Merging the definitions of osteoporosis into the framework of CKD-MBD

Paul D. Miller, M.D., HDSc (HON)
Distinguished Clinical Professor of Medicine
University of Colorado Health Sciences Center
Medical Director
Colorado Center for Bone Health
Lakewood, CO
millerbonecenter.com

DISCLOSURES

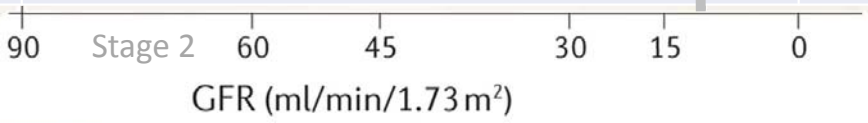
NONE

Chronic Kidney Disease (CKD) - Stages

CKD by GFR* categories: KDIGO 2012

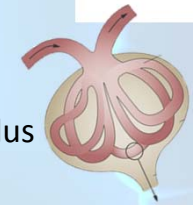
Dialysis

Stage		
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	



nephron

glomerulus



* **Glomerular filtration rate** (**GFR**) estimates how much blood passes through the glomeruli each minute.

Merging Osteoporosis and CKD-MBD

Back to Basics

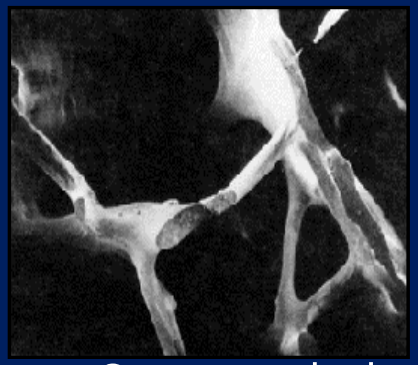
kidney-associated bone disease could be a more appropriate term because it emphasizes the renal osteodystrophy component and includes, in the broad term, osteoporosis as well.

Pazianis M and Miller PD Am J Kid Dis 2021

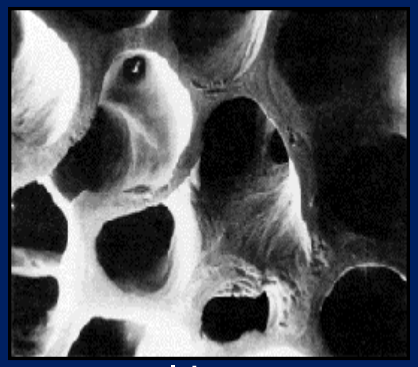
Osteoporosis: Identifying the Problem

"A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture." "Bone strength is a composite of bone density and bone quality"

NIH Consensus Development Conference on Osteoporosis, 2000.



Osteoporotic bone



Healthy bone

Definition of Chronic Kidney Disease-Mineral and Bone Disorder 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

Moe S et al KI 2008

Renal Osteodystrophy or Kidney Induced Osteoporosis

Can Coexits?

Moe S Curr Osteoporosis Reports 2017

Miller PD Am J Kid Dis 2017

Pathophysiology of Osteoporosis

Bone resorption exceeds bone formation

Negative Calcium Balance

Armas LAG and Recker RR: Endo Clinic North Amer 2012

Diagnosis of Osteoporosis

- By Central DXA of spine, hip, or wrist (T-score of -2.5 or lower)

- By Fragility fracture after the age of 50 years fractures of vertebrae, hip, wrist, pelvis, humerus, or tibia) once other causes of fragility fractures are excluded (osteomalacia, primary hyperparathyroidism, renal bone disease, OI, HYPP).– independent of the "T-score."

