

Bones and the Nephrologist

Is it osteoporosis or renal-related
bone disease (CKD-MBD) ? :
Assessing bone disease in
patients with kidney disease

Paul D. Miller, M.D.
Distinguished Clinical Professor of Medicine
University of Colorado Health Sciences Center
Medical Director
Colorado Center for Bone Research

Disclosures

- 1. Research Grants: Amgen, Merck, Lilly, Novartis, Roche-GSK, The Alliance for Better Bone Health
- 2. Scientific advisory boards: Amgen, Lilly, Novartis, The Alliance for Better Bone Health
- 3. Speakers bureaus: Amgen, Lilly, Novartis, Roche-GSK, The Alliance for Better Bone Health

The Fracture

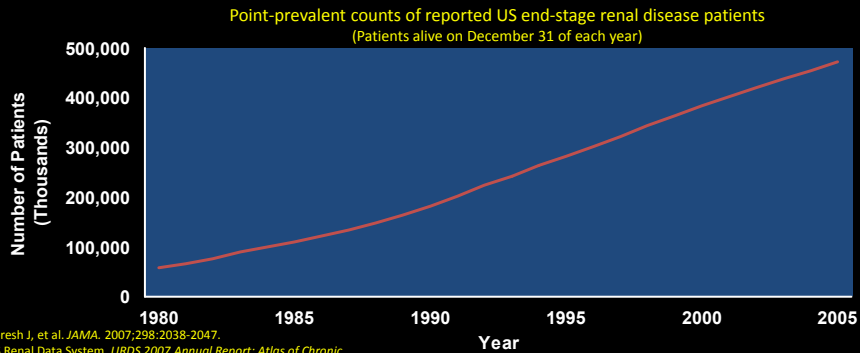
Is it “Osteoporosis” or is it Fracture related to decreased GFR per se?

Aging is Associated with both
Reductions in GFR and Increased
Prevalence of Osteoporosis

Increase population screening by BMD testing and automatic reporting of eGFR will bring these two situations more to the forefront

Prevalence of Chronic Kidney Disease and End-Stage Renal Disease Patients in the US

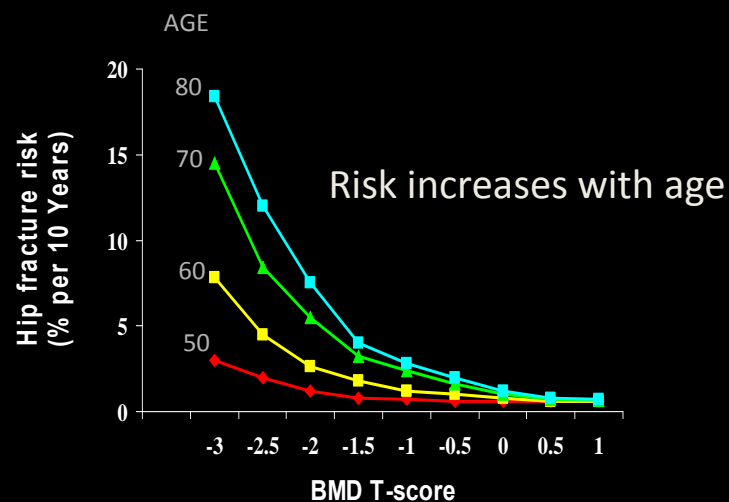
- 1 in 9 adults in America (> 26 million) has CKD
- Prevalence of CKD 1–4 has increased from 10% (NHANES I 1988–1994) to 13% (NHANES III 1999–2004)
- Increased prevalence of CKD is partly explained by increases in the aging population, obesity, and diagnosed diabetes and hypertension



Coresh J, et al. JAMA. 2007;298:2038-2047.
US Renal Data System. URDS 2007 Annual Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2007.

