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

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The Fracture

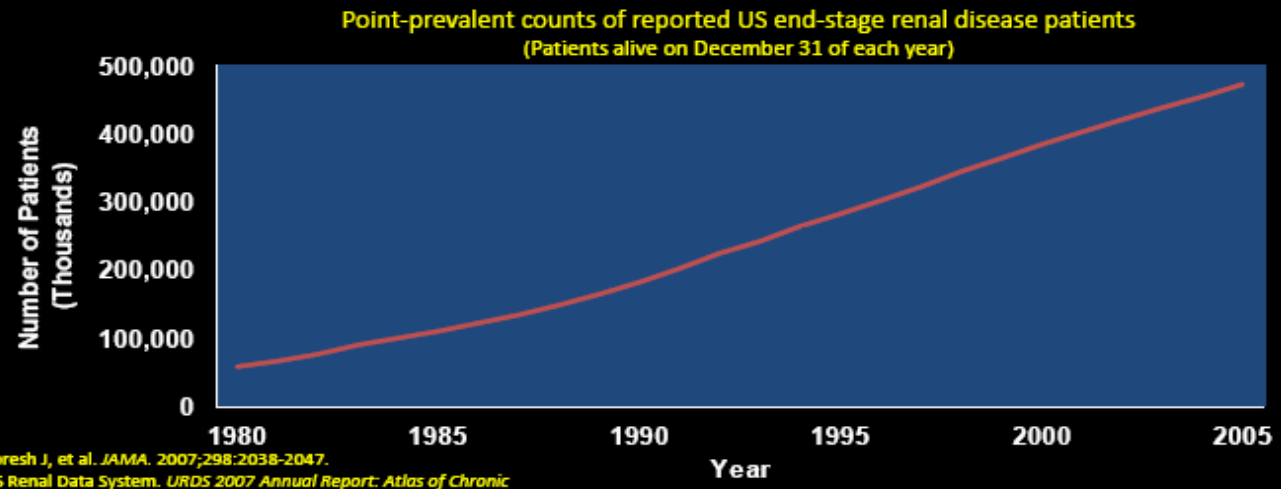
Is it “Osteoporosis” or is it Fracture related to decreased GFR per se?

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

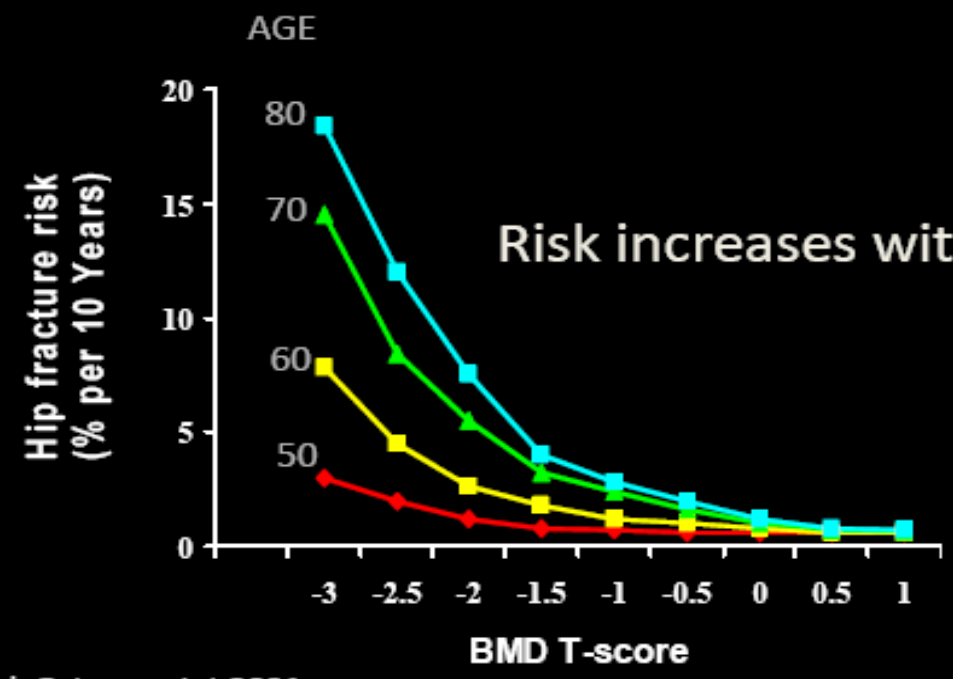
- 1 in 9 adults in America (> 26 million) has CKD
- Prevalence of CKD 1–4 has increased from 10% (NHANES I 1988–1994) to 13% (NHANES III 1999–2004)
- Increased prevalence of CKD is partly explained by increases in the aging population, obesity, and diagnosed diabetes and hypertension



