The Treatment of Osteoporosis in CKD

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Objectives

- How do we assess fracture risk in CKD
- Can pharmacologic agents prescribed for osteoporosis be utilized in patients with CKD?
- Does prescribing vary with stage?
- Are some treatments better than others?

Disease Outcome Quality Initiative (DOQI) Guidelines: NKF-Stages of Chronic Kidney Disease

- Stage 1 CKD: GFR 80+ ml/min
- Stage 2 CKD: GFR 60-80 ml/min
- Stage 3 CKD: GFR 30-60 ml/min
- **Stage 4 CKD: GFR 15-30 ml/min**
- **Stage 5 CKD < 15 ml/min or ESRD**

DOQI Guidelines Am J Kid Dis 2002

CKD* and Osteoporosis

Age Group	Prevalence
20-29	0.0%
30-39	0.0%
40-49	0.0%
50-59	0.0%
60-69	7.3%
70-79	21.3%
80+	53.9%

Klawansky et al OI 2003

eGFR <35 ml/min

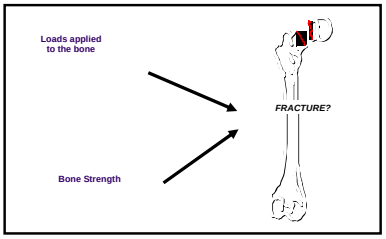
Fractures in CKD

- Increased hip fracture risk
  - NHANES: eGFR < 60 ml/min: OR = 2.12 (1.18 to 3.8)
  - SOF: eGFR 45-59 ml/min: HR = 1.57; eGFR < 45 ml/min: HR = 2.32
- Stage 5 CKD:
  - Up to 50% prevalence of fractures
  - Up to 50% excess mortality
  - Fractures occur at least 10 years earlier

The Dilemma

I have a dialysis patient with a **hip fracture** and a **T-score of - 4.0**
What drug should I prescribe?

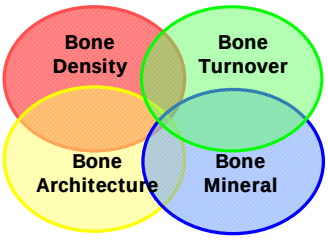
What disease do they have?



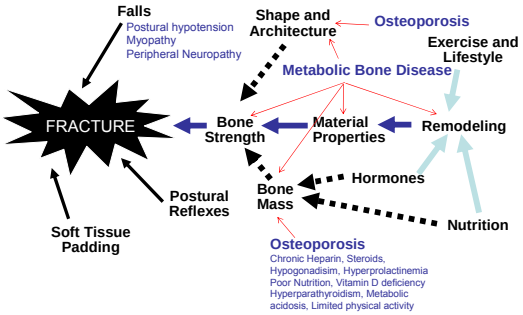
$$\frac{\text{Applied Load}}{\text{Bone Strength}} > 1, \text{ fracture will occur}$$

Bouxsein MJ Bone Joint Surg Am. 2001

Contributors to Bone Strength

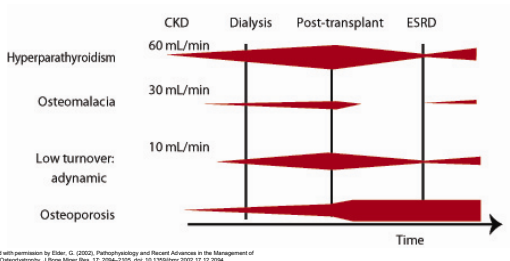


Fractures are Multifactorial



Adapted from Heaney RP, *Bone*. 2003;33:457-465.

Natural History of Various Bone and Mineral Disorders in CKD



Printed with permission by Elder, G. (2002). Pathophysiology and Recent Advances in the Management of Renal Osteodystrophy. J Bone Miner Res, 17: 2094–2105. doi: 10.1359/jbmr.2002.17.12.2094

How is Osteoporosis Diagnosed in CKD ?

- By The World Health Organization Criteria (1994) WHO- BMD) Criteria? : T-scores -2.5 or lower?
- NO!
- All forms of renal bone disease may have low BMD

How is Osteoporosis Diagnosed CKD ?

- By fragility (low-trauma) fractures?
- NO!
- All forms of renal bone disease may fracture

How is Osteoporosis Diagnosed in CKD ?

