Secondary Hyperparathyroidism (SHPT)

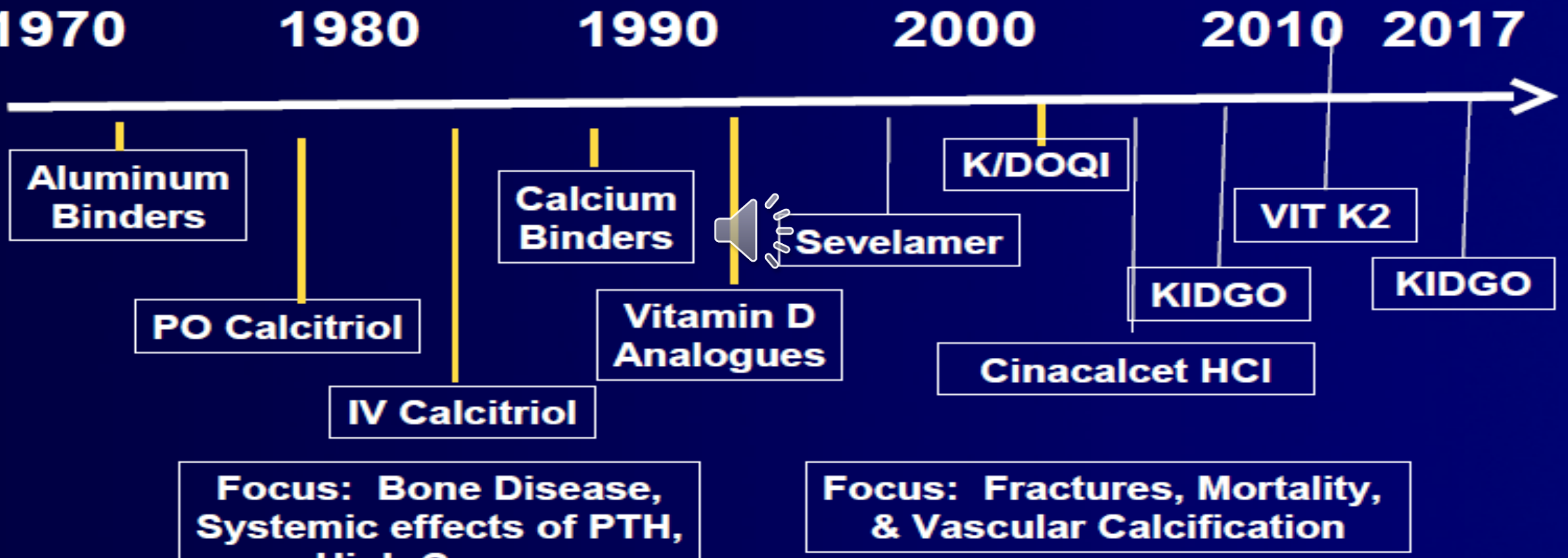
In Chronic Kidney Disease

Dr. H Sanadgol feb 2021

Agenda

- The size of the problem (CKD-MBD)
- Definitions & Classifications
- Bone disease in CKD (B)
- Vascular calcifications/CVD (V/C)
- Role of Calcium and Phosphorus (L)
- Importance of Vitamin D in CKD-MBD (L)
- CKD & SHPT (L)
- Frequency of Monitoring
- CKD-MBD 2017 Guidelines (Diagnosis of CKD-MBD & VC)

History of Treatment Strategies for Secondary Hyperparathyroidism



Pathophysiologic mechanisms of ROD

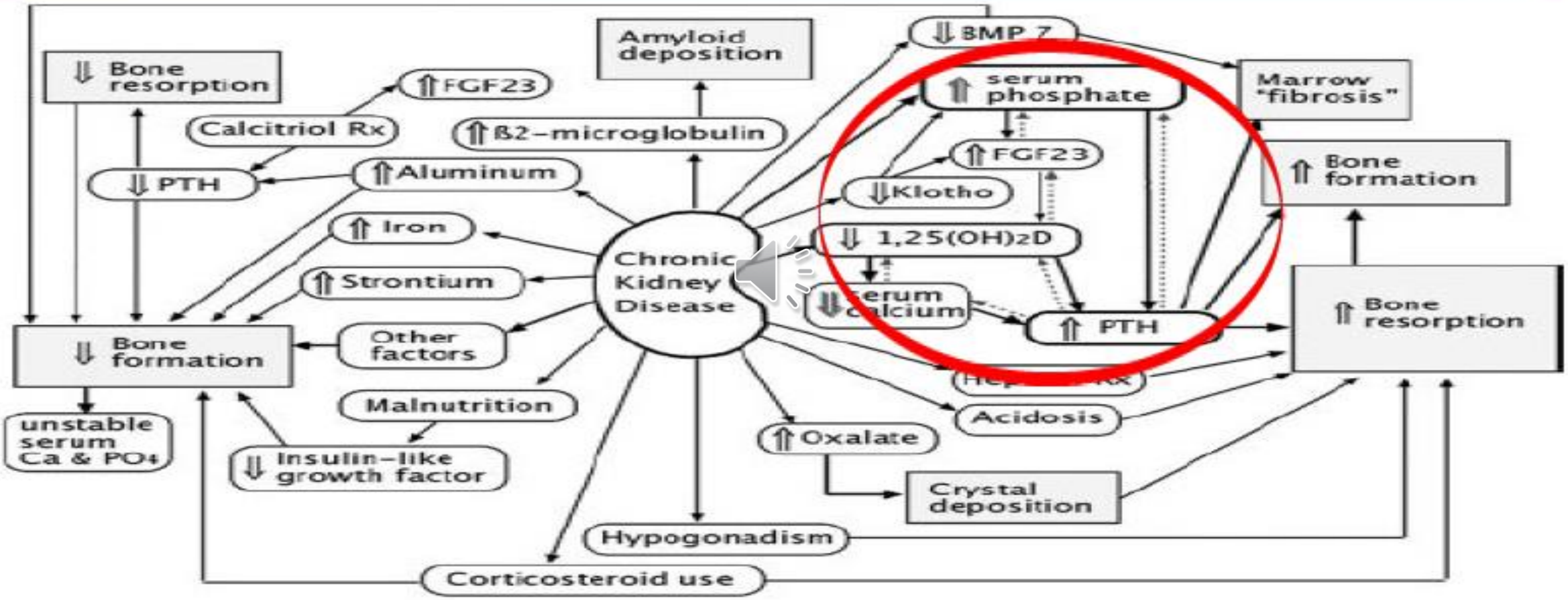


Figure 1. Pathophysiologic mechanisms of renal osteodystrophy. The dashed arrows show feedback loops that are "frustrated" by the renal dysfunction.

Bone Turnover:
Biomarkers and Images

Significance Statement

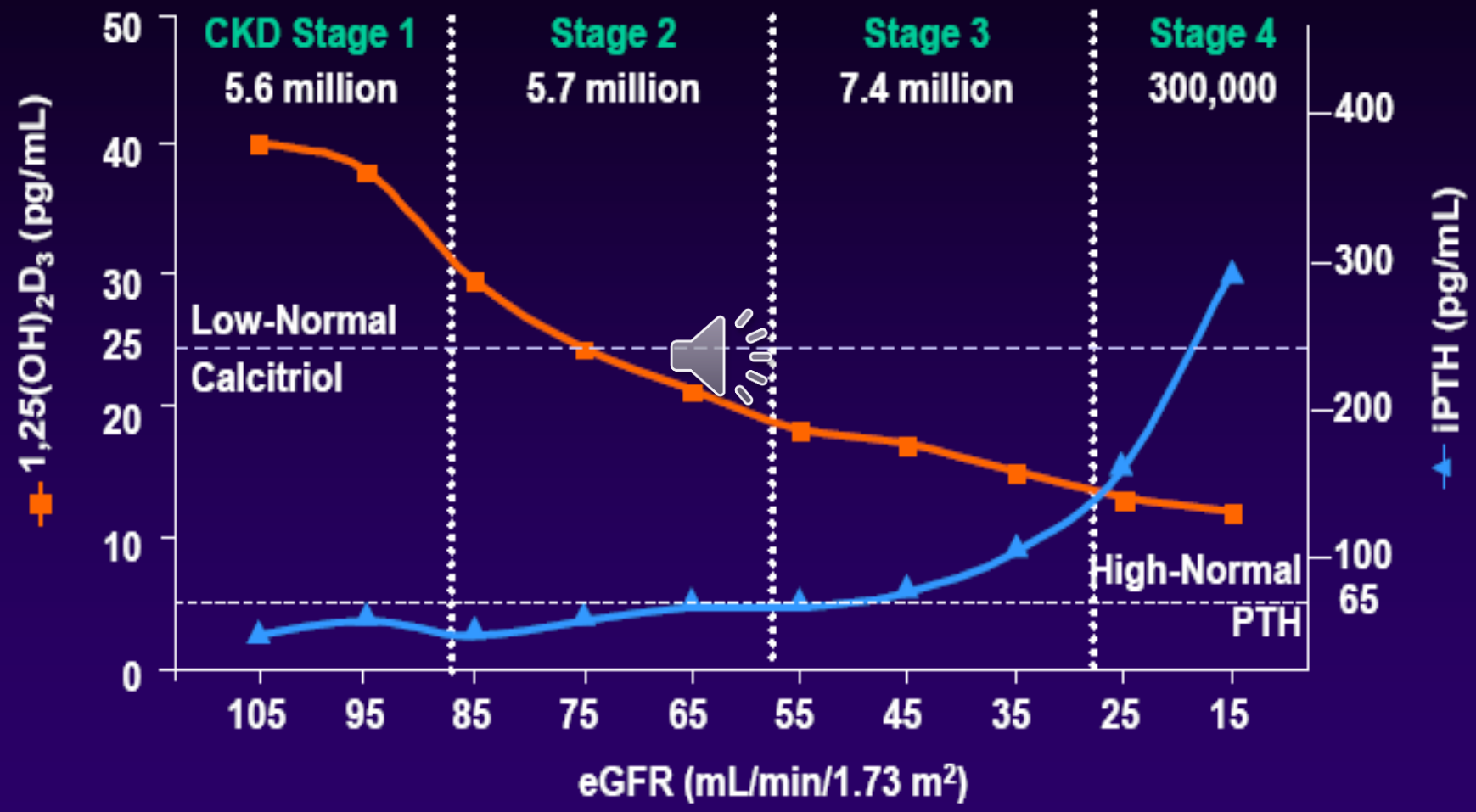
Abnormal bone turnover of renal osteodystrophy in advanced CKD can only be diagnosed using bone biopsy (gold standard). However, this is an invasive and painful procedure, and thus, it is rarely performed. This study found that three bone biomarkers (bALP, intact PINP, and TRAP5b) and high-resolution bone imaging of distal radius can discriminate patients with low bone turnover from those with nonlow bone turnover as assessed by bone histomorphometry. Hence, the biomarkers and bone imaging may have the potential to replace bone biopsy, particularly in discriminating patients with low bone turnover. They may also be useful in selecting patients for future clinical trials that aim to reduce their fracture risk.