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

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)		
Dukas[1]	5,481	GFR: <65 mL/min	Hip 1.57* (1.18–2.09)	Vertebral 1.31* (1.19–1.55)	Radial 1.79* (1.39–2.31)
Ensrud[2]	9,704	Tiered GFR		Hip†	
		≥60 mL/min		1.0	
		45–59 mL/min		1.57 (0.89–2.76)	
		<45 mL/min		2.32 (1.15–4.68)	
Fried[3]	4,699	Tiered Cystatin-C	Men at Hip		Women at Hip†
		<0.92 mg/L	1.0		1.0
		0.92–1.05 mg/L	0.91 (0.41–2.11)		1.20 (0.75–1.92)
		1.05–1.22 mg/L	0.80 (0.35–1.83)		1.49 (0.92–2.41)
		≥1.22 mg/L	1.25 (0.57–2.73)		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

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

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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

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

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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
- Hypogonadisim
- 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.

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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

Moe S et al Kid Internat 2006

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

Moe S et al. *Kidney Int.* 2006;69:1945.
Moe SM et al. *Kidney Int Suppl.* 2009;113:S1.

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 likley 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”

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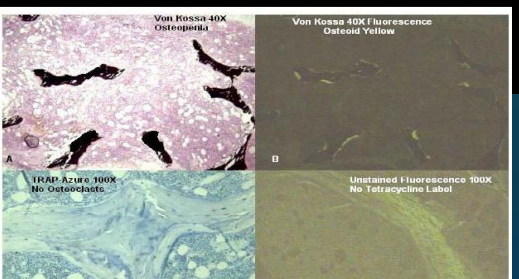
Why

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?

Renal Adynamic Bone Disease



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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 20005
Dukas LC et al OI 2005

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 ≤ 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).

Fractures in CKD and prevention

TABLE 1. Risk factors associated with fracture in dialysis patients

Risk factor	References
Older age	(1,2,15,16,18,24–27,69)
Female gender	(2,15,16,18,24–27)
Longer time on dialysis	(15,16,24–27,52,69)
Diabetes	(16,18)
CVD or PVD	(16,24)
Low BMI	(16,18,24)
Psychoactive medications	(15)
Caucasian race	(1,24)
Previous kidney transplant	(15,16,24–27)
History of any fracture/vertebral fracture	(49)
PTH (high or low)	(1,3,15,16,49,54)
ALP (high or low)	(1,3,46)
Low albumin	(15)
Hyperhomocysteinemia	(63)

PTH, parathyroid hormone; ALP, alkaline phosphatase; CVD, cerebrovascular disease; PVD, peripheral vascular disease; BMI, body mass index.

TABLE 2. Checklist for fracture risk in patients with CKD

Steps to determine fracture risk
Take a history and assess risk factors for fracture (Table 1)
Assess bone turnover with biochemical markers (e.g., extremes of PTH and ALP)
Decide whether a DEXA should be performed
Lateral spine X-ray to assess for prevalent vertebral fracture
Assess the risk of falls; falls diary/functional testing
Determine if a bone biopsy is required

CKD, chronic kidney disease; PTH, parathyroid hormone; ALP, alkaline phosphatase; DEXA, dual-energy X-ray absorptiometry.

