Case Discussion

CKD-MBD

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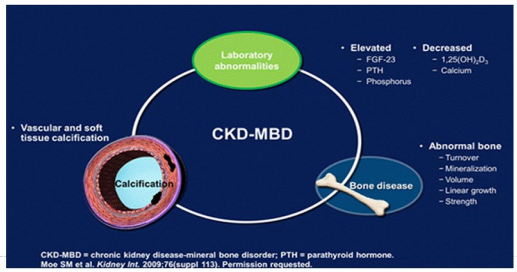
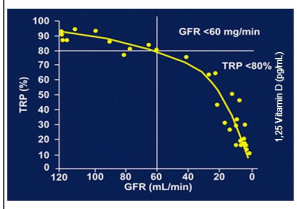
Overview

- CKD-MBD: A complex, multisystem, hormonal disease
- Association of CKD-MBD with morbidity and mortality



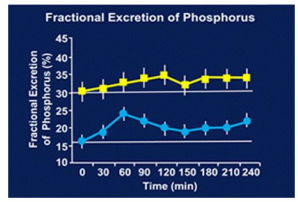
CKD-MBD = chronic kidney disease-mineral bone disorder; PTH = parathyroid hormone.
Moe SM et al. *Kidney Int.* 2009;76(suppl 113). Permission requested.

Tubular Reabsorption of Phosphorus in Patients with CKD



J Clin Invest 1968;47:1865-74

The Fractional excretion of Phosphorus dramatically rises in CKD



J Am Soc Nephrol 2008;19:615-623

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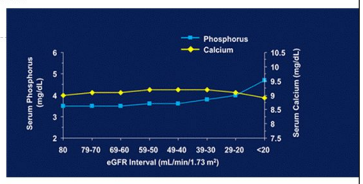
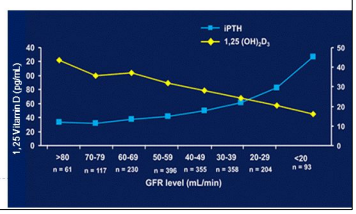
Phosphorus levels remain in the Normal Range Until Late in CKD



Serum PTH Increases and 1,25 vitamin D Decreases Early in CKD



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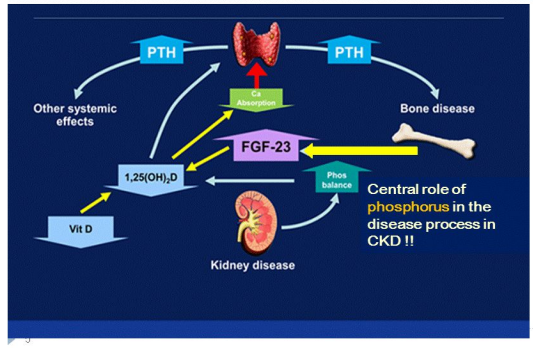
New Paradigm of CKD-MBD



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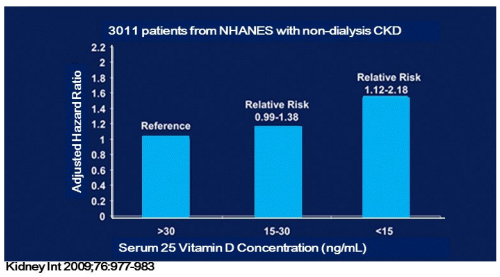
Association of CKD-MBD with Morbidity/Mortality



Kidney Int 2009;76:977-983

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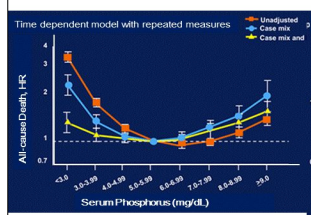
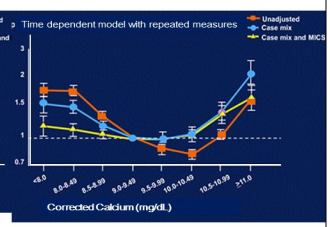
Phosphorus