NHANES - National Health and Nutrition Examination Survey

Age & Risk of Fracture with Low BMD



Kanis et al, Osteopor Int 2001

Mortality is Much Higher Following Hip Fracture in ESRD Patients than Age-Matched Controls

1 year mortality after hip fracture in stage 5D
CKD: **60%**

1 year mortality after hip fracture in age-matched
controls: **15% female 30% male**

*Leinaw L and Perazella MA. Sem Dialysis 19: 75-79, 2006
Blive D, et al. JAMA 301: 513-521, 2009*

It's Just Not ESRD

All stages of CKD have higher fracture
risk than aged-matched persons
without CKD

Studies of Fracture Risk Associated with Age-Related Reductions in GFR

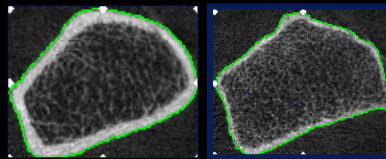
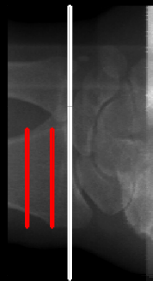
Author	N	Kidney Function	OR for Fracture (95% Confidence Interval)		
			Hip	Vertebral	Radial
Dukas ¹	5,481	GFR: <65 mL/min	1.57* (1.18–2.09)	1.31* (1.19–1.55)	1.79* (1.39–2.31)
Ensrud ²	9,704	Tiered GFR ≥60 mL/min 45–59 mL/min <45 mL/min		Hip† 1.0 1.57 (0.89–2.76) 2.32 (1.15–4.68)	
Fried ³	4,699	Tiered Cystatin-C <0.92 mg/L 0.92–1.05 mg/L 1.05–1.22 mg/L ≥1.22 mg/L	Men at Hip 1.0 0.91 (0.41–2.11) 0.80 (0.35–1.83) 1.25 (0.57–2.73)	Women at Hip† 1.0 1.20 (0.75–1.92) 1.49 (0.92–2.41) 1.66 (1.01–2.73)	
Nickolas ⁴	6,270	GFR: <60 mL/min		Hip 2.12 (1.18–3.80)	

*P<0.01; †P for trend <0.05

- Mild to moderate kidney impairment is associated with an approximate doubling in OR of all fractures as compared to age-matched people with normal kidney function

- Dukas L et al. *Osteoporos Int.* 2005;16:1683.
- Ensrud KE et al. *Arch Intern Med.* 2007;167:133.
- Fried LF et al. *J Am Soc Nephrol.* 2007;18:282.
- Nickolas TL et al. *J Am Soc Nephrol.* 2006;17:3223.

3D HRpQCT Imaging (Scanco Xtreme CT): Bone Microarchitecture



- Peripheral skeleton - non-dominant radius and tibia
- Acquisition of 3-D stack of 110 high resolution CT slices at distal end of radius and tibia
- ~ 3 min scan time, < 4 μSv
- Reproducibility:
 - Density: 0.8 - 3.7%
 - Trabecular structure: 3.8 - 7.3%

Courtesy of Dr. John Bilezikian and Elizabeth Shane

The Fracture in CKD

Is it CKD-MBD or “Osteoporosis”

Fractures In Chronic Kidney Disease As classified by renal osteodystrophy

- 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

Clinical Risk Factors for Osteoporosis in CKD

- Chronic Heparin
- Steroids
- Hypogonadism
- Hyperprolactinemia
- Poor Nutrition
- Vitamin D deficiency
- Hyperparathyroidism
- Metabolic acidosis

Lindberg JS, and Moe SM *Semin Nephrol* 19: 115-122
Cunningham J, et al. *Am J Kidney Dis.* 2004; 43(3):566-71
Miller PD *Current Osteoporosis Reports* 2005; 3(1): 5-12
Gal-Moscovici A and Sprague SM *Semin Dialysis* 2007; 20 (5) 423-430.

KDIGO:

Kidney Disease Improving Global
Outcome
(beyond just “renal osteodystrophy”)

Linking the metabolic bone abnormalities to
the systemic vascular disease process:

**Chronic Kidney Disease-Bone and Mineral
Disorder:**

CKD-MBD

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

Bone Disease in CKD: Differentiating Between Osteoporosis and CKD-MBD

CKD Stages 1–3

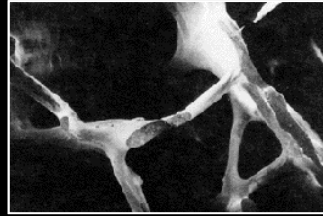
- Patient has low bone mass or fragility fracture
- Osteoporosis is more likely than CKD-MBD

CKD Stages 4–5/5D

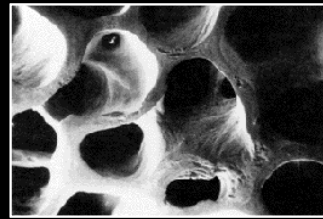
- Bone biopsy may be necessary to differentiate between different types of bone disease, including osteoporosis
-

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”



Osteoporotic bone



Healthy bone

NIH Consensus Development Conference on Osteoporosis, 2000.