Vitamine D

CJASN ePress. Published on September 28, 2010 as doi: 10.2215/CJN.03940510

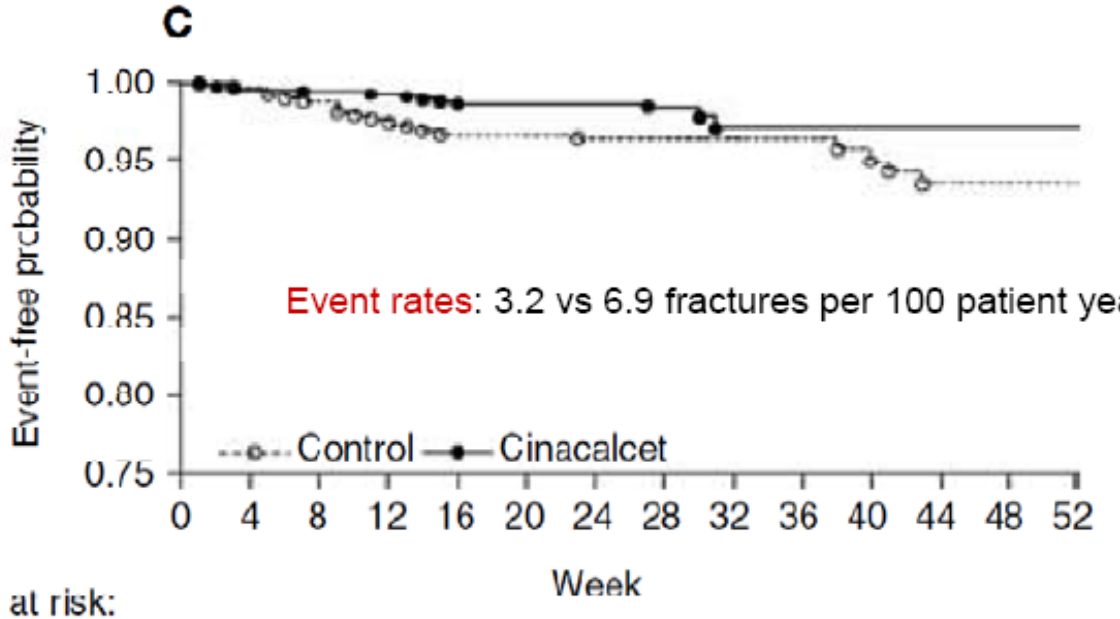
Vitamin D Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Observational Studies and Randomized Controlled Trials

Praveen Kandula,* Mirela Dobre,†‡ Jesse D. Schold,§‖ Martin J. Schreiber, Jr.,§ Rajnish Mehrotra,¶** and Sankar D. Navaneethan§

"….none of the available studies explored the effect of vitamin D supplementation on bone mineral density, fracture risk, cardiovascular disease, and mortality in CKD."

Cinecalcet

Fracture rates with Cinacalcet:



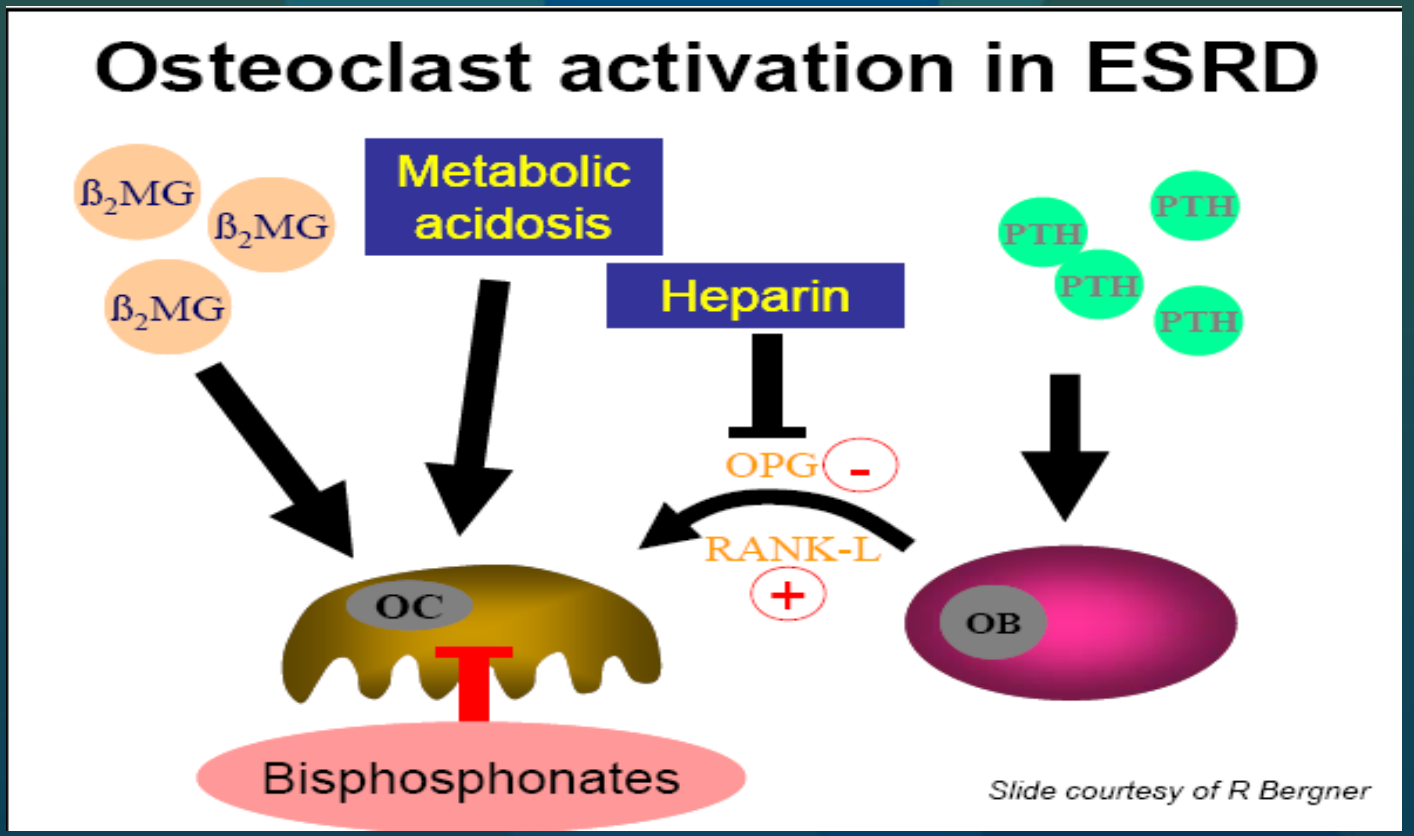
Event rates: 3.2 vs 6.9 fractures per 100 patient years.

Subjects at risk:														
Placebo (*N*)	487	470	445	419	404	383	367	314	136	132	120	117	112	109
Cinacalcet (*N*)	697	656	614	574	554	513	485	392	132	131	125	115	110	106

Cunningham J et al, KI, 2005 – summative data from 4 clinical trials, involving 1184 patients.

Agent	Action	Use in CKD
Bisphosphonates	Antiresorptive, reduce bone turnover, inprove mineralization. Concern over microfractures.	Very little data. Concern re adynamic bone disease. Dosing - ? Double interval
Strontium	Increased bone formation and decreased resorption. Improves cortical thickness.	?
PTH (teriparatide)	Increase in bone formation markers, followed by increase in resorption. “Anabolic window.”	Doesn’t make sense for CKD.
Denosumab	RANK-ligand binding and neutralizing. Marked reduction in bone resorption.	? No data. Concern re adynamic bone disease.