- By exclusion of other causes of forms of renal bone disease in a patient with CKD and low BMD or who is having fragility fractures with:
  Quantitative Bone Histomorphomtery

Quantitative Bone Histomorphometry

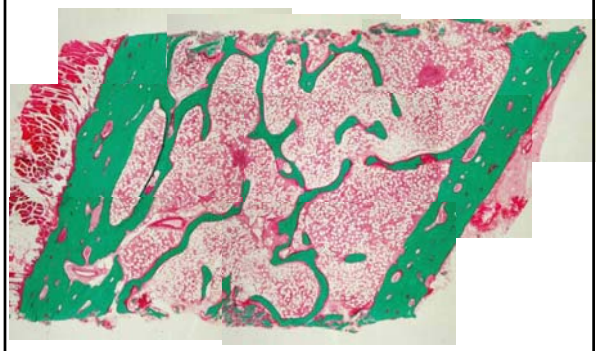
Classification based on turnover and mineralization:

- Hyperparathyroid bone disease
- Osteomalacia
- Adynamic bone disease
- Mixed bone disease

NKF K/DOQI Guidelines AJKD 2002

Bone Biopsy

- Tetracycline labeling (no calcium or dairy):
  - 250 mg QID day 1 and 2
  - Nothing for day 3 to 14
  - 250 QID for 4 days (day 15 to 18)
  - Biopsy 3 to 5 days after last dose
- Day of biopsy:
  - surgery room, sterile gowns, gloves and drapes
  - BP, HR and oximetry monitoring
- IV
- For CKD pts: dDAVP 20µg IV in 30 min



Identifying the Type of Bone Disease is Critical

- Different bone diseases have different treatments
- Antiresorptive agents may make adynamic bone disease worse

Limitations of Histomorphometry

- Invasive
- Specialized expertise
- Costly
- Histology may be "fluid"

Non Invasive Fracture Risk Assessment

- BMD testing by DXA
- pQCT/HR-pQCT
- Bone turnover markers-**only non static assessment of bone**
- Neuromuscular testing

Take Home Message - DXA

- BMD at hip and spine poor discriminators of fracture status in stage 5 CKD
- Proximal forearm may be useful
- Stage 3 to 5 CKD- hip BMD may be useful
- Limited to cross sectional data

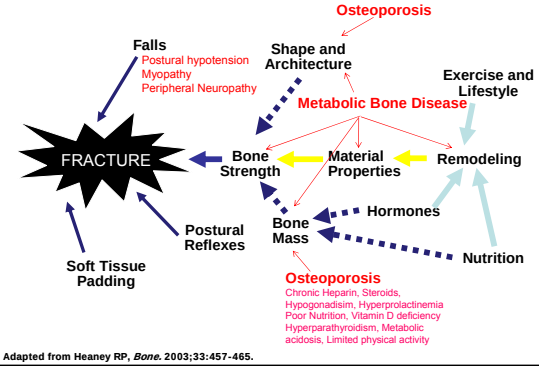
Take Home Messages - pQCT

- Able to discriminate fracture status
- In pm women adds to fracture prediction by DXA; not so in our CKD cohort
- Clinical utility needs to be rigorously tested
  - Cost
  - Limited availability

Take Home Message- Markers

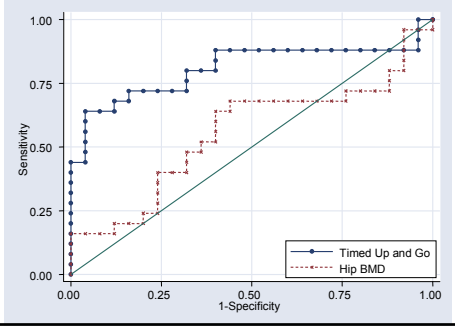
- Limited by cross sectional data
- Bone turnover markers may be useful
- Longitudinal studies needed

Fractures are Multifactorial

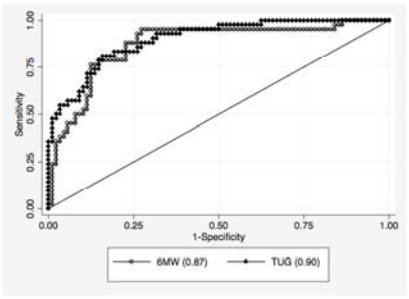


Adapted from Heaney RP, *Bone*. 2003;33:457-465.

Ability of BMD (AUC 0.6), TUG (AUC 0.8) to Discriminate Fracture Status



Relationship between sensitivity and specificity of the 6 minute walk (6MW) and the timed up and go (TUG) and the ability to identify patients with fracture†. The area under the receiver operating characteristic curve for the 6MW was 0.87, and for TUG was 0.90 (p>0.05).



†Fracture defined as self reported low trauma fracture since age 40 and

Take Home Messages- Muscle Strength Testing

- Easy, minimal equipment, inexpensive
- Excellent discriminators of fracture status in early and late CKD
- Cross sectional data

Exceptions to the Biopsy Rule?