Calcium



Kidney Int 2006;70:771-780

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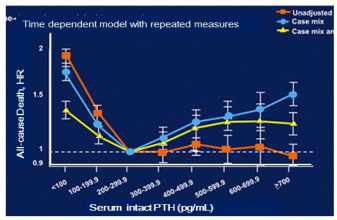
iPTH



Kidney Int 2006;70:771-780

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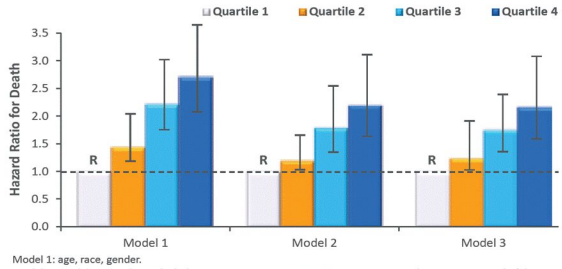
FGF23



Model 1: age, race, gender.
Model 2: Model 1 + smoking, alcohol, DM, HTN, CVD, BMI, SBP, GFR, treatment arm, homocysteine, Hgb, folate, B1 albumin, calcium, 25(OH)D, 1,25$(OH)_2$D, iPTH, phosphate, HDL, LDL, triglycerides, total cholesterol.
Model 3: Model 2 + use of medications.

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Clinical Management Strategies for the CKD-MBD

Control Serum Phosphorus
+
Vitamin D sterols
+
Calcimimetics

- Minimize P, Ca, and iPHT burden
- Prediction and Prevention of Morbidity
- Optimal management

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4 Cases

- General medical management of Ca/P/Vitamin D disturbance
- Treatment of SHPT using calcimimetics
- Vascular and soft tissue calcification
- Fracture

Case 1

- C/C: 전신에 뻐가 다 아파요…
- M/48
- DM-ESRD on HD since 8 YA
- Drug compliance: very decreased
- V/S 170/110 mmHg – 71 BPM
- Interdialytic wt gain 3.0-3.5 kg

Case 1

Lab findings…

- Hgb 9.6 g/DL
- Ca/P 9.2/5.8 mg/dL

intact PTH 670 pg/mL

Na/K/Cl/Co2 138/5.1/106/17 mEq/L

BUN/Cr 88.2/7.8 mg/dL

What's the best practice for this case?

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General steps for management of CKD-MBD

- Step 1
  - Identify the CKD stage
  - Identify biochemical targets according to CKD stage
  - Is there an indication for parathyroid scan or parathyroidectomy?
  - Is there any evidence of tissue, vascular, or valvular calcification?
- Step 2
  - Diet counseling
  - Dialysate calcium
  - Drug prescription
    - Ca Phosphate binder
    - Vitamin D or Vitamin D analoques
    - Calcimimetics

Therapeutic decisions must based on trends rather than on a single laboratory value!!

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KDIGO. *August 2009*

Case 1

Lab findings...

- Hgb 8.6 g/DL
- Ca/P 9.2/5.8 mg/dL

intact PTH 670 pg/mL

Na/K/Cl/Co2 138/5.1/106/17 mEq/L

BUN/Cr 88.2/7.8 mg/dL

- CKD stage 5D
- Dx: Secondary HPT

- Biochemical target ?
- Is alkaline phosphatase is important here?
- Is Vitamin D measurement is important here?

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Suggested target range for phosphorus, calcium and PTH			
CKD stage	Serum Phosphorus	Serum Calcium	Intact PTH
3-5 not on dialysis	Maintain within normal range (4.1.1) (2C)	Maintain within normal range (4.1.1) (2C)	Optimal level is not known (4.2.1) (2C)
5D	Lower toward normal range (4.1.1) (2C)	Maintain within normal range (4.1.1) (2C)	Maintain level in the range of approximately 2-9 times the upper limit of normal for the assay (4.2.3)(2C)

- Ca/P 9.2/5.8 mg/dL, iPTH 670
- Prescribed medication: calcium carbonate three times with meals
  bonky (alphacalcidol 1mcg)
  - Decision is reasonable ??
  - How about ALP and vitamin D measurement?