Bifosfonaten

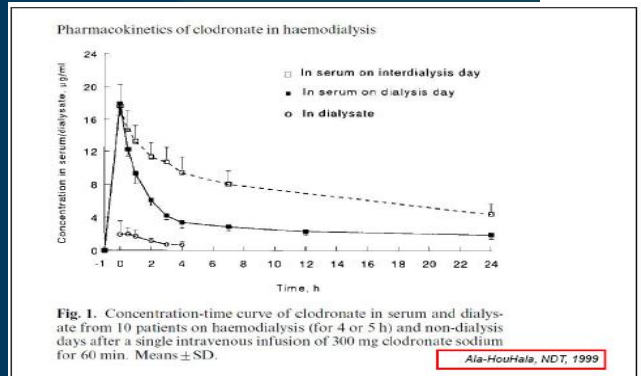


Pharmacokinetics in renal disease

- <1% of oral doses absorbed
- 40-60% then binds to calcium in hydroxyapatite and remains in bone for months to years
- The rest is renally excreted

- Very few studies in CKD – most advise halving the dose or doubling the interval at GFR < 30ml/min.

Very little safety data, most does not report particular problems.



Wetmore JB et al, Nephrology, 2005

31 HD patients randomised to alendronate or placebo for 6 months.

Data for T scores.

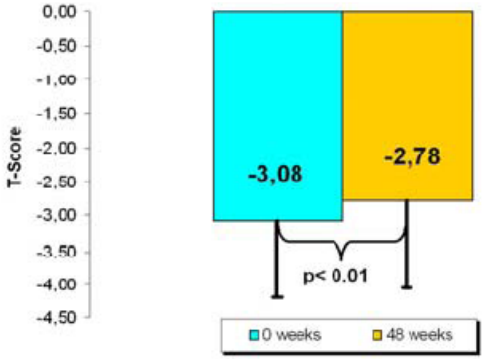
	Alendronate			Placebo			Between group
Site	Baseline	6 months	P-value	Baseline	6 months	P-value	P-value
Ward's triangle	-2.7	-2.7	NS	-1.8	-2.0	0.05	0.04
Femoral neck	-1.8	-1.8	NS	-1.1	-1.3	0.04	NS
Total hip	-1.8	-1.8	NS	-0.9	-1.0	NS	NS
Lumbar spine	-0.2	-0.4	NS	1.3	1.3	NS	NS

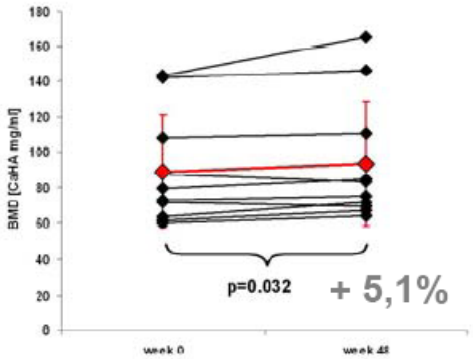
Pooled analysis of 9 risedronate trials:
Miller PD et al, JBMR, 2005

- 4496 patients on risedronate 5 mg/day for up t 3 years
- Renal function:
  - Mild – GFR < 80 (Cr 0.4 – 1.6 mg/dl)
  - Moderate – GFR 50-80 (Cr0.6-1.9 mg/dl)
  - Severe – GFR < 30 (Cr 0.7 – 2.7 mg/dl)
- Compared to placebo: no difference in side effect profile or change in renal function in any group
- Preservation of BMD similar in all groups

Bone mineral density (BMD)