Kanis J et al. WHO Technical Report 1994

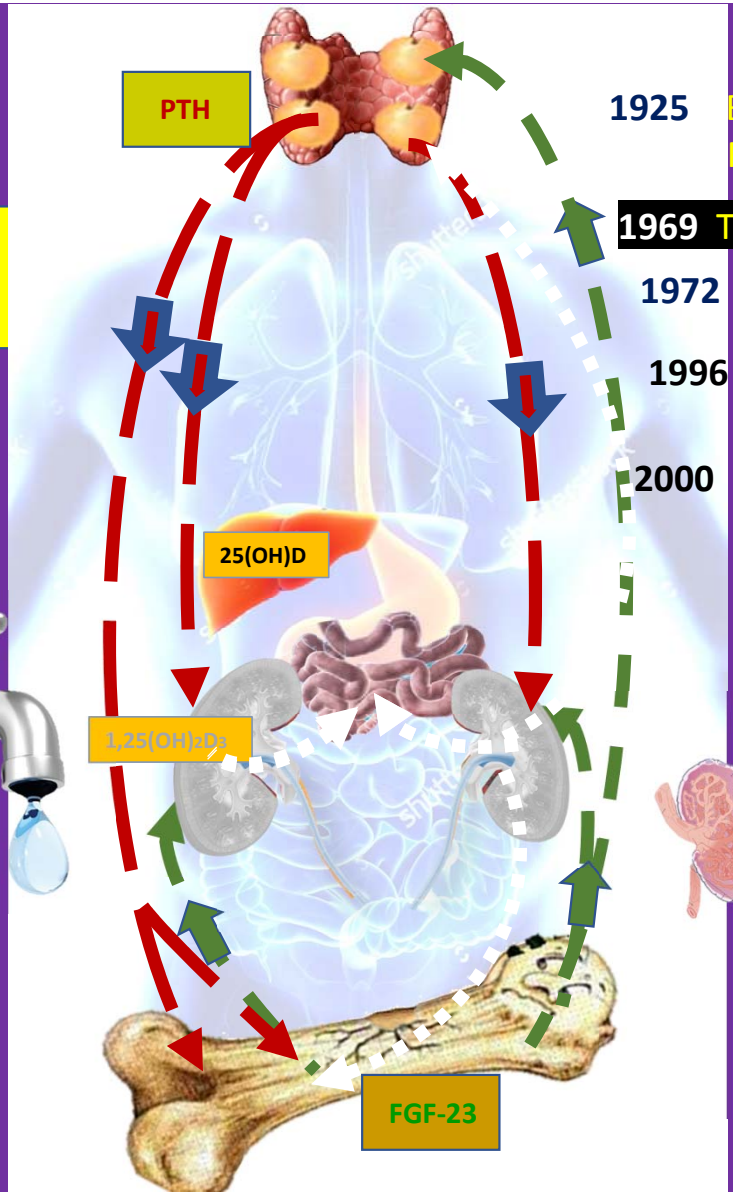
Pathophysiology of CKD-MBD

starts with Phosphate Retention

Trade off Hypothesis

Secondary Hyperparathyroidism Occurs in Major Degree as a "Trade Off" for the Adaptation in Phosphorus Excretion Required to Maintain External Phosphorus Balance in Advancing Renal Disease

Bricker NS, Slatopolsky E, Reiss E, Avioli LV. Arch Intern Med 1969;123:543-553



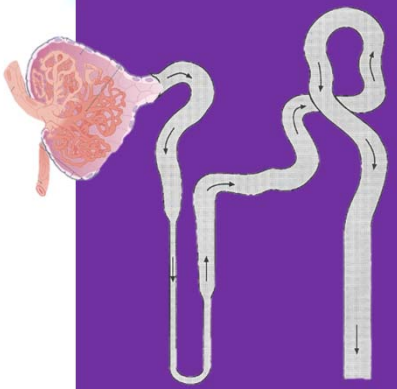
1925 Biologically active Parathyroid extract

1969 Trade off Hypothesis

1972 1,25 $(OH)_2D$

1996 Pi action on Parathyroids

2000 FGF-23



Nephron

Diagnosis of CKD-MBD

- Elevated serum FGF 23 plus…
- Elevated PTH
- Elevated (at times) serum phosphorus
- Exclude other forms of renal bone disease (adynamic, osteomalacia, hyperparathroid bone disease)