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Alkaline phosphatase

- Elevated total ALP (t-ALP) levels have been recognized as a possibly independent variable associated with an increase in the RR of mortality in patients with CKD stage 5D

3.1.2: Reasonable monitoring intervals would be:

- In CKD stages 4-5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).

3.2.3. In patients with CKD stages 3–5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).

Vitamin D

3.1.3.

- In patients with CKD stages 3–5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

Treatment of CKD-MBD: Abnormal PTH Levels

4.2.4. In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH *(2B)*.

- We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).
- We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D).
- We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).

Case 1 -2

1 month later...

- Ca/P 9.2/5.8 mg/dL ➔ 10.0/6.0 mg/dL
- intact PTH 670 ➔ 412 pg/mL
- Bone pains were similar...

4.1.5. In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia *(1B)*.

What's the appropriate next steps?

- Renagel 800mg TM
- stop bonky injection
- Change to zemplar iv

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Case 1 -3

3 month later...

- Aggravated bone pain
- Ca/P 10.0/6.0g/dL ➔ 9.8/6.2 mg/dL
- intact PTH 670 ➔ 412 ➔ 1027 pg/mL

4.1.8. In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C)

What's the appropriate next steps?

- Cinacalcet 30mg/day + Renagel 800mg TM

This is all we can do?

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Case 1 -3

1 month later...

- Ca : 9.8 ➔ 8.2 mg/dL
- P : 6.2 ➔ 5.3 mg/dL
- intact PTH 670 ➔ 412 ➔ 1027 ➔ 441 pg/mL

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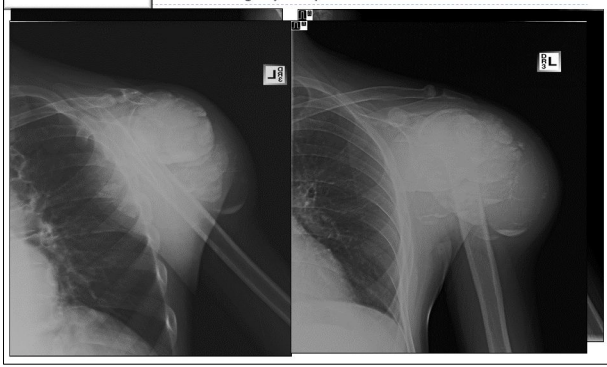
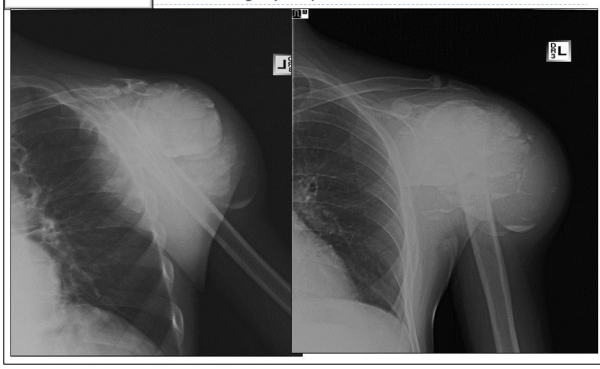
Case 2

- C/C: 오른쪽 어깨부위에 뭐가 만져져요...
- M/31
- GN-ESRD on HD since 12 YA
- V/S 110/80 mmHg – 71 BPM
- Could not reach to dry body weight d/t low BP... (2.5kg overweight compared to dry wt)
- Med: nesp 60mcg/week, iv zemplar 2 times/week, renagel 2T TM, midodrine

Case 2 X-ray (Rt)

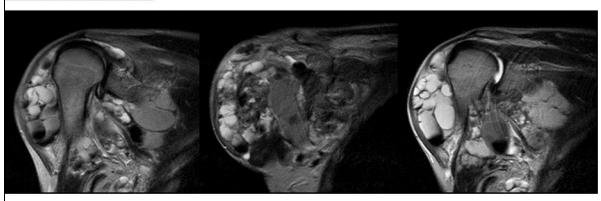


Case 2 X-ray (Lt)