From the *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th Edition.*
www.asbmrprimer.org

Table 1. Pathology and Diagnosis of Bone Turnover in CKD

I. Predominant hyperparathyroidism, high-turnover ROD
   a. Intact PTH > 500 pg/ml
   b. Elevated alkaline phosphatase or bone-specific alkaline phosphatase
II. Low-turnover disease
   a. Adynamic bone disorder
      1. Intact PTH < 100 pg/ml
      2. Normal alkaline phosphatase or bone-specific alkaline phosphatase
      3. Low osteocalcin
   b. Osteomalacia
      1. Intact PTH < 100 pg/ml
      2. Normal alkaline phosphatase or bone-specific alkaline phosphatase
      3. Low osteocalcin
      4. Elevated Al^{3+}
III. Mixed uremic osteodystrophy
   a. PTH > 300 pg/ml
   b. Elevated Al^{3+}
V. Unknown
   a. PTH > 100 < 500 pg/ml

SHPT Occurs Early in CKD Progression



N = 150.

Adapted from Martinez et al. *Nephrol Dial Transplant.* 1996;11(suppl 3):22-28.

- Bone metabolism and disturbances occur in early stage of renal impairment and continue throughout progression loss of kidney function.
- Early management is crucial to improve QOL and longevity of CKD patient

Consequences of SHPT

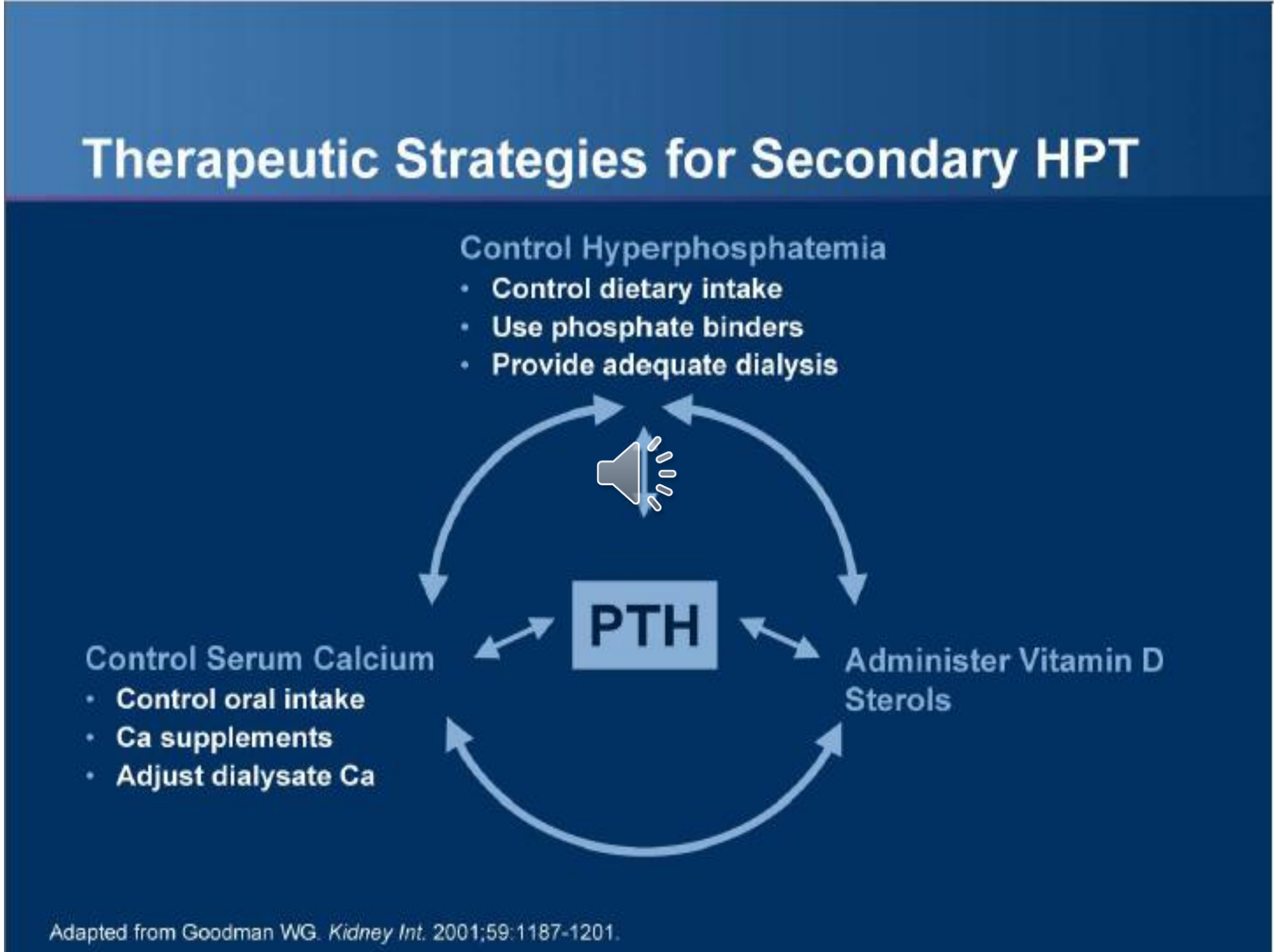
Skeletal Associations
High-turnover bone lesions
Osteitis fibrosa
Brown tumors
Bone pain
Osteopenia
Fractures
Hypercalcemia
Hyperphosphatemia
Calciphylaxis

Extraskeletal Associations
Nervous system Neuropathy
Heart Hypertension LVH, interstitial fibrosis Myocardial/valvular calcification
Glucose intolerance
Hyperlipidemia
Anemia

LVH = left ventricular hypertrophy.

Cunningham. *Semin Dial*. 2000;13:275-278.

Therapeutic Strategies for Secondary HPT



Adapted from Goodman WG. *Kidney Int.* 2001;59:1187-1201.