Pazianas M and Miller PD. JBMR Dec 2020

Elevated Serum Phosphorus

Is the stimulus for the early increase in FGF 23
and, later, PTH

Perspective

FGF23

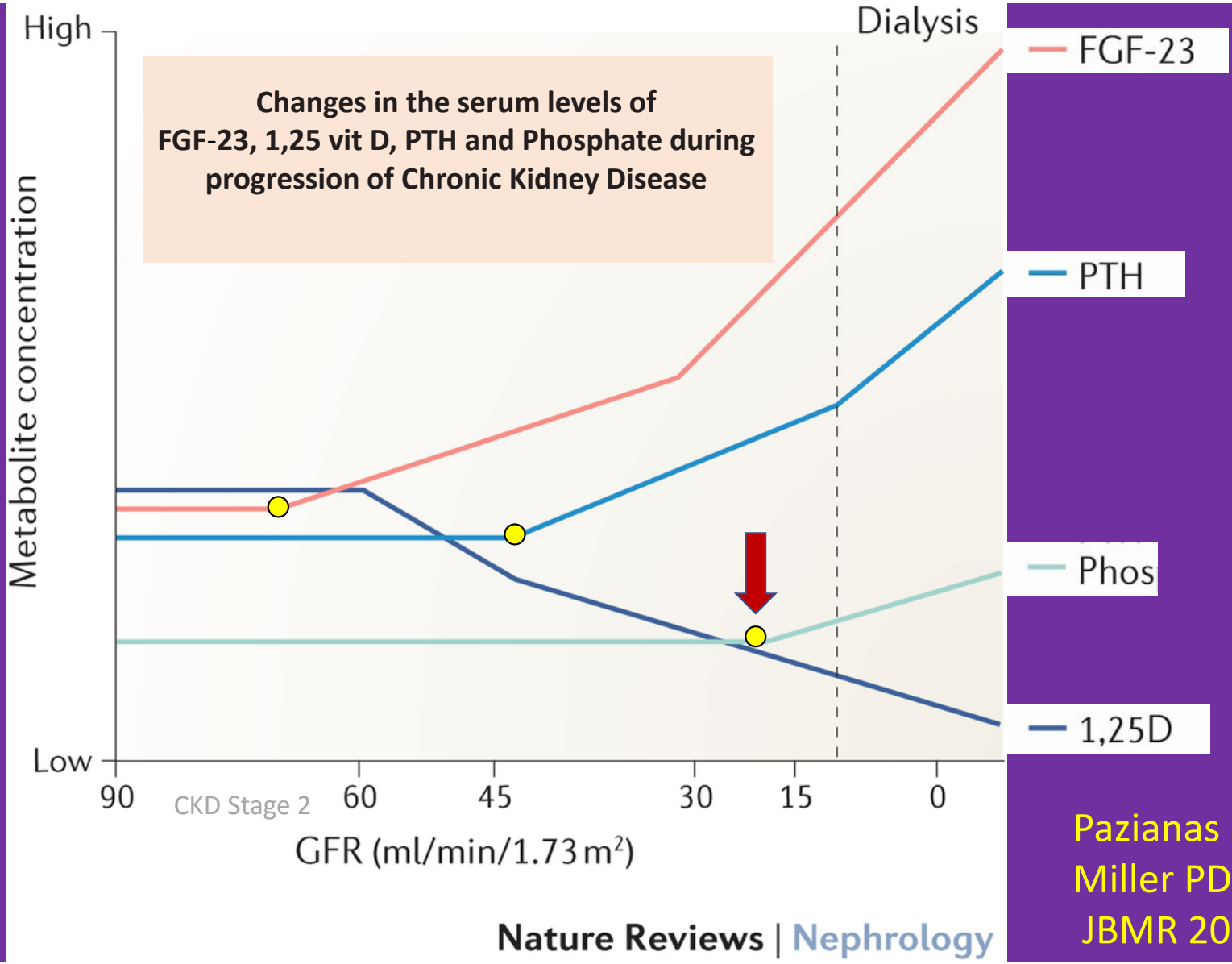
more than a regulator of renal phosphate handling?

Harald Jüppner, Myles Wolf, and Isidro B. Salusky JBMR 2010

What does FGF-23 do?

- Phosphaturic
- Inhibits the kidney production of 1,25 dihydroxy vitamin D
- Inhibits PTH production and secretion
- Effect on bone microenviroment
- Effect on cardiac muscle
- The FGF23 level in patients with CKD can even indicate their life expectancy.

Batra J et al. FGF-23 and CV Disease: A Review. Curr Opinion Endocrinol Diabetes..
Juppner H. Kid Internat 2011.
Li X. Front Med 2019



Pazianas M and
Miller PD
JBMR 2020

Regulation of FGF 23 Production

- Phosphorus stimulates
- PTH stimulates
- 1,25 D stimulates

> Partners to collectively to decrease serum phosphorus

- FGF 23 effect on bone: disturbs osteoblast function and matrix mineralization

Goltzman D et al. Front Hormonal Res 2018
Zhang DD et al. Exp Molecular Med 2019

Should Clinician's be Ordering FGF-23 ?

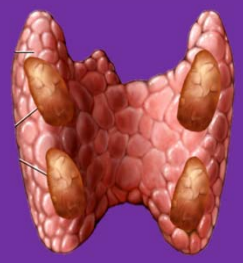
- 1. In CKD ?
- 2. In persistent hypophosphatemia ?
- 3. In unexplained osteomalacia ?
- 4. In patients with normal 25 (OH) D but low 1,25 OH D and normal GFR ?
- 5. In unexplained elevated BSAP ?
- 6. In RTA ?

Miler PD JCD 2012

How can we prevent hyperphosphatemia ?

- Diet ?-Ubiquitous in all food chains.
- GI Phosphate binders ?
- GOOD LUCK
- All poorly effective-why?