17

The Clinical Diagnosis of Osteoporosis in Specific Populations (PMO, elderly men, etc) without any known reduction in GFR Can be Made By:

- 1. Low trauma fractures (once other causes of fragility fractures are excluded, e.g. osteogenesis imperfecta, etc)
- 2. World Health Organization (WHO) bone mineral density criteria using central dual energy x-ray absorptiometry (DXA): T-score - 2.5 or lower

Baim S, Binkley N, Bilezikian J et al. J Clin Densit 2008
Schousboe J, Vokes T, Broy S et al. J Clin Densit 2008

Diagnosis of Osteoporosis in Populations with Known Reduced GFR

- 1. Stage 1-3 CKD (GFR <90 -30 ml/min): same as patients without NKF defined CKD as long as there are no other biochemical abnormalities suggesting CKD-MBD
- 2. Stage 4-5 CKD (GFR < 30 ml/min): Cannot use WHO criteria and/or fragility fractures since all forms of severe renal osteodystrophy (histomorphometry defined) may have low T-scores or low trauma fractures

Moe S et al KI 2009
Miller PD Sem Dialysis 2008

Secondary Hyperparathyroidism

- 1. CKD-MBD
- 2. 25 OH D deficiency
- 3. Malabsorption (e.g. also Celiac disease)
- 4. Hypercalciuria
- 5. FHH
- 6. Lithium

- So it may not necessarily be CKD-MBD

Diagnosis of “Osteoporosis” in Stage 4-5 CKD

Is a diagnosis of exclusion
Biochemical and Histomorphometry

Biomarkers in Stage 4-5 CKD

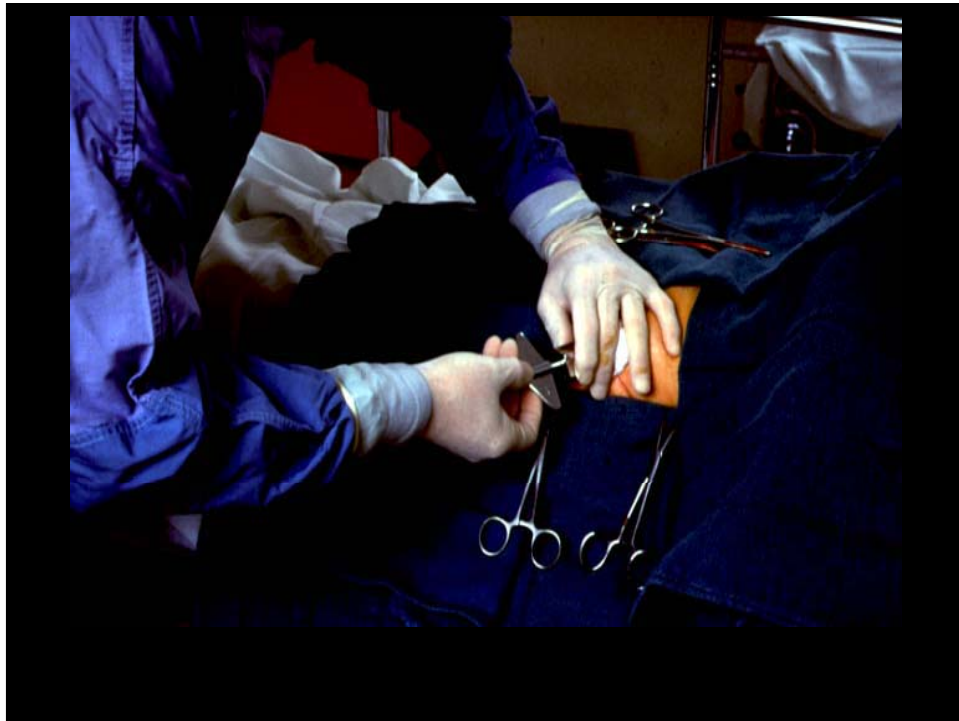
- 1. An elevated BSAP excludes adynamic bone disease and is not seen in osteoporosis (osteomalacia, severe hyperparathyroidism), if other causes of elevated BSAP are excluded (Paget's, metastatic Ca, etc)
- 2. An elevated (6X the upper limit of the normal range) intact PTH (old Nichols assay) most likely excludes adynamic bone disease; far more likely to be OFC.
- 3. A normal BSAP or a normal or mild elevation of PTH does not exclude adynamic bone disease.
- 4. A intact (1-84) PTH < 150 pg/ml: high PPV for adynamic bone disease.