16 HD patients, open label study, 2mg ibandronate every 4 weeks for 12 doses.

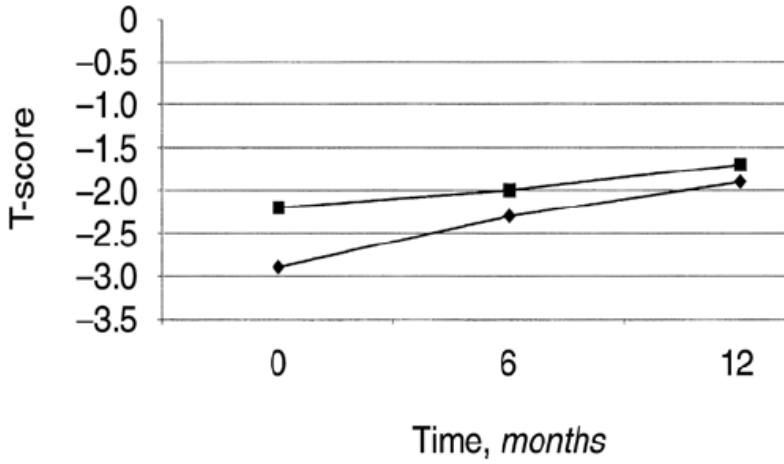




Bergner et al. NDT 2005 (suppl.)

Bone mineral density (B

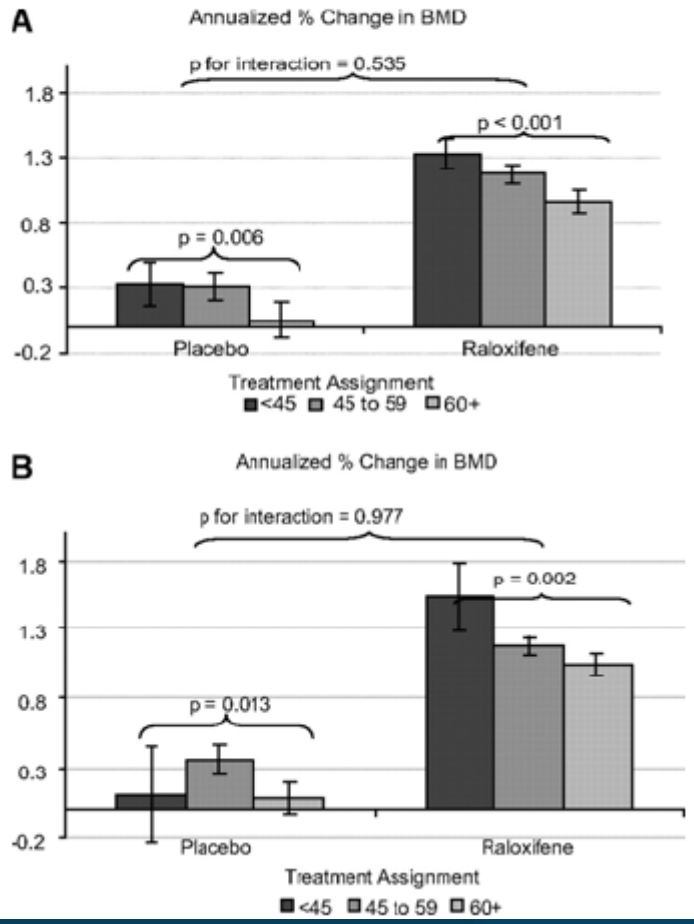
13 HD patients, 60mg pamidronate every 8 weeks for 6 dos label. All with PTH> 500pg/ml.



Torregrosa

Raloxifene

Annualized percentage change in BMD at the lumbar spine by baseline CrCl category [A] (n = 5596; placebo n = 1837; raloxifene n = 3759) or MDRD category [B].



***post hoc* analysis of data from the MORE study**

Ishani, A. et al. J Am Soc Nephrol 2008;19:1430-1438

Teriparatide

Summary of Teriparatide – mod CKD

Miller PD et al, Osteoporosis Int, 2007

- the effects of teriparatide were statistically consistent across renal function categories for:
  - reducing the incidence of vertebral and nonvertebral fragility fractures
  - the effects of teriparatide on bone formation, as assessed by PINP, and of increased BMD, as assessed by lumbar spine and femoral neck bone densitometry
  - the incidences of treatment-emergent and renal-related adverse events (espec increased Ca and Uric acid)
  - Teriparatide induced changes in mean GFR were unaffected by baseline renal function.

Summary

- Manage the CKD-MBD – but does it work?
- Vitamin D should (probably) be part of this.
- Cinacalcet?
- Bisphosphonates? – maybe OK in selected patients (no adynamic bone disease)
- SERMs?
- Teriparatide?