Goal of Therapy

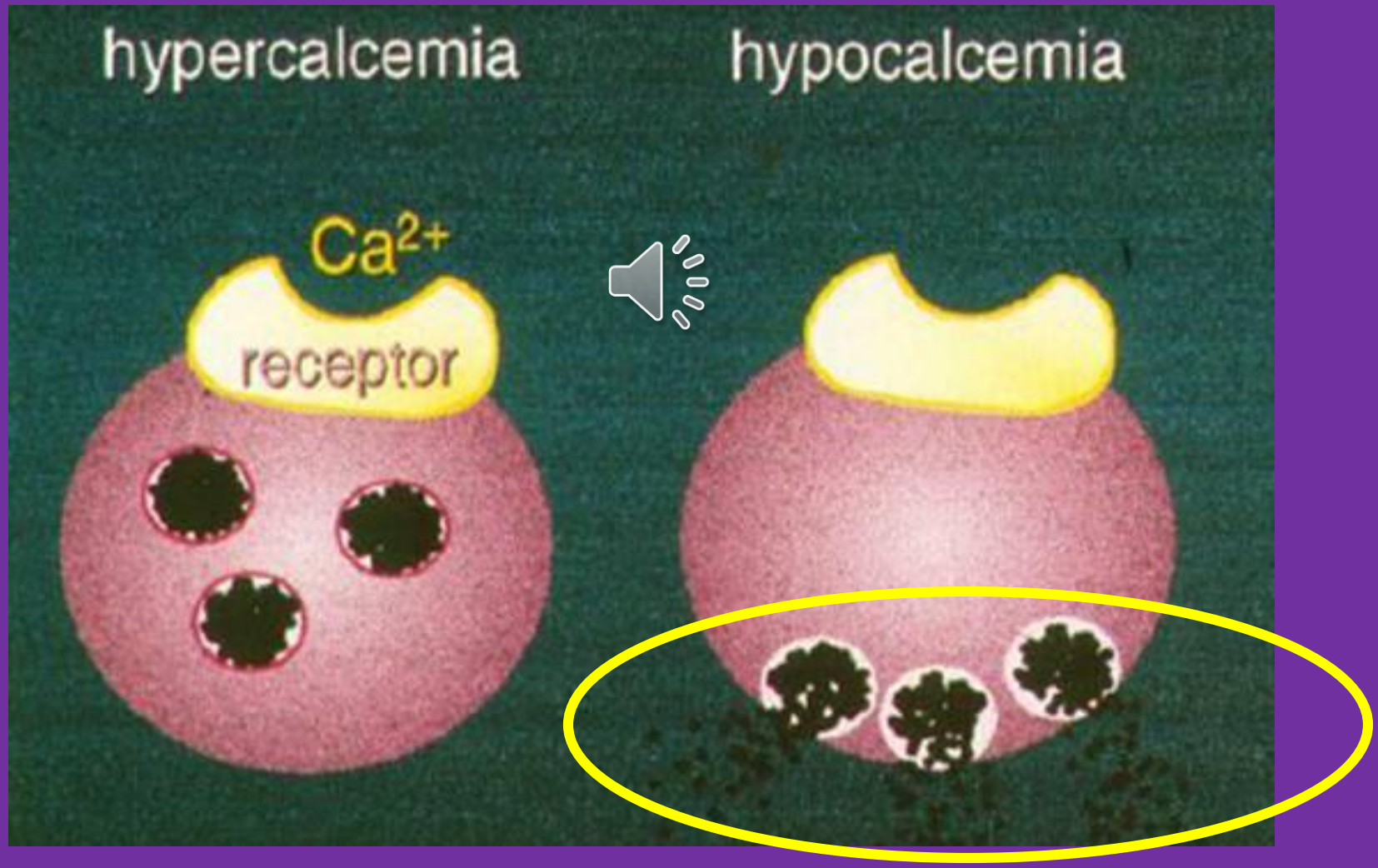
- Maintain serum calcium and phosphorus level within normal range
- Prevent or reduce development of hyperparathyroid hyperplasia
- Restore skeleton to near normal as possible
- Prevent extraskeletal calcification
- Avoid exposure to toxic agents (eg: aluminium)
- Reduce cardiovascular morbidity and improve long-term outcome

Target Range of corrected Ca^{++} , P and Ca-P product

Stage CKD	Serum P (mg/dL [mmol/L])	Corrected Ca^{++} (mg/dL[mmol/L])	Ca-P product (mg^2/dL^2 [$mmol^2/L^2$])
3	2.7-4.6 (0.87-1.49 mmol/L)	8.4-10.2 (2.1-2.54 mmol/L)	<55 (<4.5$mmol^2/L^2$)
4			
5	3.5-5.5 (1.13-1.78 mmol/L)	8.4-9.5 (2.1-2.37 mmol/L)	

Ref: KDOQI 2017

Calcemic response to PTH



How does serum P affect calcemic response to PTH?

1st mechanism:

High serum P

↓

Interact with free serum Ca^{++}

↓

Less free serum Ca^{++}

↓

Lowers parathyroid gland's ability to detect Ca++

↓

Promote PTH release

2nd mechanism:

High serum P

↓

Downregulating calcium sensing receptors in parathyroid gland cells

↓

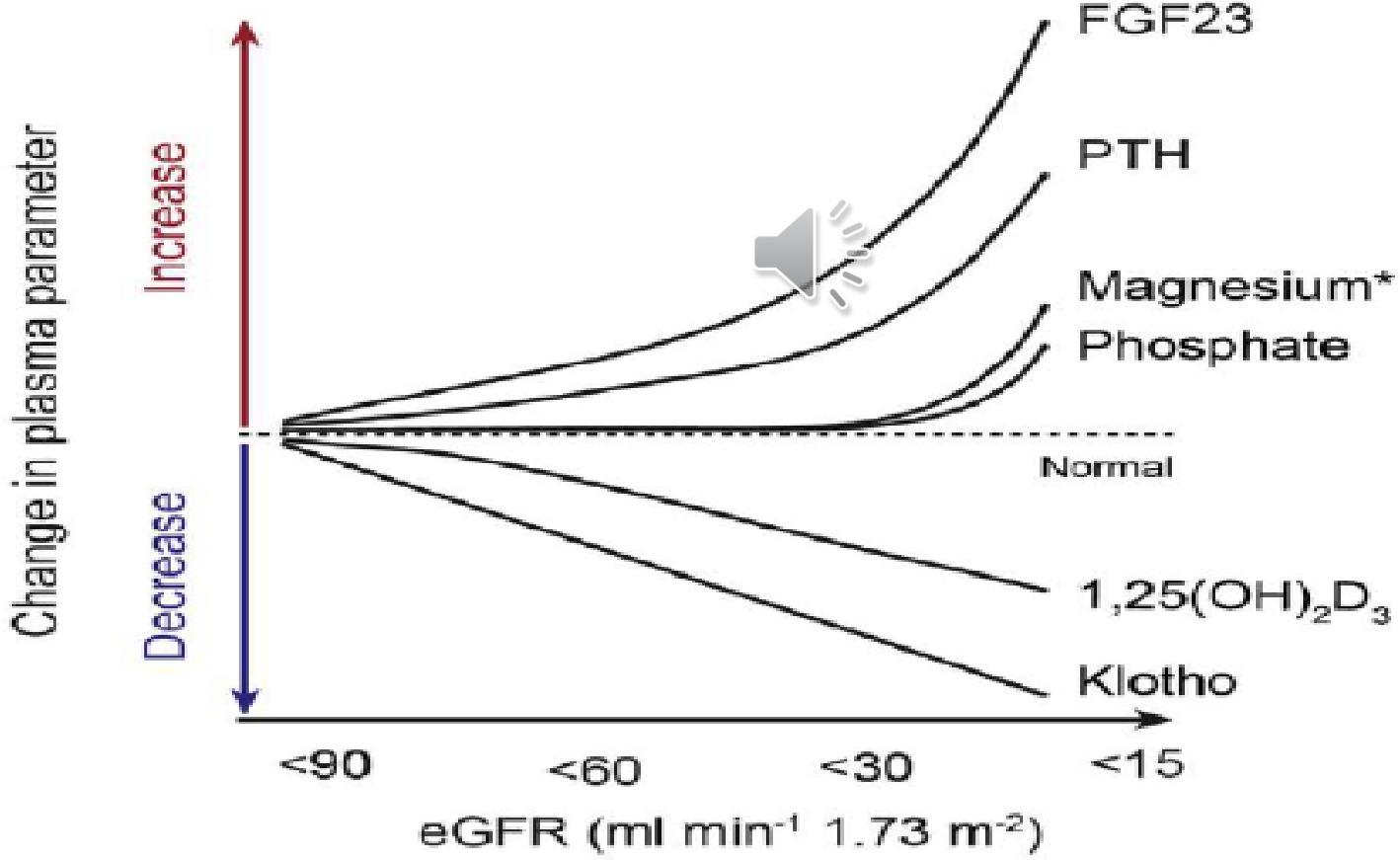
Parathyroid gland fail to response to high serum Ca level

Paolo Raggi and Michael Kleerekoper (March 5, 2008).Contribution of Bone and Mineral abnormalities to Cardiovascular Disease in Patients with Chronic Kidney Disease, Clin J Am Soc Nephrol 3:836-843.