Barreto FC et al KI 2008

Carmen SM et al Am J Kid Dis 2000

Bone Biopsy in CKD

- 1. Is the “gold standard” for diagnosis of renal bone disease and for defining the bone turnover activity.
- 2. Require double tetracycline labeling for quantitative bone histomorphometry
- 3. Is safe and has very low morbidity (including post-op pain) in experienced operators
- 4. May be especially important before bone turnover is “turned down”



Why

In CKD-MBD is excluding low bone turnover an evolving important issue as well as use of any pharmacological agent that may reduce bone turnover?

Preliminary Data Exists

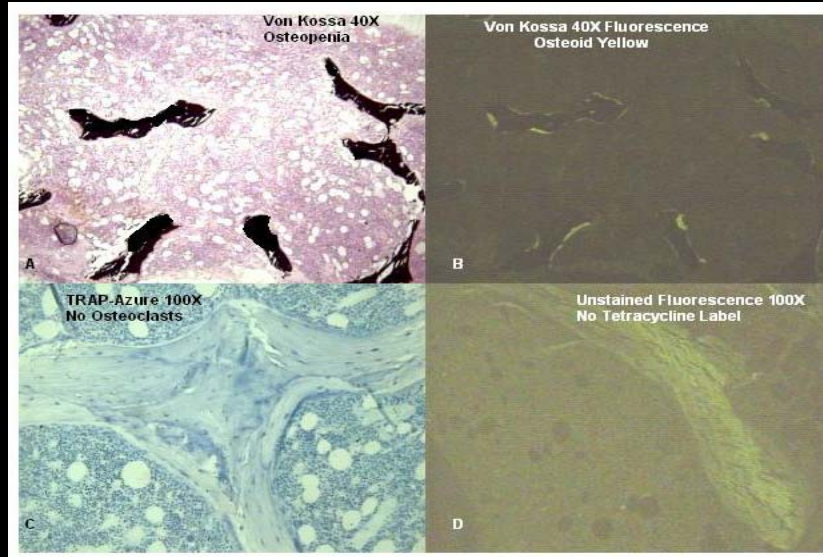
That even in mild (stage 3) CKD (GFR: 60-30 ml/min) bone turnover may be reduced, fracture risk increased,

And,

Reduced bone turnover may be linked to the greater risk for systemic vascular disease so prevalent in CKD

Hruska K et al Seminars Dialysis 2007
Cohen G J Nephrol 2005
Dukas LC et al OI 2005

Renal Adynamic Bone Disease



Conclusions

- 1. Patients with CKD (stage 1-3) and with low T-scores or fragility fractures more likely to have “osteoporosis” than other forms of renal bone disease (CKD-MBD).
- 2. The WHO criteria ($T \leq 2.5$) or fragility fractures, applicable for the diagnosis of PMO, cannot be applied to stage 4-5 CKD.
- 2. CKD (stage 4-5/5D) requires an assessment of biochemical profiles and, at times, a bone biopsy to differentiate among the heterogeneous forms of bone disease (including osteoporosis) that accompany CKD especially in those that fracture and in whom anti-resorptive agents are being considered off-label (bisphosphonates) or on-label (denosumab).

Thank You
ASN

For the invitation
Paul D. Miller, M.D.