McDonald's



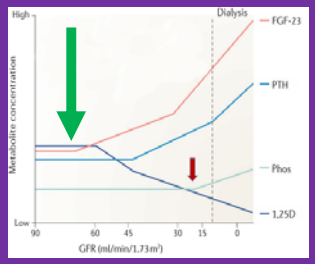
New Concepts

Prevention & Treatment Of CKD - MBD

Pazianas M and Miller PD
JBMR 2020

Am J Kid Dis 2021

Intermittent PTH Administration in Stage 2 CKD may:



- 1.Hand the **Control** of **Phosphate** levels back to PTH

-2.**Control FGF-23** levels
and **Eliminate** or **Reduce significantly** the risks associated with increased circulating **FGF-23**

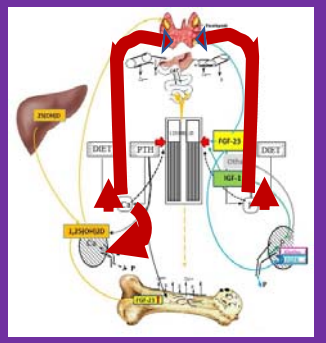
-3.**Achieve a better control** of **1,25(OH)$_2$D** levels

-4.**Reduce** the risk of **Atherosclerosis** and **Cardiovascular Disease**

5. Prevent the elevation of **PTH**

-6.**Protect** the **Parathyroid Glands** from Hyperfunction and **Prevent** Hyperplasia

-7.**Protect** the **Skeleton** from the Catabolic Effects caused by the Continuously Elevated circulating **PTH**



Fractures In Chronic Kidney Disease

- 1. Hyperparathyroidism
- 2. Adynamic bone disease
- 3. Osteomalacia
- 4. Post-transplantation
- 5. Osteoporosis

Atsumi K, et al Am J Kidney Dis 1999; 33(2):287-93.
Gupta A, et al. Journal of Bone and Mineral Research 12(Suppl. 1):S274.
Stehman-Breen CO, et al. Kidney Int 2000; **58**(5):2200-5.
Fried LF et al J Am Soc Nephrol 2007; 18: 282-286
Coco M and Rush H. Am J Kid Dis 2000; 36 (6): 1115-1121
Nickolas TL et al. Kid Internat 2008; 74(6): 721-731

Diagnosis of Osteoporosis in Stage 1-3A CKD

- Use the same criteria as is used in folks without CKD

Diagnosis of “Osteoporosis” in Stage 3B-5 CKD

Is a diagnosis of exclusion

Biochemical and Histomorphometry

Biochemical Markers of Bone Turnover

PTH and BSAP
combining the best of both worlds

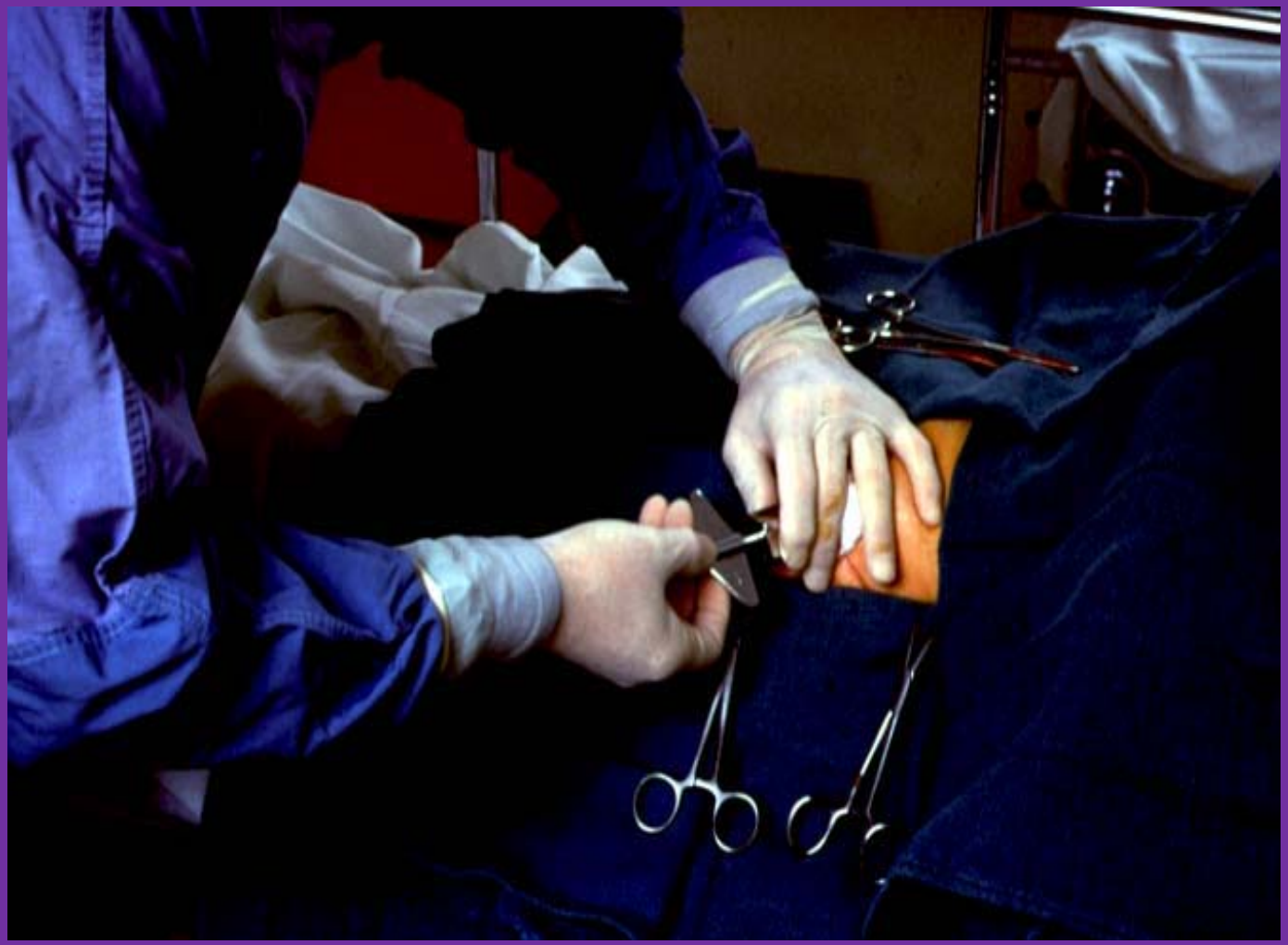
- 1. PTH “extremes” (< 100 pg/ml) or (> 600pg/ml) high specificity for adynamic and OFC.
- 2. Bone specific alkaline phosphatase (< 20 IU/L) has a high PPV (80%) for low bone turnover .
- 3.BSAP correlate with PTH values in stage 5D CKD: both are increased on bone biopsy in established high bone turnover.
- 4. Combining the lower quartile BSAP and PTH < 100-150 have a high PPV (90%) for adynamic bone disease.