CKD-MBD:
Changes in Plasma Mineral Parameters

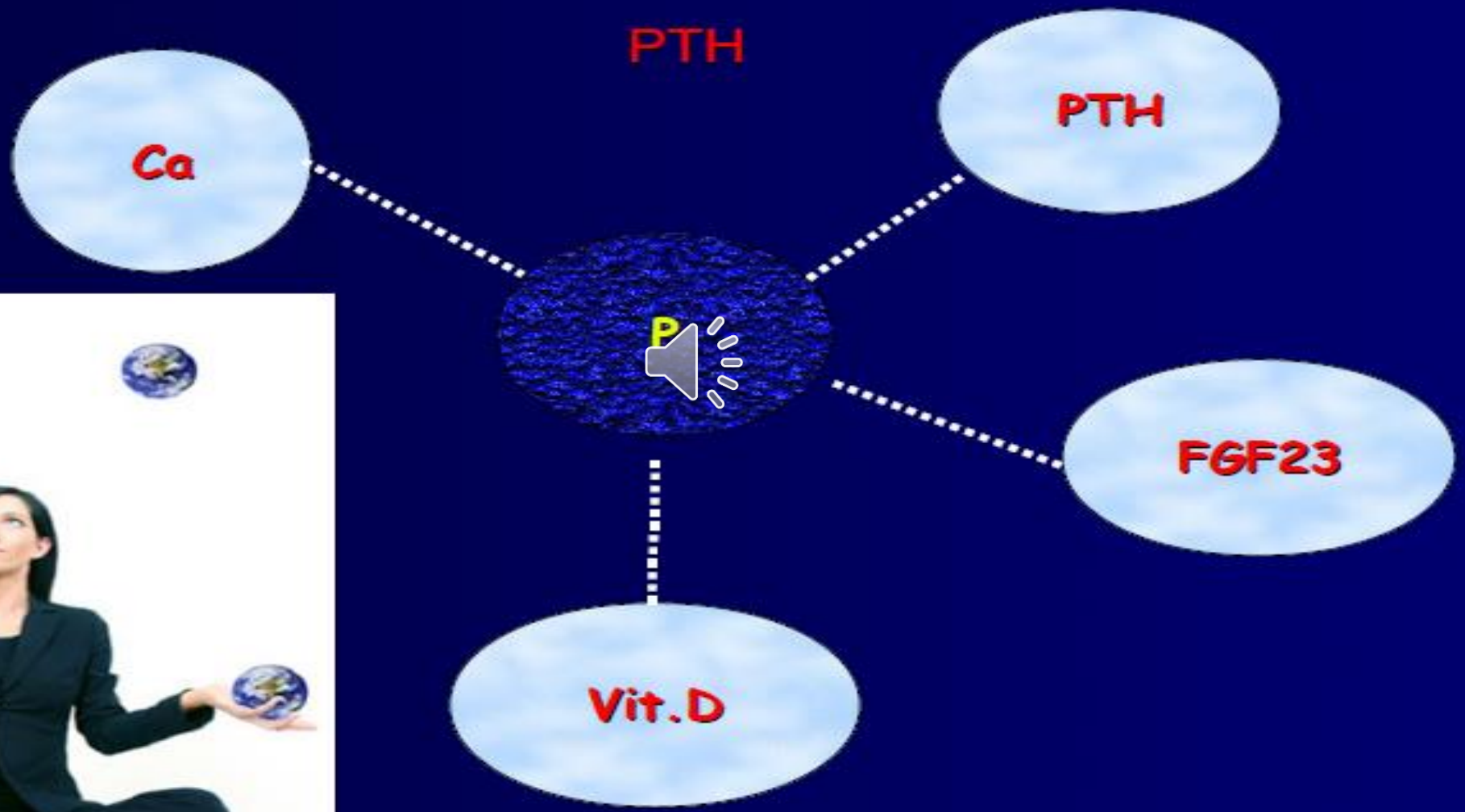
Chronic Renal Disease, Second Edition, 2020