Case 2

Shoulder MRI



1) Extensive calcific bursitis of subdeltoid bursa with large mass formation
2) Extenstion to axillar (subscapular space, beneath latissimus dorsi)
3) Inferior displacement of axillar artery and vein, and brachial plexus due to mass
4) Posterior subluxation of glenohumeral joint with joint effusion.
5) Partial tear of subscpularis tendon

Case 2

Lab findings	4 weeks later
Hgb 7.6 g/DL	
Ca/P 9.2/8.6 mg/dL	→ 7.1/8.5 mg/dL
intact PTH 1741.3 pg/mL	→ 1815.6 pg/mL
ALP 577 IU/mL	
Iron/TIBC/Ferritin	

Dx: SHPT with extraosseous calcification
Tx: Add cinacalcet

Tx: Cinacalcet stop / op

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Case 2

Parathyroidectomy

4.2.5. In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy *(2B)*.

Is parathyroid imaging is indicated?

1) Parathyroid scan
2) NecK CT
3) X-ray to detect vascular calcification

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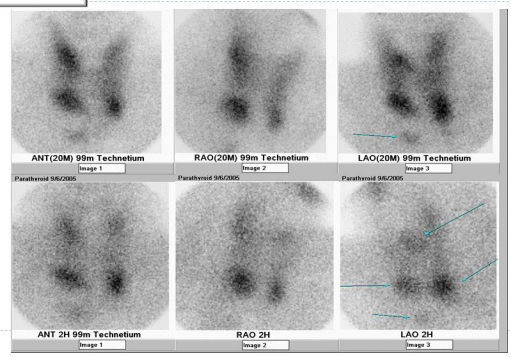
Case 2

Tc-99m MIBI Parathyroid scan (Ant)



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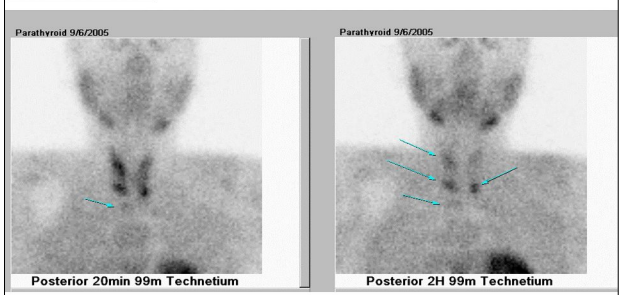
Case 2

Tc-99m MIBI Parathyroid scan (Post)



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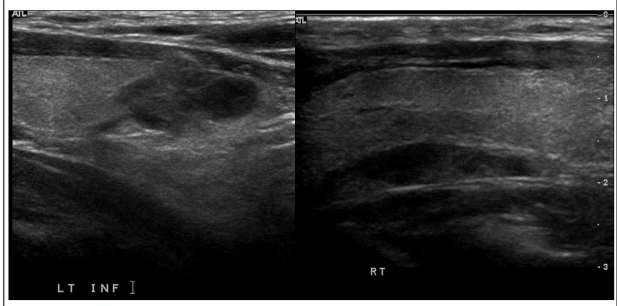
Case 2

Neck US



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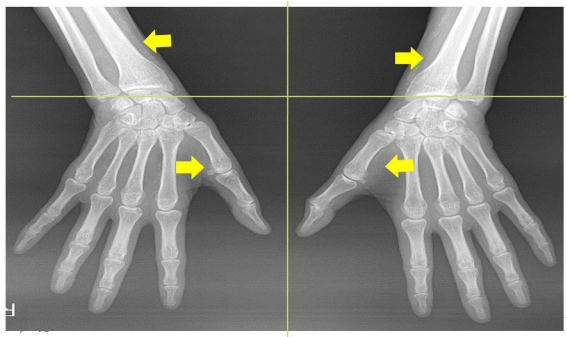
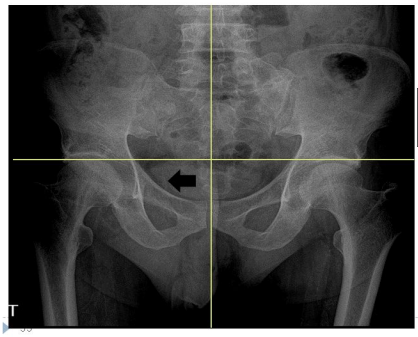
Case 2