Garrett G et al CJASN 2013
Couttenye C et al Nephrol Dialysis Transpl 2009
Eastell R and Sprague S

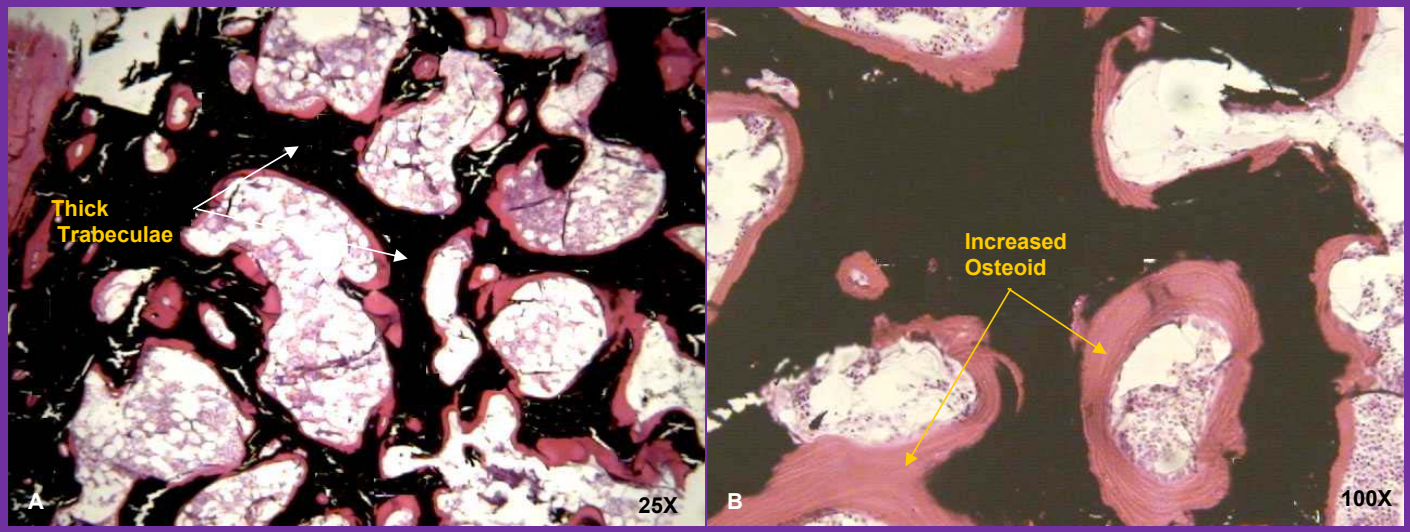
2 Bone Diseases to avoid "turning bone turnover down"

- Osteomalacia
- Adynamic bone disease (idiopathic)

May not want to use anti-resorptive in these 2 conditions that already have a low bone turnover to start