2nd Edition, 2020



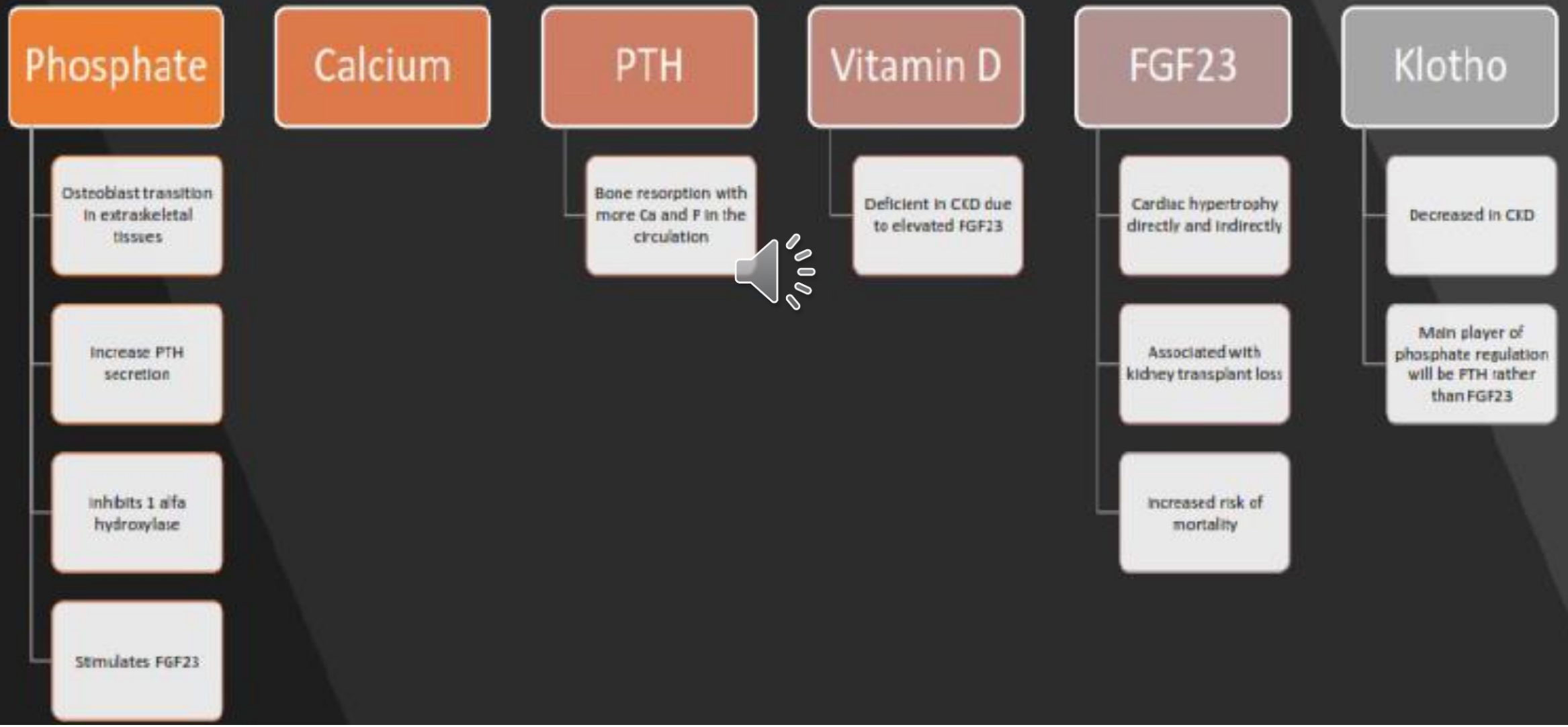
CKD-M(B/V)D Key Players

Complex interdependence of calcium, phosphorus, vitamin D, FGF23 & PTH

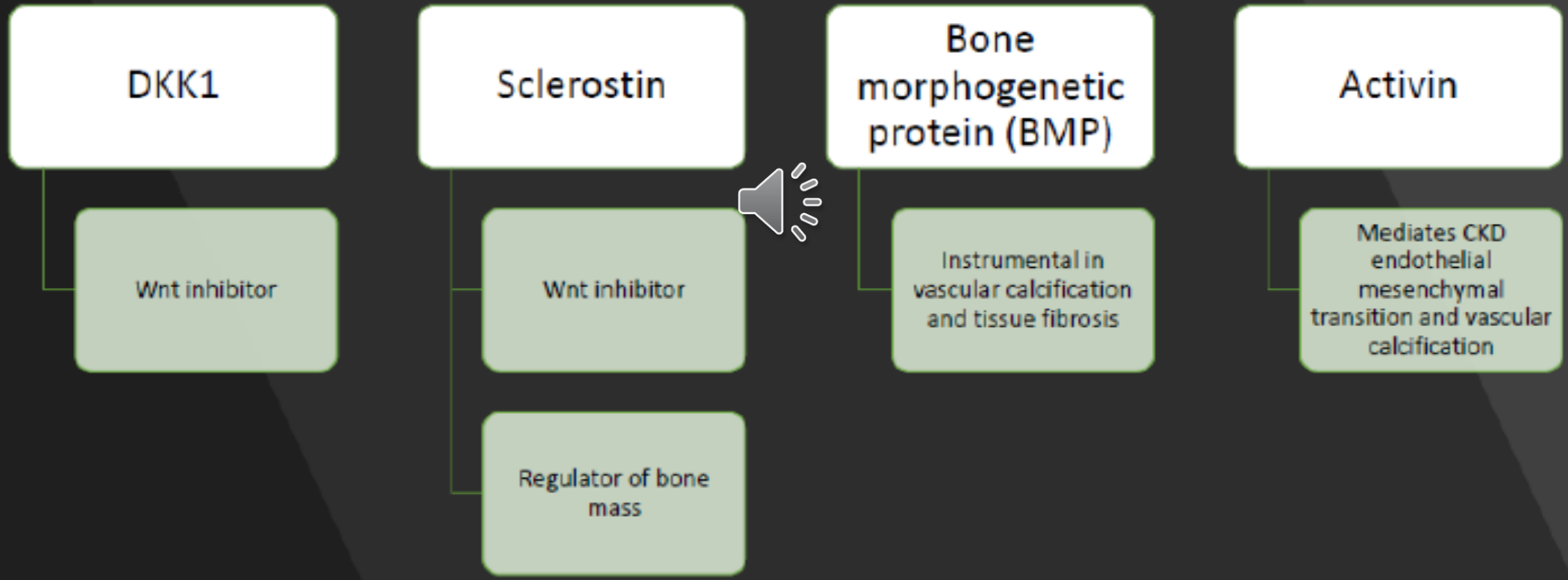


Bone and Mineral Balance

Recognized Players of CKD-MBD



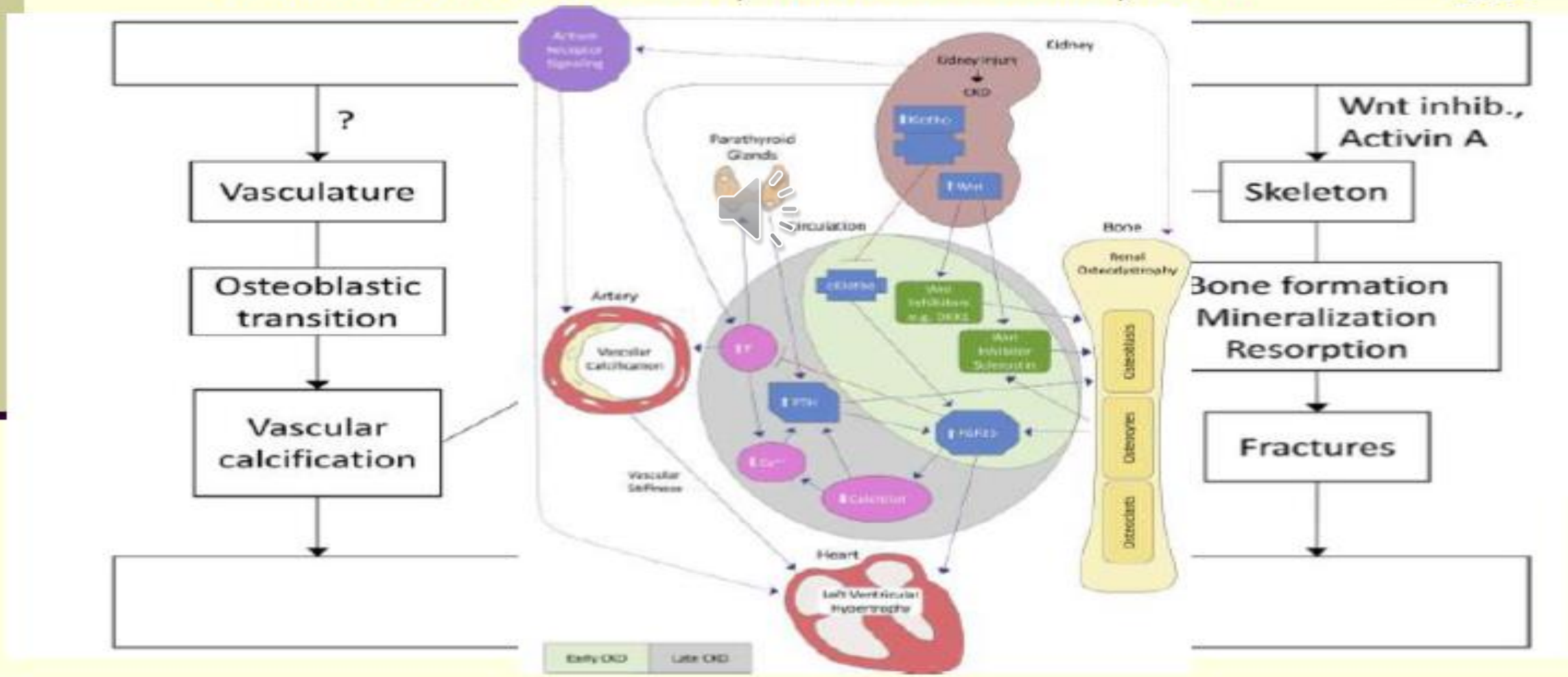
New Players in CKD-MBD



CKD-MBD: An Overview

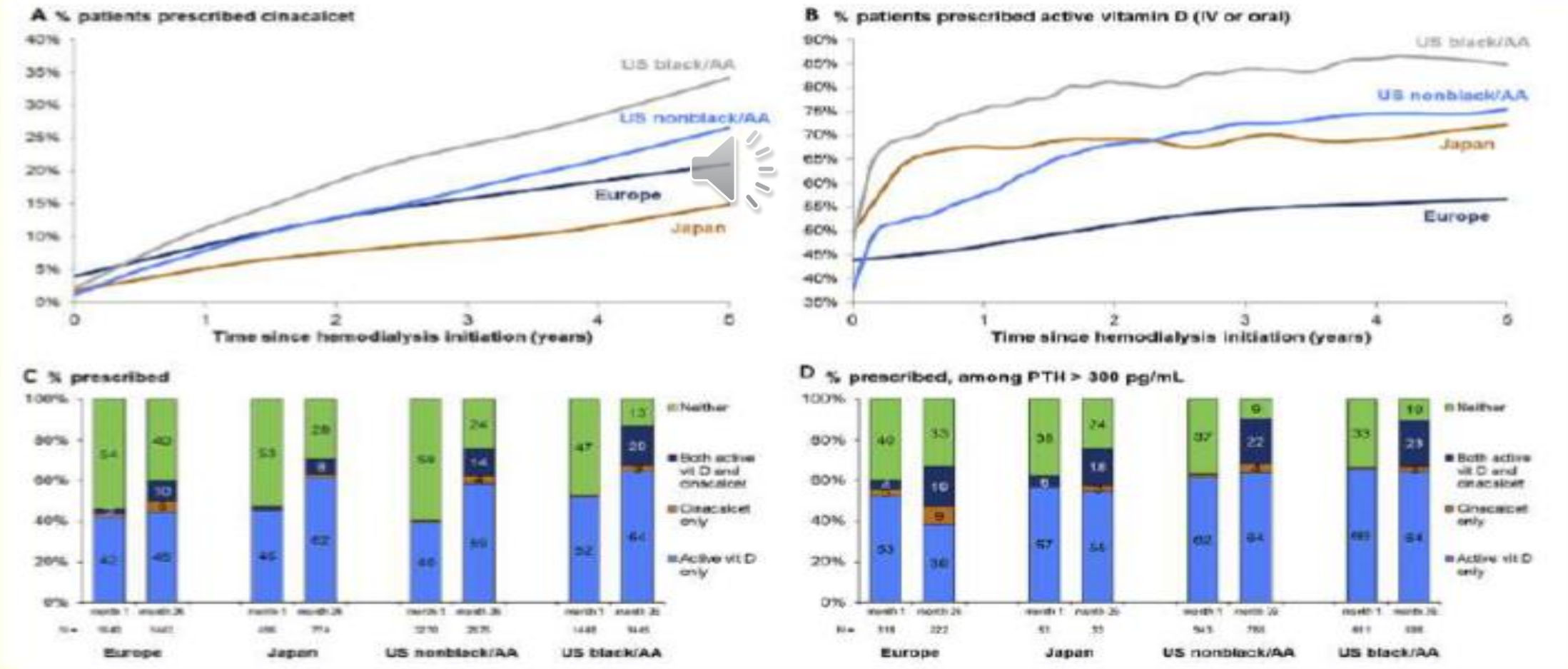
2nd Edition, 2020

Chronic Renal Disease, Second Edition, 2020



CKD-MBD:
International and Racial Differences

Kidney Med Vol 1 | Iss 3 | May/June 2019



CHAPTER 3.3:

DIAGNOSIS OF CKD–MBD: VASCULAR CALCIFICATION

ASSESSMENT

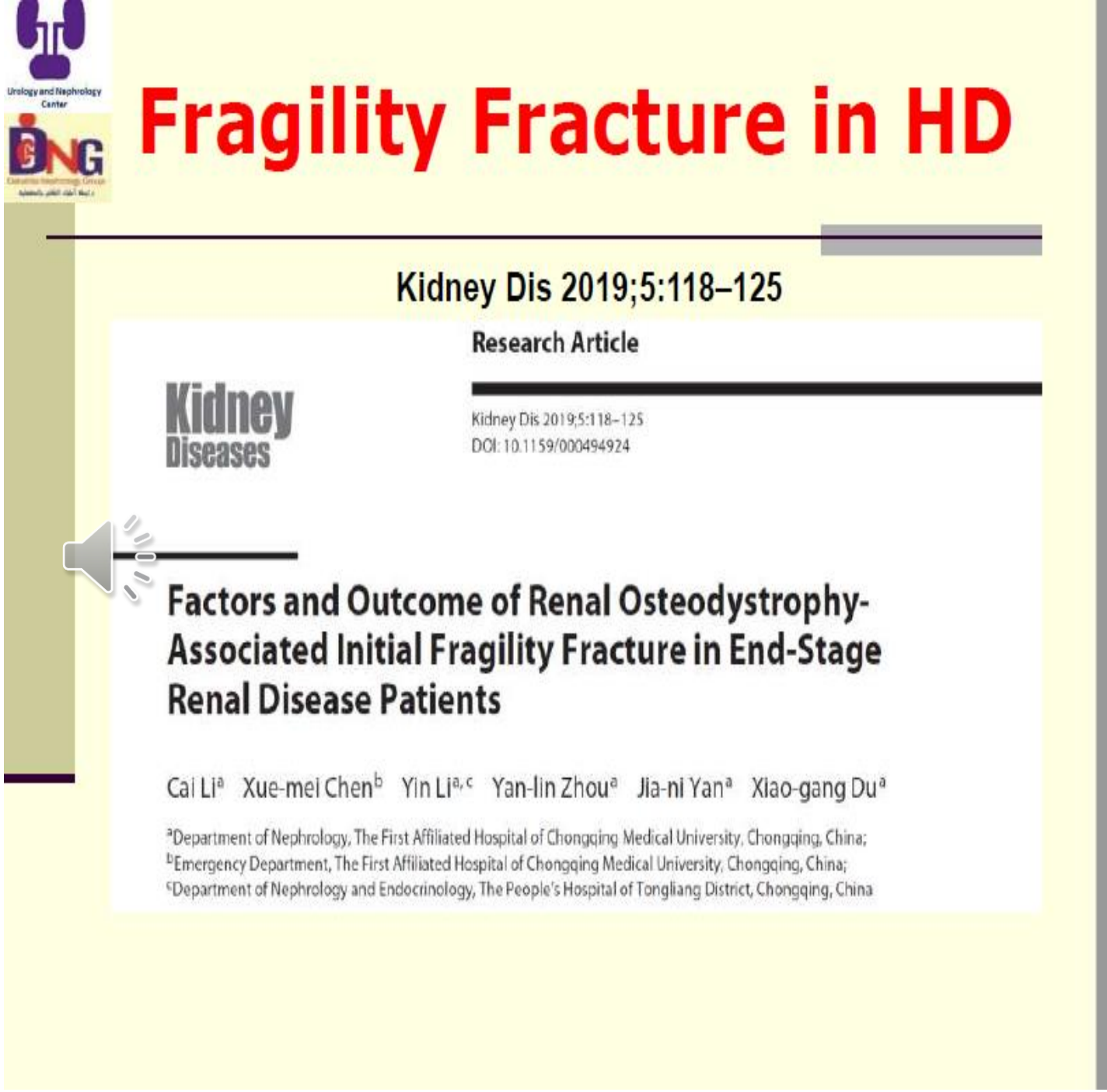
3.3.1: In patients with CKD G3a–G5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging *(2C)*.