- When certain there is no adynamic bone disease
  - Prevalence is felt to be low before stage 5 CKD
- If ruled out hyperparathyroidism/osteomalacia
  - 25 hydroxy vitamin D level
  - Serum PTH
- Then WHO criteria and/or the fragility fractures can be used to diagnose osteoporosis in Stages 1-4 CKD
- Stage 5 CKD biopsy before treatment

With Certainty

An elevated BSAP or a low- low normal PTH or unexplained hypercalcemia in a patient with stage 4-5 CKD must be defined before considering with bisphosphonates

US/European Labeling States:

Oral bisphosphonates are not recommended in patients with creatinine clearance
< 30 mL/min: (Stage 4-5 CKD)

Renal Function

- FDA Label suggests measuring a creatinine clearance and avoiding bisphosphonates if CrCl < 35 ml/min
- Measurement of CrCl is not a standard of care in the management of PMO
- Osteoporosis clinical trials did not measured CrCl for randomization (used serum creatinine)
- Using eGFR may become standard of care in the management of PMO

Strategies to Prevent Fractures

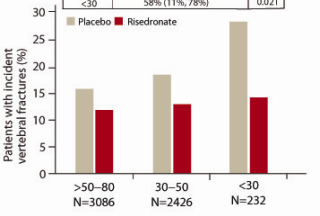
Bold indicates data for fracture risk reduction in CKD.

- Reduce bone resorption:
  - **Bisphosphonates**
  - **Denosumab**
  - **Raloxifene**, estrogen replacement treatment, calcitonin
- Increase bone formation:
  - **Teriparatide**
- Address abnormal mineral metabolism:
  - Lower phosphate
  - Supplement vitamin D
  - **Calcimimetics** **or** **parathyroidectomy**
- Prevent fall-related injuries:
  - Hip protection

Drug data are based on post hoc analyses, generally of trials where patients had otherwise normal mineral metabolism.

Risedronate Reduces Incident Fractures in Stages 2-4 CKD

eGFR (mL/min)	Treatment effect, risedronate vs placebo (95% CI)	P value
>50–80	32% (14%, 46%)	0.001
30–50	45% (31%, 57%)	<0.001
<30	58% (11%, 78%)	0.021



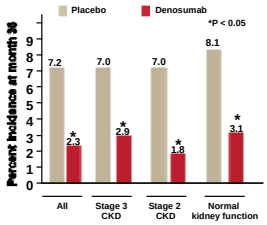
Combined analysis from nine placebo-controlled studies on risedronate treatment for up to 3 years:

- Constant risk of vertebral fracture in patients with active treatment
- Placebo group shows increased risk with more severe renal impairment, consistent with higher age and more severe osteoporosis

Bisphosphonates have not been studied in stage 5/5D CKD

Adapted from Miller PD et al., 2005

Denosumab Reduces Incident Fractures in Stages 2- 4 CKD



Denosumab has not been studied in dialysis patients.

- Pivotal study of denosumab versus placebo in older women (age 72.3 ± 5.2 years):
  - Renal function was normal (stage 1) or impaired (stages 2–4); no patients on dialysis
  - Fracture rate over 3 years was significantly reduced with denosumab in each CKD stage
- Renal function did not interact significantly with fracture rate
- Denosumab metabolism is independent of renal function

Adapted from Jamal SA et al., 2011.

Prolia – Proceed with Caution

- Antiresorptive agent- not appropriate in patients with low turnover bone disease
- Profound supression of bone turnover- can result in symptomatic hypocalcemia in those with vitamin D deficiency

Raloxifene Reduces Incident Vertebral Fractures in Stages 2-4 CKD

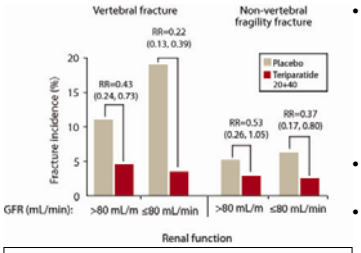
	Fracture rate (n/N (%))	Treatment effect on incident vertebral fracture OR (95% CI)
Total cohort	479/6472 (7.4)	0.57 (0.47 to 0.69)
eGFR <45	25/282 (8.9)	0.74 (0.32 to 1.68)
eGFR 46–59	265/3497 (7.6)	0.54 (0.42 to 0.69)
eGFR ≥60	189/2693 (7.0)	0.60 (0.44 to 0.80)

Raloxifene has not been studied in stage 5/5D CKD.

- Placebo controlled study of patients with postmenopausal osteoporosis plus baseline CKD, followed over 3 years
- BMD measures confirm significant improvement at hip and spine
- No significant improvement in non-vertebral fracture rate in any category of CKD

Ishani A et al., 2008.

Teriparatide Reduces Incident Fractures in Stages 2-4 CKD



- Patients with normal (GFR ≥80), mildly impaired (GFR 50–79) or moderately impaired (GFR 30–49 mL/min) kidney function
- Evaluated over median 21 months
- All had normal baseline thyroid and parathyroid hormone levels

Teriparatide has not been studied in stage 5/5D CKD.