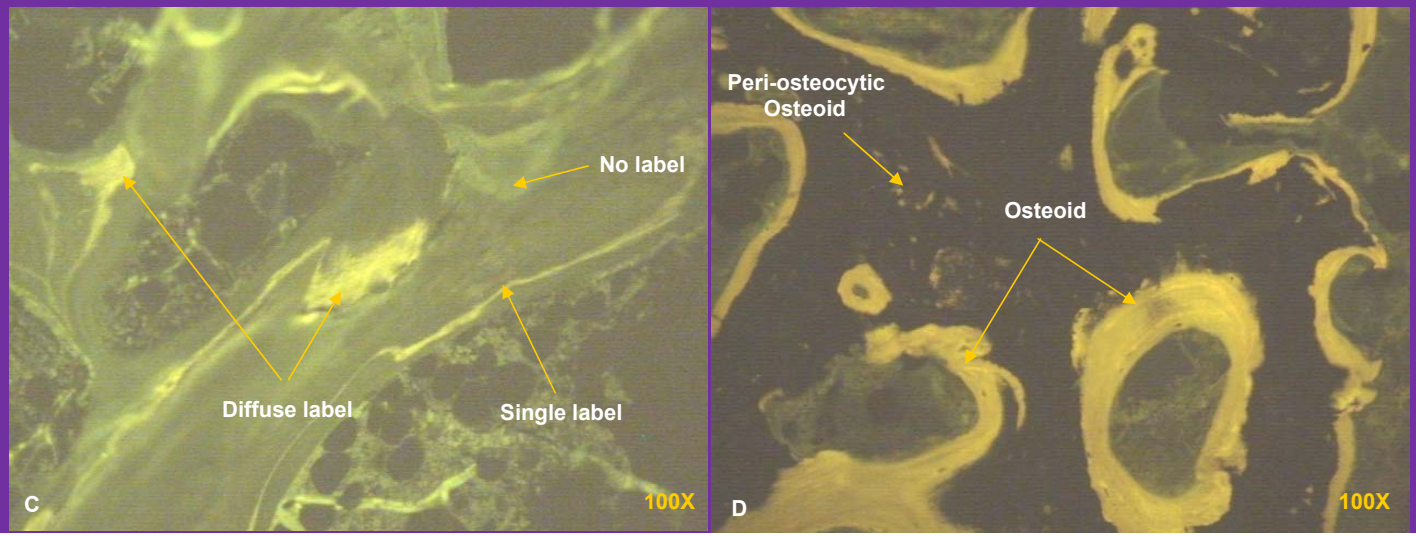


Von Kossa, H&E Stain for Calcium and Osteoid: Osteomalacia



Unstained, Fluorescent for Tetracycline

Von Kossa, H&E Stain, Fluorescent for Osteoid



Osteomalacia: always has a cause

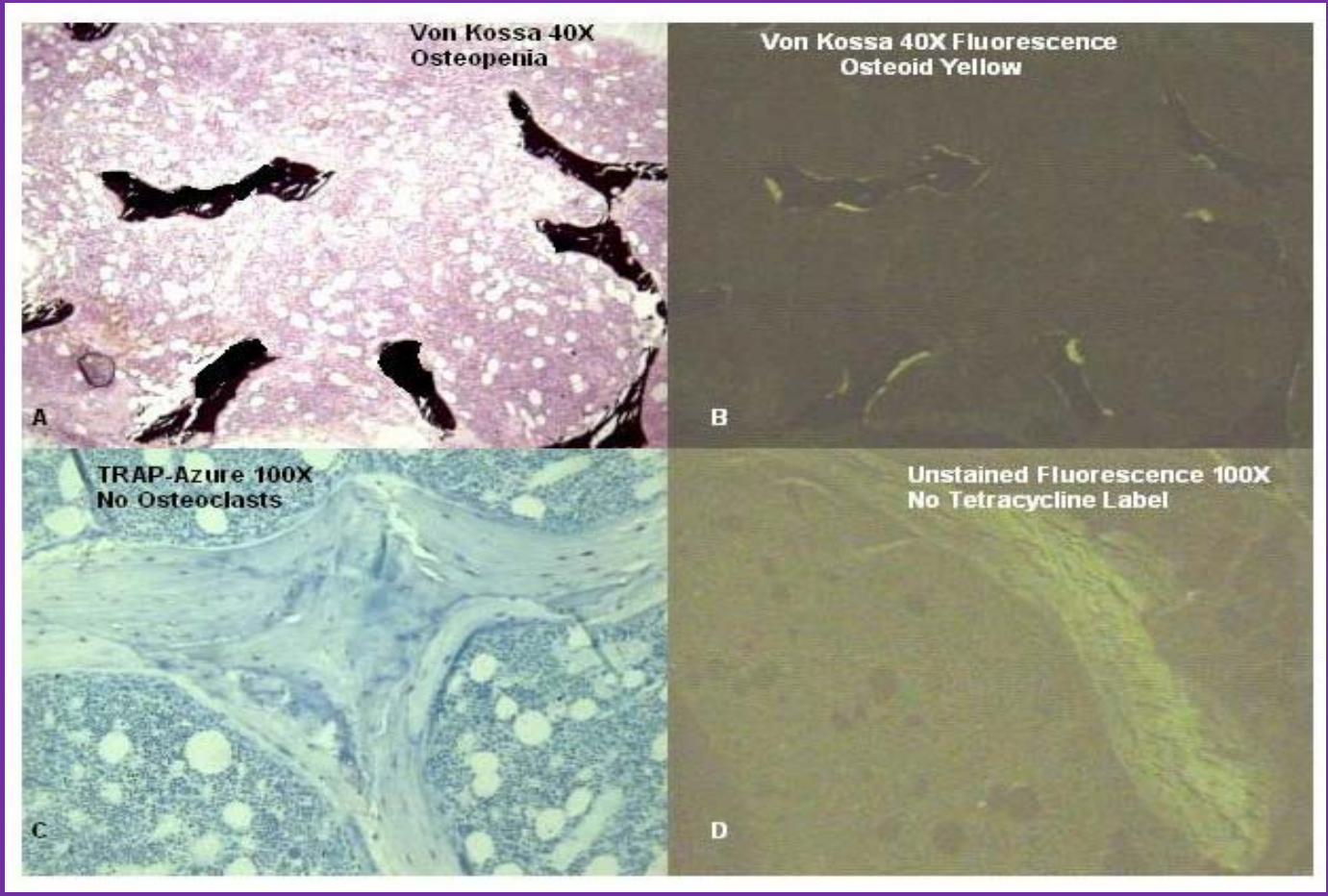
- Severe 25 OHD deficiency (< 8 ng/ml).
- Chronic hypophosphatemia
- Vitamin D resistant rickets
- Renal tubular acidosis
- Oncogenic osteomalacia (low serum PO^4, elevated FGF 23, low, 1, 25 D, phosphaturia)