3.3.2: We suggest that patients with CKD G3a–G5D with known vascular or valvular calcification be considered at highest cardiovascular risk *(2A)*.

It is reasonable to use this information to guide the management of CKD-MBD *(Not Graded)*.

Fragility Fracture in HD

Key Messages: Patients with hypertension, diabetes, excessive suppression of PTH, and poor nutritional status are more prone to fractures. Serum corrected calcium and ALP were independent risk factors of fragility fracture. Patients with initial fragility fracture had more CV events and higher mortality.



Kidney Dis 2019;5:118–125

Research Article

Kidney Diseases

Kidney Dis 2019;5:118–125
DOI: 10.1159/000494924

Factors and Outcome of Renal Osteodystrophy-Associated Initial Fragility Fracture in End-Stage Renal Disease Patients

Cai Li[a] Xue-mei Chen[b] Yin Li[a,c] Yan-lin Zhou[a] Jia-ni Yan[a] Xiao-gang Du[a]

[a]Department of Nephrology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China;
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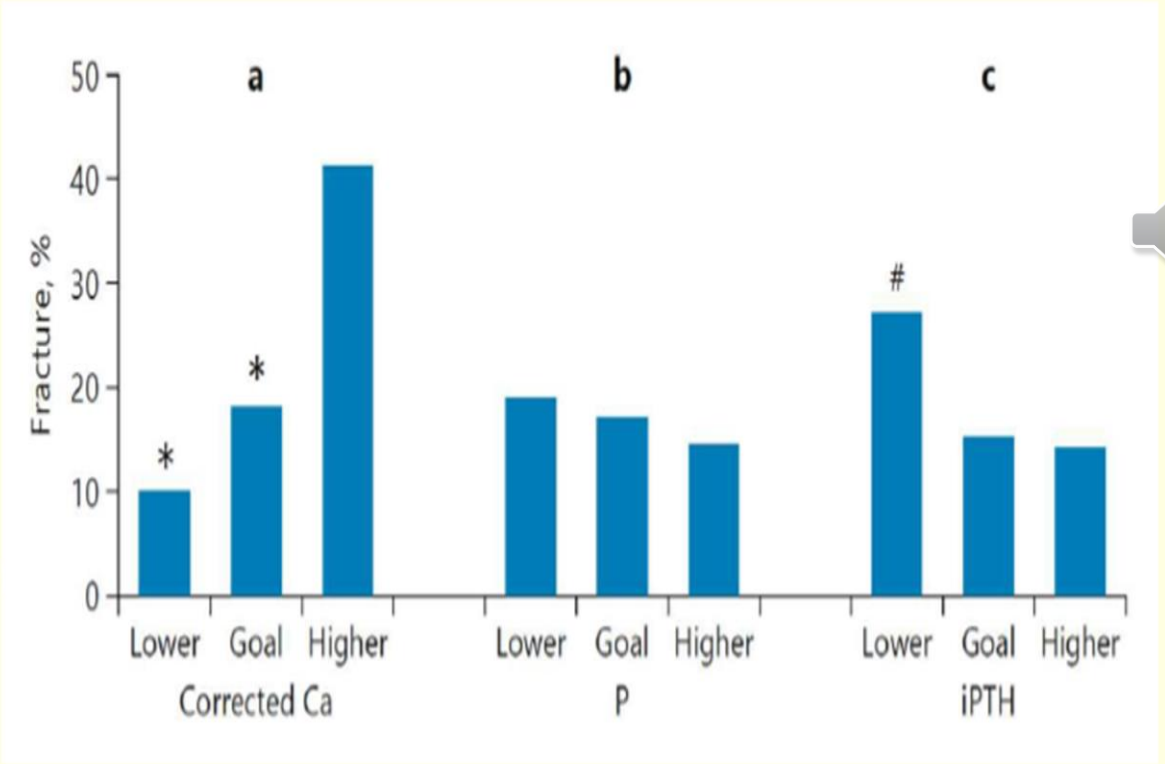
Fragility Fracture in HD: Which is Correct?

Kidney Dis 2019;5:118–125



Alterations of mineral-bone metabolism are associated with increased risk of fracture. In this study, we analyzed the changes of mineral-bone metabolism-associated parameters in ESRD patients with initial fragility fracture. Higher serum ALP, corrected calcium, and lower serum iPTH levels were found in the FF group compared with the control group ($p < 0.05$).

No significant differences in phosphorus and calcium-phosphorus product were found between the two groups.

We further assessed the incidence of initial fragility fracture in patients with different levels of serum corrected calcium, phosphorus, and iPTH. According to the KDIGO recommendations regarding target corrected calcium (8.4–10.2 mg/dl) and phosphorus (2.7_4.6 mg/dl) or K/DOQI guideline recommendations about target iPTH (150–300 pg/mL) in CKD5 patients, the 354 patients were divided into three subgroups: lower, target, and higher level subgroups, respectively. As shown in Figure 2, fractures were more likely to occur in the higher level subgroups by corrected calcium levels as well as in the lower iPTH group ($p < 0.05$). However, no differences were found among the various serum phosphorus subgroups ($p > 0.05$).

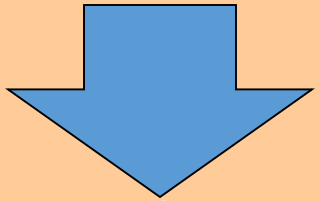
Phosphate Restriction / Phosphate Binder

- avoid high protein diet, milk, carbonated beverage, cheese, sardine, soybean

- to keep dietary phosphorus at 800-1000mg/day (or 800-1200mg/day if patient undergoes dialysis)

- Use Phosphate Binders
(Calcium Carbonate / Aluminium Hydroxide / Sevelamer / Lanthanum)

Dietary P restriction



Reduced PTH level

(independent of Ca & calcitriol level)

Phosphate Binders

Chronic Renal Disease, Second Edition, 2020, Chapter 41

TABLE 41.2 Phosphate Binders in Clinical Use

Cation	Formulation	Adverse Effects	Cost per Dose
Al^{3+}	Aluminum hydroxide	Osteomalacia Encephalopathy Microcytic anemia	
La^{3+}	Lanthanum carbonate	GI upset Unknown effect on bone	
Ca^{2+}	Calcium acetate Calcium carbonate	Hypercalcemia Ectopic calcification Adynamic bone disease	
Mg^{2+}	Magnesium carbonate	Diarrhea Hypermagnesemia	
Fe^{2+}	Sucroferric oxyhydroxide Ferric citrate	Diarrhea Nausea	
Sevalemar	Sevelamer hydrochloride Sevelamer carbonate	Diarrhea Constipation Metabolic acidosis	

