocardiogram
  - Patients with known vascular/valvular calcification can be considered at highest cardiovascular risk
  - It is reasonable to use this information to guide the management of CKD–MBD

Treatment of CKD-MBD: Phosphorus and Calcium

Defining Normal

“Normal” Phosphorus	**2.5 mg/dl – 4.5 mg/dl**
“Normal” Calcium	**8.5 mg/dl – 10mg/dl or 10.5 mg/dl**
“Normal” iPTH **(varies with the assay used)**	**10 pg/ml - 65 pg/ml** **[Centers for Disease Control recommendations]**

- “Normal” means within the above ranges. These are normal ranges for healthy individuals.

Treatment Target Ranges

CKD Stage GFR mL/min/1.73m2	Target Phosphate	Target Calcium	Target PTH
Stage 3 30-59 Stage 4 15-29 Stage 5 ND <15	Maintain within normal range*	Maintain within normal range*	If serum PTH in rising and remains above the upper limit of normal despite addressing modifiable factors, treat with calcitriol or vitamin D analogs.
Stage 5D	Treat toward the normal range*	Maintain within normal range*	Two to nine times the upper limit of the normal range*

Frequency of Monitoring Biomarkers of CKD-MBD

CKD stage GFR (mL/min/1.73 m2)	Calcium	Phosphorus	PTH	Alkaline phosphatase	25 (OH) D (Calcidiol)
Stage- 3 30-59	Every 6-12 months	Every 6-12 months	Based on baseline level and CKD progression	NA	Measure with repeated testing determined by baseline values
Stage- 4 15-29	Every 3-6 months	Every 3-6 months	Every 6-12 months	Every 12 months, or more frequently in the presence of elevated PTH	Measure with repeated testing determined by baseline values
Stage-5 or 5D <15	Every 1-3 months	Every 1-3 months	Every 3-6 months	Every 12 months, or more frequently in the presence of elevated PTH	Measure with repeated testing determined by baseline values

Treatment of CKD-MBD: Phosphorus and Calcium

- In patients with CKD stages 3-5, the suggestions are to:
  - Maintain serum phosphorus in the normal range[a]
  - Maintain serum calcium in the normal range[b]
- Phosphate binders are suggested in the treatment of hyperphosphatemia[c]
- For choice of phosphate binder, it is reasonable to take into account[c]:
  - CKD stage
  - Presence of other components of CKD-MBD
  - Concomitant therapies
  - Side-effect profile

Treatment of CKD-MBD: Phosphorus and Calcium

- In patients with CKD stages 3-5D and hyperphosphatemia, the recommendation[a] is to:

  ⇨ Restrict calcium based phosphate binders in the presence of:

  - Arterial calcification
  - Adynamic bone disease
  - Persistently low serum PTH levels

  ⇨ Restrict the dose of calcium based phosphate binders and/or restrict the dose of calcitriol or vitamin D analog are suggested[b], in the presence of:

  - Persistent or recurrent hypercalcemia

Treatment of CKD-MBD: Phosphorus and Calcium

- In patients with CKD stages 5D, the suggestion is to:
  - Lower elevated phosphorus levels toward normal range[a]
  - Use a dialysate calcium concentration between 1.25 and 1.5 mmol/l (2.5 and 3.0 meq/L)[b]

PTH Levels

Treatment Initiation Ranges

Stage	Treatment Initiation Range iPTH
3	KDIGO: **> Upper limit of Normal** 4.2.2 (2C) KDOQI**: 35-70 pg/Ml**
4	KDIGO: **> Upper limit of Normal** 4.2.2 (2C) KDOQI: **70-110 pg/mL**
5	KDIGO: **> Upper limit of Normal** 4.2.2 (2C) KDOQI: **150-300 pg/mL**
5D	KDIGO: **2 to 9x upper limit of Normal** 4.2.3 (2C) KDOQI: **150-300 pg/mL**

Treatment of Abnormal PTH levels in CKD-MBD

- In patients with CKD stages 3-5 not on dialysis, the optimal PTH level is unknown
- In patients with levels of intact PTH (iPTH) above the upper normal limit of the assay, the suggestion[a] is to, first evaluate for:
  - Hyperphosphatemia
  - Hypocalcemia
  - Vitamin D deficiency
- It is reasonable to correct these abnormalities with any or all of the following[b]:
  - Reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D
- The suggestion[c] is to treat with calcitriol or vitamin D analogs if:
  - Serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors

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- In patients with CKD stage 5D, the suggestion[a] is to:
  - Maintain iPTH levels in the range of approximately two to nine times the upper normal limit for the assay
- To lower PTH, when it is elevated or rising, the suggestion[a] is to use:
  - Calcitriol
  - Or vitamin D analogs
  - Or calcimimetics
  - Or a combination of calcimimetics and calcitriol or vitamin D analogs
- In patients with severe hyperparathyroidism who fail to respond to medical/pharmacological therapy parathyreidectomy is suggested

Treatment of Abnormal PTH Levels In CKD-MBD

- In patients with hypocalcemia, the suggestion[a] is to reduce or stop:
  - Calcimimetics depending on severity, concomitant medications, and clinical signs and symptoms
- If intact PTH levels fall below two times the upper limit of normal for the assay, the suggestion[b] is to reduce or stop:
  - Calcitriol
  - Vitamin D analogs
  - And/or calcimimetics

Treating Bone abnormalities

CKD STAGES 1 and 2	With osteoporosis and/or high risk of fracture, as identified by world Organization criteria (WHO)	Manage as per general population. G 4.3.1 (1A)
CKD STAGE 3	With PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by WHO criteria …….. With biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures..	Treat as per the general population. G 4.3.2 (2B) ……. When treating, take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of bone biopsy. G 4.3.3 (2D)
CKD STAGES 4-5D	With biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures….	Perform additional investigation with bone biopsy prior to therapy with antiresorptive agents. G 4.3.4 (2C)

Conclusion

- Disorders of mineral and bone metabolism are common sequelae of CKD, with secondary hyperparathyroidism encompassing most of the biochemical abnormalities.

- There is an increased risk of all-cause and cardiovascular mortality in patients with disorders of mineral metabolism.

- Among dialysis patients with elevated PTH levels, a stepped approach to the management of hyperparathyroidism and bone mineral abnormalities is recommended.

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Conclusion

- This approach requires a complex balance of four medications, namely calcium-containing binders, non- calcium-containing binders, calcimimetics, and either calcitriol or synthetic vitamin D analogs.

- Most current ABD cases result from excessive suppression of the parathyroid glands due to increased and earlier use of vitamin D analogs and calcium-containing phosphate binders.

- Among patients with refractory hyperparathyroidism, prompt parathyroidectomy is suggested.

THANKS
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