Simple X-ray of hands



Case 2

Simple X-ray of Pelvis



Vascular calcification on iliac and femoral arteries

Case 2

Dx

- #1. Tertiary hyperparathyroidism with parathyroid adenoma formation
- #2. Metastatic vascular calcification due to hyperparathyroidism

Op

- Total parathyroidecomy with autotransplantation

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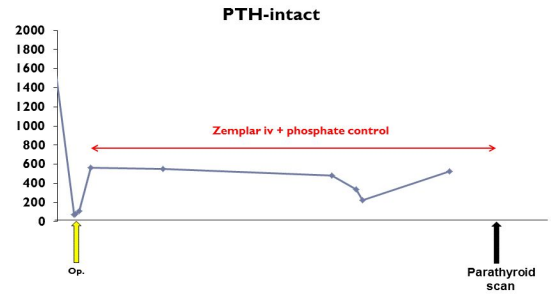
Case 2

Post-op



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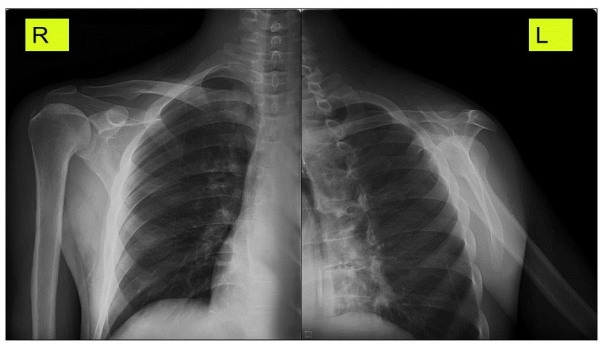
Case 2

Follow-up shoulder X-ray after 6 month



Case 3

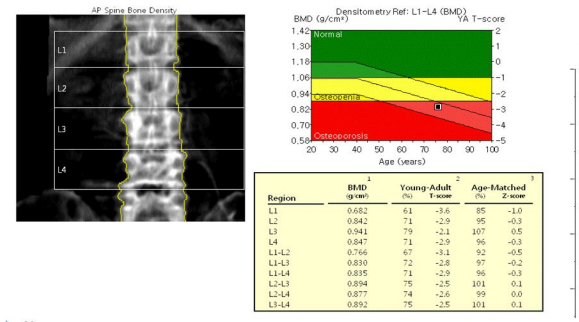
- C/C: Pain on Lt hip
- M/76
- HTN-ESRD on HD since 2013.03, oCVA
- Trauma history: none
- V/S 160/70 mmHg – 91 BPM

Case 3

Pelvic X-ray

Case 3

BMD



Region	BMD (g/cm²)	Young-Adult (%) T-score	Age-Matched (%) Z-score
L1	0.682	61	-3.6	85	-1.0
L2	0.842	71	-2.9	95	-0.3
L3	0.941	79	-2.1	107	0.5
L4	0.847	71	-2.9	96	-0.3
L1-L2	0.766	67	-3.1	92	-0.5
L1-L3	0.830	72	-2.8	97	-0.2
L1-L4	0.835	71	-2.9	96	-0.3
L2-L3	0.894	75	-2.5	101	0.1
L2-L4	0.877	74	-2.6	99	0.0
L3-L4	0.892	75	-2.5	101	0.1