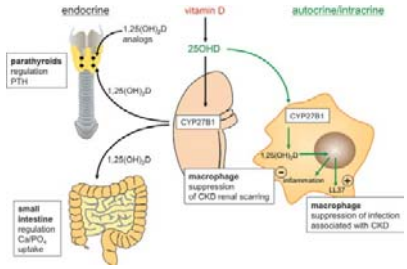
GFR = glomerular filtration rate.

Miller PD et al., 2007.

Teriparatide for All?

- Increases bone formation, decreases bone resorption
- Dose and frequency of administration in men and women with CKD unknown

Vitamin D



Cholecalciferol deficiency (D3 from skin, diet, supplements)
- Reduced sun exposure
- Reduced skin synthesis
- Reduced ingestion of foods
- Proteinuria with loss of vitamin D–binding protein
- Loss in peritoneal fluid in patients on peritoneal fluid

Calcidiol deficiency (25 OH vitamin D)
- Reduced availability of cholecalciferol
- Reduced liver synthesis of calcidiol

Calcitriol deficiency (1, 25 OH vitamin D)
- Reduced availability and activity of renal 1-hydroxylase
- Reduced endocytotic uptake by megalin and cubulin
- Increased activity of 24,25(OH)2D enzyme by elevated PTH diverting calcidiol to inactive metabolite
- Increased activity of 24-hydroxylase by FGF-23 ; increased degradation of 1,25(OH)2D

Calcitriol resistance
- Loss of VDR in parathyroid glands
- Impaired binding of active vitamin D to VDR and impaired binding of the vitamin D–VDR complex to the vitamin D receptor element

Vitamin D Replacement

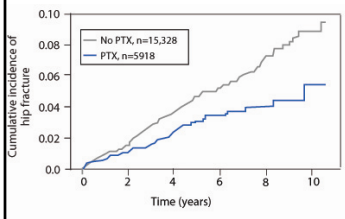
- Cross sectional, observational cohort studies report that lower serum 25(OH)D is associated with greater mortality, cardiovascular disease
- Meta analysis* (5 RCT and 17 Observational Studies): vitamin D supplementation (ergo or cholecaliferol) increased vitamin D, increased PTH, no data on clinical outcomes

*Kandula CJASN 2011

What is my Approach?

- Measure 1, 25 and 25 (OH) D
- Treat both to obtain as near normal values as possible
- NB: I do not use the PTH to infer the 1,25 D level

Long-term Reduction in Fracture Risk for Stage 5 CKD Patients Following Parathyroidectomy



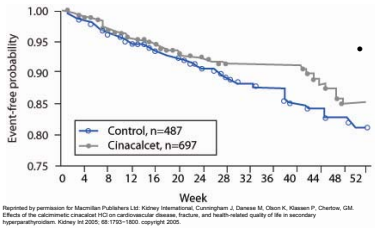
Parathyroidectomy was associated with:

•32% lower risk of hip fracture (95% CI 0.54 to 0.86; p<0.001)

•31% lower risk for any analyzed fracture (95% CI 0.57 to 0.83; p<0.001)

Rudser KD et al., 2007.

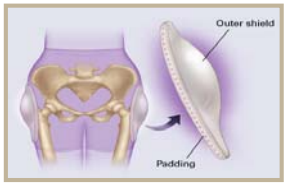
Reduced Fracture Rate Over 1 year of Calcimimetic Treatment



- Cinacalcet decreases PTH, calcium and phosphate in ESRD
- Combined analysis from four year-long studies in 1184 patients :
  - Decreased risk of fracture (RR=0.46; 95% CI 0.22 to 0.95)
  - Decreased cardiovascular hospitalizations (RR=0.61; 95% CI 0.43 to 0.86)

Cunningham J et al., 2005.

Hip Protectors: No Evidence But No Harm



- 90% of hip fractures occur due to falls
- 5 to 10% of falls result in fractures
- Fear of falling reduces independence and mobility
- No data to support use of hip protectors in CKD
- Note: meta-analysis proves that hip protectors do not work if the patient does not wear them

Kannus P et al., 2000; Michael YL et al., 2010.

Take Home Messages - Treatment

- With low T-scores and/or fragility fractures, osteoporosis is probably the correct diagnosis if r/o osteomalacia, severe hyperparathyroid bone disease or adynamic bone disease (rare before stage 5 CKD)
- Stage 5 CKD requires a double tetracycline-labeled bone biopsy to be certain of the diagnosis - Our Case
- Oral bisphosphonates in FDA-registered doses for PMO are probably safe in CKD stages 1-4 for a 2-3 year duration of treatment

Acknowledgements

- CIHR New Investigator Award
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