Adynamic Bone Disease

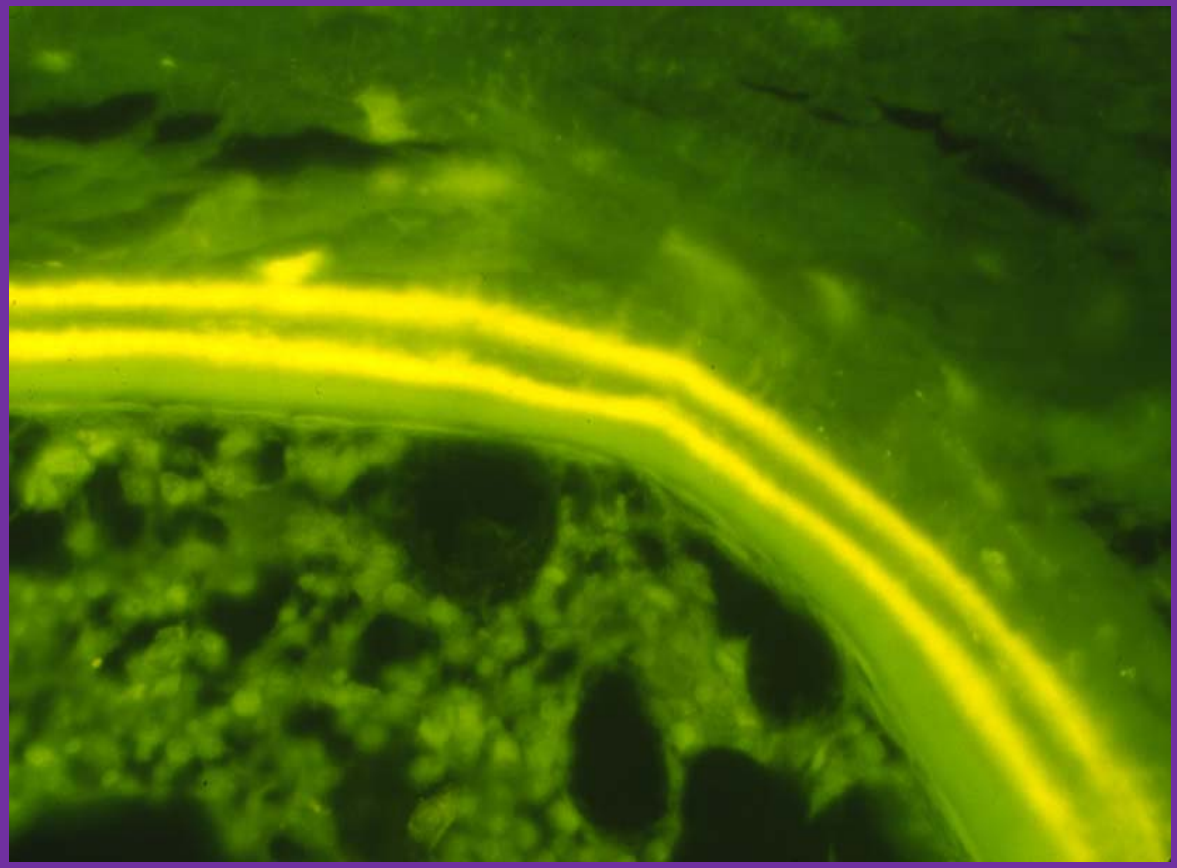
Absence of single tetracycline labels

BONE BIOPSY

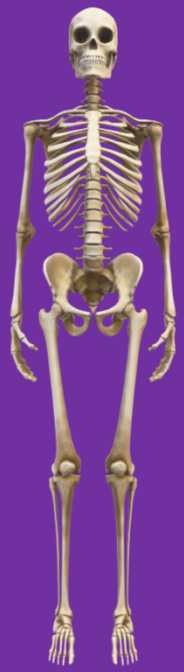
Renal Adynamic Bone Disease



Miller PD CJASN 2007



Treatment of Osteoporosis



Antiresorptive agents

Anabolic agents

Treat the same at GFR's of 90-45 ml/min (stage 1-3A CKD)

Therapies for osteoporosis: USA

- Hormone therapy
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin
- Teriparatide
- Denosumab (anti-rank ligand antibody)
- Abaloparatide
- Monoclonal antibody to Rank-L

Treatment of Osteoporosis in CKD

- 1. Stage 1-3 CKD: Treatment does not differ as in patients with PMO since clinical trials randomized patients down to "GFR" of 30 ml/min
- 2. Stage 4 CKD: Management dependent on considerations for "off-label" use:
- Post-hoc analysis show efficacy and safety through 3 years of risedronate, alendronate and raloxifene down to eGFR of30ml/min; and ,denosumab down to eGFR of 15 ml/min for 2-3 years. Teriparatide and Abaloparatide to an eGFR of 30 ml/min..
- 3. Stage 5/5D CKD: No data- off-label consideration for fracturing patients , e.g. very high risk with established osteoporosis.

Treatment of Osteoporosis in Stage 3B-5CKD

- Know what bone disease you are treating: adynamic, hyperparathyroidism, osteomalacia that may also be associated with osteoporosis.
- Most approved therapies for PMO have a FDA registration “warning” label to avoid use in patients with an eGFR of < 30 ml/min.
- No limitation for denosumab which can be used at eGFR <15 ml/min
- Teriparatide and abaloparatide “warning” is < 30 ml/min.
- Both teriparatide andabaloparatide can reverse “idiopathic” renal bone disease.
- In the future, romosozumb which inhibits sclerostin binding to osteoblasts may be the targeted therapy to renal “low bone turnover” disease, since serum sclerostin levels increase as eGFR decreases.

Stage 3B -5CKD ???

- Denosumab (Prolia ™). Approved REGARDLESS of GFR since it is not cleared by the kidney; has no negative effect on renal function.