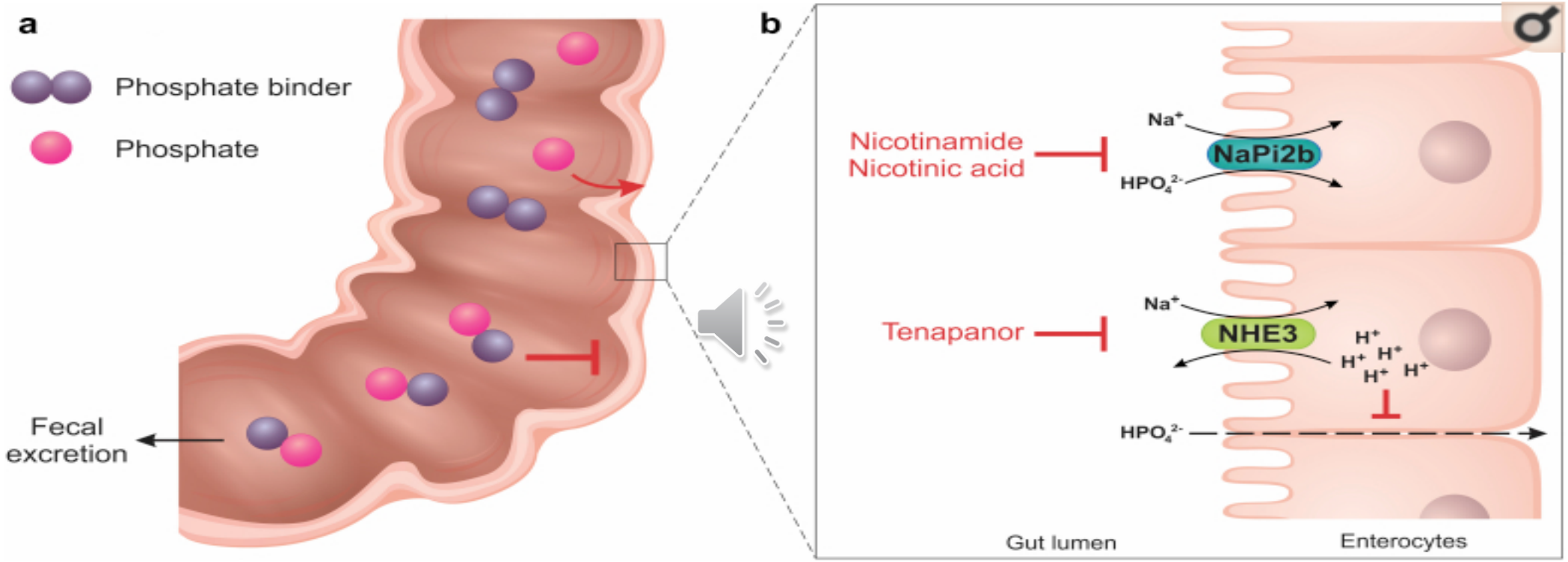
Phosphate Binders

Kidney Int Rep. 2019 Jun 20;4(8):1043-1056

Drug	Usual dose (pill burden)°	Advantages	Disadvantages
Calcium carbonate	500–1250 mg (3–6 tablets)	Lower pill burden	Calcium overload
Calcium acetate	667 mg (6–12 capsules)	As effective as calcium carbonate	Calcium overload High pill burden
Magnesium carbonate	63 mg (2–6 capsules)	Good GI tolerance, lower pill burden	Hypermagnesemia
Sevelamer hydrocloride	800 mg (6–12 capsules)	↓ LDL-cholesterol levels, better survival in HD	High pill burden, GI side effects, metabolic acidosis
Sevelamer carbonate	800 mg (6–12 capsules)	↓ LDL-cholesterol levels, better survival in HD	High pill burden, GI side effects
Bixalomer	250 mg (6–14 capsules)	Good GI tolerance	High pill burden
Lanthanum carbonate	250–1000 mg (3–6 chewable tablets)	Lower pill burden, good GI tolerance	Low solubility Tissue accumulation, eg, bone
Ferric citrate	210 mg (4–5 tablets)	Lower pill burden, ↓ iron suplementation ↓ ESA doses	GI side effects (mild)
Sucroferric oxyhydroxide	500 mg (2–6 chewable tablets)	Lower pill burden	GI side effects (mild)

Published online 2019 Jun 20. doi: 10.1016/j.ekir.2019.06.002

Figure 1



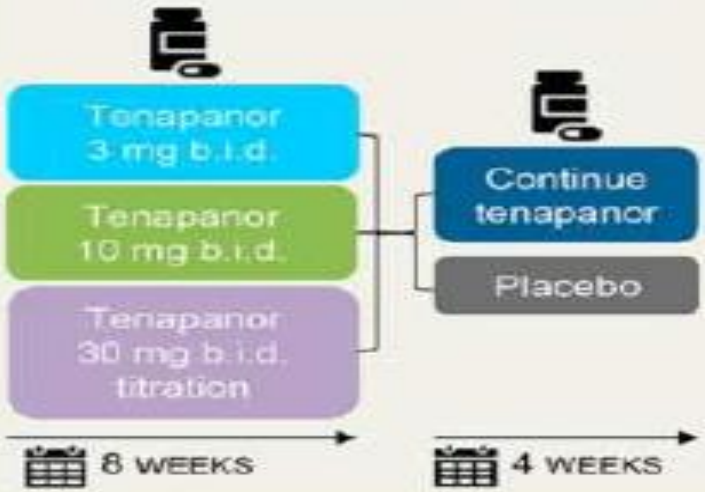
Mechanisms of action of phosphate-lowering pharmacological agents. (a) Phosphate binders reduce the intestinal absorption of dietary phosphate by forming a nonabsorbable compound in the gastrointestinal tract lumen that is excreted in the feces. (b) Nicotinic acid (niacin) and nicotinamide (niacinamide) inhibit sodium-dependent, active intestinal phosphate absorption via a reduction in NaPi2b expression; tenapanor reduces intestinal sodium and phosphate absorption by inhibiting the sodium/hydrogen ion-exchanger isoform 3 (NHE3), leading to intracellular proton accumulation and inducing a conformational change in tight junction proteins, thereby decreasing permeability to paracellular phosphate transport.

Phosphate Control in HD: Tenapanor Scenario

J Am Soc Nephrol. 2019 Apr;30(4):641-652

METHODS

219 patients across 41 US sites



RESULTS

Change in serum phosphate

CONCLUSION

Tenapanor significantly reduced elevated serum phosphate in patients on hemodialysis with hyperphosphatemia.

Conclusion

The PCT showed to be efficient in the maintenance of serum phosphorus in the individuals who adhered well to the tool, without the administration of phosphate binders. Such a method can assist in patient adherence to treatment and enables better diet flexibility

Phosphorus Control in HD: Effect of PCT

Clin Nutr ESPEN. 2019 Aug;32:153-157

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Phosphorus Counting Table for the control of serum phosphorus levels without phosphate binders in hemodialysis patients

Vivianne Rêis Bertonsello-Catto [a, *], Leandro Junior Lucca [b], José Abrão Cardeal da Costa [c]

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Phosphorus Control in CKD3b/4 CKD: COMBINE Trial

EDITORIAL www.jasn.org

Dual Inhibition of Gastrointestinal Phosphate Absorption: More Questions Than Answers

Wing-Chi G. Yeung,[1] Nigel D. Toussaint,[2,3] and Sunil V. Badve[1,4]

[1]Department of Renal Medicine, St. George Hospital, Sydney, Australia; [2]Department of Nephrology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia; [3]Department of Medicine, University of Melbourne, Parkville, Victoria, Australia; and [4]Renal and Metabolic Division, The George Institute for Global Health, University of New South Wales Medicine, Sydney, New South Wales, Australia

Paricalcitol Vs. Calcitriol in Dialysis Patients

Therapeutic Apheresis and Dialysis Feb 2019; 23(1):73–79

Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 2019; 23(1):73–79
doi: 10.1111/1744-9987.12760

Comparison of Paricalcitol and Calcitriol in Dialysis Patients With Secondary Hyperparathyroidism: A Meta-Analysis of Randomized Controlled Studies

Tong Zhang,[1] Hongbo Ju,[2] Haojun Chen,[2] and Wen Wen[3]

Departments of [1]Gastroenterology, [3]Nephrology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, and [2]Nephrology Department, Fenghua People's Hospital, Ningbo, China

Paricalcitol and calcitriol result in similar ≥50% reduction of parathyroid hormone, calcium concentration, phosphate concentration, calcium phosphate, alkaline phosphatase, hypercalcemia, adverse events, and serious adverse events for secondary hyperparathyroidism in dialysis patients.

TABLE 1 Survival outcomes after PTX in dialysis patients

Author	Year	Population	Time period	Study design	Result
Li-Chun Ho et al[135]	2016	Nationwide dialysis cohort, Taiwan	1998-2010	Case-control study with matching for propensity and for radionuclide PTH imaging	PTX had significant 20%-25% lower risk for all-cause mortality
Ivarsson et al[159]	2015	Swedish Renal Registry	1991-2009	Nested case-control study matched for gender, age, cause of ESRD (N: 423/1234).	RR of death for PTX: 0.80 (95% CI 0.65-0.99)
Komaba et al[129]	2015	Registry - Japanese Society for Dialysis Therapy	1-year follow up	4428 with PTX vs 4428 propensity matched controls	PTX reduced all-cause mortality by 34% and cardiovascular mortality by 41%.
Kestenbaum et al[160]	2004	USRDS	1998-2001	Case-control study matched by age, race, gender, cause of ESRD, dialysis duration, prior transplant status, dialysis modality. (N: 4558/4558)	PTX 30-day postoperative mortality rate 3.1%; higher short-term, and lower long-term mortality rates; Median survival PTX: 53.4 mo (95% CI: 51.2-56.4); Control: 46.8 mo (95% CI: 44.7-48.9).
Apetrii et al[128]	2017	MEDLINE Cochrane Library Clinicaltrials.gov EMBASE	Inception to October 2016	Meta-analysis: 15 retrospective cohort studies including 24 048 patients	PTX decreased: a) all-cause mortality (RR 0.74; 95% CI of 0.66-0.83) b) cardiovascular mortality (RR 0.59)
Chen et al[161]	2016	MEDLINE Cochrane Library EMBASE	1974-2015	Meta-analysis: 13 retrospective studies; 10 052 patients treated with PTX vs 12 001 medically treated.	PTX −28% reduction in all-cause mortality; 37% in cardiovascular mortality.