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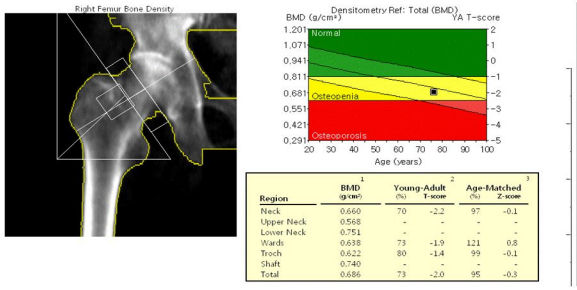
Case 3

BMD



Region	BMD (g/cm²)	Young-Adult (%) T-score	Age-Matched (%) Z-score
Neck	0.660	70	-2.2	97	-0.1
Upper Neck	0.568	-	-	-	-
Lower Neck	0.751	-	-	-	-
Wards	0.638	73	-1.9	121	0.8
Troch	0.622	80	-1.4	99	-0.1
Shaft	0.740	-	-	-	-
Total	0.686	73	-2.0	95	-0.3

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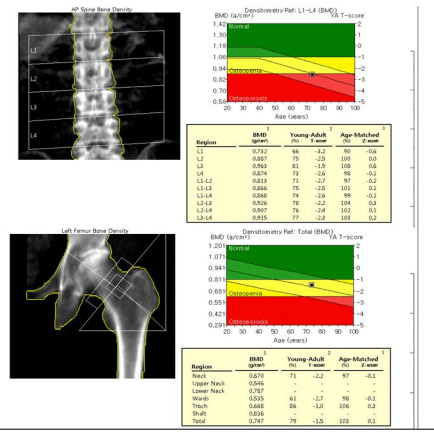
Case 3

BMD 2012



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BMD and Fracture Risk in Older Individuals with CKD

- Evaluated 2754 older communitiy-living individuals (aged 70-79 years) who had BMD at baseline and 384 incidence fracture during follow-up
- 21% of participants (n=587) with eGFRs <60 mL/min/1.73m²
- Compared strength of association of BMD with fracture risk by CKD status

Association of Femoral Neck BMD with Risk of Fracture

	Hazard Ratio (95% CI)			*P* Value for CKD-BMD Interaction
	Overall	No CKD	CKD	
Unadjusted	2.42 (2.14-2.74)	2.45 (2.13-2.82)	2.32 (1.79-3.01)	.72
Adjusted for age, race, sex, and BMI	2.26 (1.94-2.64)	2.14 (1.80-2.55)	2.69 (1.96-3.69)	.70
Positive PTH status and vitamin D status	2.30 (1.96-2.68)	2.15 (1.80-2.57)	2.74 (1.99-3.77)	.68

Relationship between BMD and fracture risk were as strong in patients with CKD as in participants without CKD

Clin J Am Soc Nephrol 2012;7:1130-36

Predicting Fracture in Patients Undergoing Hemodialysis

- Measured BMD annually in 485 hemodialysis patients in Japan, 2003-2008
- All prevalent and incident fractures recorded
- 46 Incident fractures occurred during follow-up

Nephrol Dial Tranplant 2012;27:345-351

Results

BMD Site	Adjusted* Hazard Ratio	95% CI	*P* Value
One-third distal radius (per SD)	0.87	0.73-1.04	.12
Lumbar spine (per SD)	0.87	0.73-1.03	.10
Femoral neck (per SD)	0.65	0.47-0.90	< .01
Total hip (per SD)	0.65	0.49-0.87	< .01

Adjusted for age, sex, dialysis vintage, and diabetes

Nephrol Dial Tranplant 2012;27:345-351

Guidelines

3.2.1

In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD–MBD (not graded).

Guidelines

3.2.2. In patients with CKD stages 3–5D, with evidence of CKD–MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of ROD (2B).

DO YOU??

- Do you order serum 25 (OH)D3 in your routine assessment of CKD-MBD?
- Do you order lumbar latera X-ray in your routine assessment of CKD-MBD?
- Do you perform bone biopsy in the presence of bone biopsy indication according to KDIGO?