- Bisphosphonates have a FDA label in their "warning section" not to use them with GFR < 35-30 ml/min-why???: bisphosphonates are cleared by the kidney and old data using IV Pamidronate had few patients had developed ATN. All recovered.
- In the IV ibandronate trials (3mg IV push Q 3 months), had no effect on renal function; and, IV zoledronic acid (Reclast™) had a transient but recoverable increase in serum creatinine, but not at an infusion rate of 30 ml/min.
- Teriparatide and abaloparatide increase renal blood flow and FDA label suggesting ("warning") not to use them at GFR < 30ml/min is based on no studies (prospective) of effectiveness at these lower levels of GFR.
- Recent data (post-hoc) does suggest effectiveness for patients with idiopathic renal adynamic bone disease and "osteoporosis" at levels< GFR of 30ml/min.(Palcu P et al: Am J Kid Dis 2015)

Off Label Use of Anti-Resorptive/Anabolic Agents is Considered in Stage 4 CKD

- 1. In very high risk patients who have osteoporotic fractures.
- 2. Whose mortality is high because of these fractures
- 3. And where in post-hoc analysis bisphosphonates, raloxifene, HT, denosumab have been shown to reduce fracture risk as compared to placebo in patients with eGFR down to 15 ml/min .
- Teriparatide and Abaloparatide also down to 30ml/min.
- May be useful for idiopathic renal adymanic bone disease.

Miller PD et al JBMR 2005
Jamal S et al JBMR 2007
Miller PD et al OI 2007
Delmas PD et al OI 2009
Sprague S et al Sem Dialysis 2007
Miller PD Sem Dialysis 2008
Miller PD Clin J Amer Soc Nephrol 2008
Miller PD Seminars Nephrology 2009

Thank You ISO 2021

Paul D. Miller, M.D., HDSc (HON)

- Founding President of ISCD
- Emeritus-Editor-in-Chief of J Clin Densitometry

- Distinguished Clinical Professor of Medicine
- University of Colorado Health Sciences Center
- Medical Director
- Colorado Center for Bone Health, Lakewood, CO
- website: millerbonecenter.com.
- 303-824-8352