Parathyroidectomy

Ren Fail. 2019 Nov;41(1):921-929

182 dialysis patients who underwent PTX between February 2012 and January 2018

RENAL FAILURE
2019, VOL. 41, NO. 1, 921–929
https://doi.org/10.1080/0886022X.2019.1666724

Taylor & Francis

CLINICAL STUDY

Evaluation of laboratory parameters and symptoms after parathyroidectomy in dialysis patients with secondary hyperparathyroidism

Yi Zhang*, Ying Lu*, Sheng Feng, Zhoubing Zhan and Huaying Shen

Department of Nephrology, The Second Affiliated Hospital of Soochow University, Suzhou, China

Conclusion: PTX is a safe and effective therapy for treating SHPT that is refractory to medical therapies and accompanied by related signs and symptoms in dialysis patients. All three operative techniques were effective in controlling SHPT.

Secondary Hyperparathyroidism: Overview

Therapeutic Apheresis and Dialysis Aug 2019; 23(4):309–318

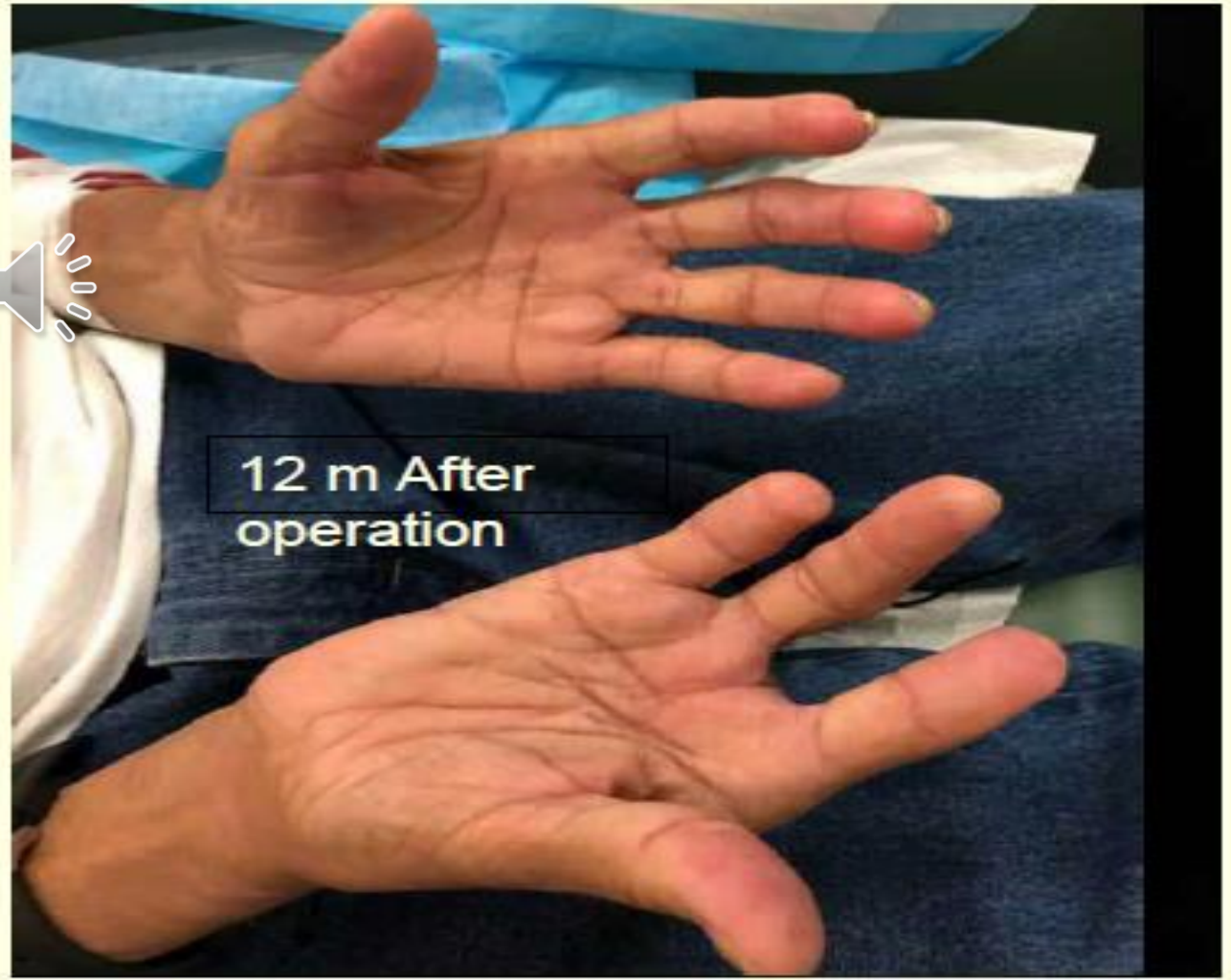
TABLE 3. *Pharmacokinetic properties of calcimimetics*

	Cinacalcet	Etelcalcetide	Evocalcet
Binding site	Transmembrane	Extracellular	Transmembrane
Half-life[†]	30–40 h	15.6 days	20–33 h
Period with a maximal decrease of PTH[‡]	4–12 h	0.5–24 h	4–12 h
Period with a maximal decrease of Ca[‡]	8–12 h	8 h–8 days	12–24 h
Metabolic organ	Liver	None	Liver
Risk of drug–drug interaction	High	Low	Low
Elimination in dialysis	0	Approximately 60%	0
CaSR activation concentration (EC_{50})	5.1×10^{-8} M	5.3×10^{-7} M	6.7×10^{-8}–1.6×10^{-7} M

[†]In dialysis patients (dialytic half-life for etelcalcetide [after three times per week of 5 mg for 12 weeks administration]). [‡]Single administration. CaSR, Ca-sensing receptor; PTH, parathyroid hormone.

Case Scenario

Am J Case Rep. 2019 Aug 9;20:1170-1174

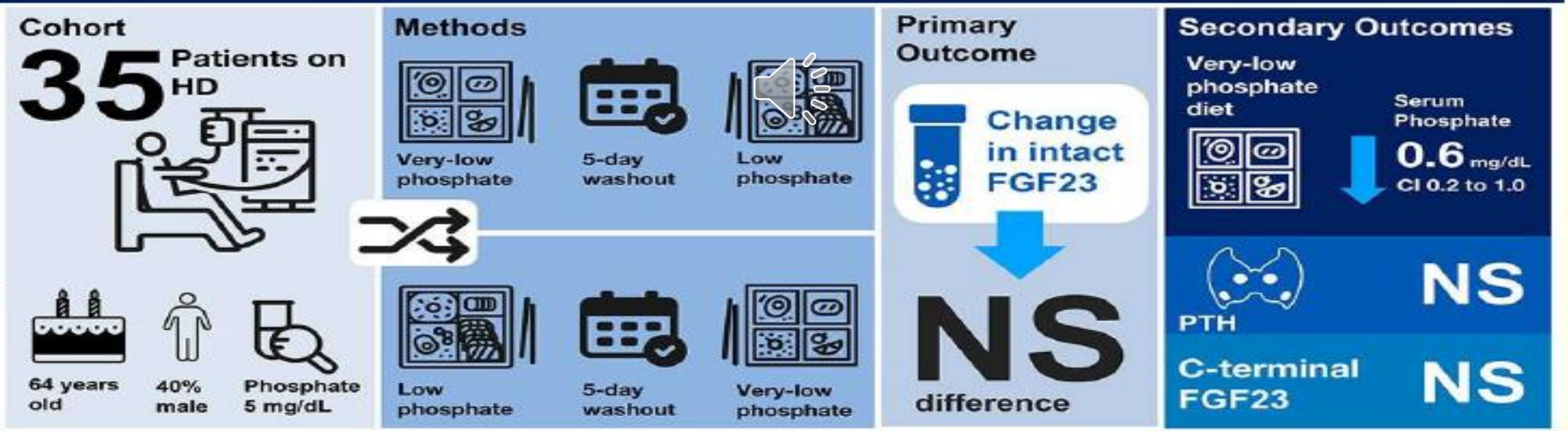


FGF-23 in Hemodialysis Patients: Effect of Low-Phosphate Diets

CJASN 14: 1475–1483, October 2019

What are the short-term effects of low-phosphate diets on FGF23 level?

CJASN
Clinical Journal of American Society of Nephrology



Conclusions The very-low-phosphate diet offered no benefit for FGF23 reduction but provided a greater phosphate-lowering effect.

Wan-Chuan Tsai, Hon-Yen Wu, Yu-Sen Peng, et al. ***Short-Term Effects of Very-Low-Phosphate and Low-Phosphate Diets on Fibroblast Growth Factor 23 in Hemodialysis Patients: A Randomized Crossover Trial.*** CJASN doi: https://doi.org/10.2215/CJN.04250419. **Visual Abstract by Pablo Garcia, MD**

Burosumab Therapy

CJASN 14: 1097–1099, July 2019

Perspective

Burosumab Therapy for X-Linked Hypophosphatemia and Therapeutic Implications for CKD

Farzana Perwad and Anthony A. Portale