
Osteoporosis in Dialysis Patients Challenges in Management

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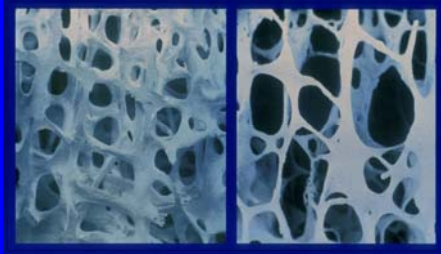
Bone Disorders in CKD

- **PTH-mediated high-turnover**
 - ★ (osteitis fibrosa)
- **Low turnover osteomalacia**
 - ★ (defective mineralization)
- **Adynamic Bone**
 - ★ Diminished formation and resorption
- **Osteomalacia**
 - ★ Mineralization lag time > 100 days
- **Mixed uremic osteodystrophy**
 - ★ (High PTH + mineralization defect)

Challenge 1: What to Treat

- **Decreased Bone Mineral Density:**
 - ★ Osteomalacia:
 - Normal bone volume
 - Decreased mineralization
 - ★ Osteoporosis
 - Decreased bone volume
 - Abnormal structure
 - ★ BOTH

Bone Structure



Normal

Osteoporotic

Osteoporosis

- **Reduced bone mass**
- **Abnormal internal architecture**
- **Increased fragility**

HIGH Turnover

- **Biopsy:** Malluche HH et al. J. Am Soc Nephrol. 2012;23:525
 - ★ Reduced mineral:matrix ratio
 - ★ Lower stiffness
- **Markers:**
 - ★ High PTH
 - ★ High Bone Specific Alkaline Phosphatase
 - ★ (lower sclerostin)
- **BMD**
 - ★ Reduced : cortical > trabecular (include radius)

LOW Turnover

- **Biopsy:** Malluche HH et al. J. Am Soc Nephrol. 2012;23:525
 - ★ Decreased cancellous bone volume
 - ★ Reduced trabecular thickness
- **Markers:** Sista SK, Arum SM. J Clin & Trans. Endocrin. 2016;5:32
 - ★ PTH < 180 pg/mL – 90% pos. predictive value
 - ★ BSAP < 12.9 ng/mL: 100% sens. 93.7% spec.
 - ★ (High sclerostin)
- **BMD**
 - ★ Reduced

Challenge 2

- **Metabolic abnormalities**
 - ★ Hyperphosphatemia
 - ★ Calcium balance
 - ★ Magnesium balance

caused by
- **Hormonal abnormalities**
 - ★PTH Calcitriol
 - ★FGF23 α Klotho Activin A
 - ★Sclerostin Dickkopf 1

Major Cations

Monovalent		Divalent	
11 Sodium	Na	12 Magnesium	Mg
22.99 Extracellular		24.31 Intracellular	
19 Potassium	K	20 Calcium	Ca
39.10 Intracellular		40.08 Extracellular	

Body Magnesium

- **Body content ~24g (1000 mmol)**
- **>50% of total in bone**
- **Only 1% extracellular**
- **In serum**
 - ★ Protein-bound ~ 33%
 - Albumin ~25%
 - Globulin ~ 8%
 - ★ Complexed ~ 5.5%
 - ★ Free (ionized) ~ 61%

Challenge 3: Magnesium

- **A normal serum level does not guarantee normal Mg balance.**
- **Mg deficiency increases PTH.**
- **PTH increases bone resorption.**
- **Excess Mg inhibits mineralization.**
- **Keep ionized Mg at upper end of normal range**

Mineral Metabolism

**Strive to achieve the
Goldilock's Principle
Not too much, not too little,
JUST RIGHT**

Management Tools

- **Nutrition**
- **Exercise**
- **Medications**
 - ★ Antiresorptive
 - ★ Anabolic

Nutrition

Building bones requires adequate

- Protein
- Calcium
- Vitamins
- Magnesium

Effects of Exercise

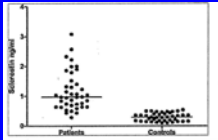
- **IRISIN, a myo-adipokine stimulates bone and muscle**
 - ★ Exercise stimulates release of irisin from muscle
- **SCLEROSTIN suppresses Wnt**
 - ★ At rest, SCLEROSTIN inhibits osteoblast differentiation and activation
 - ★ Exercise inhibits sclerostin and mobilizes osteoblasts

Immobilization and Bone

80 postmenopausal women

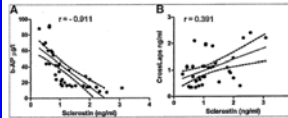
40: \geq six months post stroke 40: active controls

Sclerostin levels



Sclerostin and bone markers

Bone alk. phosphatase C-telopeptide (CTx)



Gaudio A et al. J. Clin Endocrin Metab 95(5):2248, May 2010

Challenge 4: Medications

- **High Turnover**

- ★ PTH suppressors (Cinacalcet, calcitriol)
- ★ Antiresorptive
 - Bisphosphonates, Denosumab (Prolia)

- **Low turnover**

- ★ Anabolic
 - PTH, teriparatide (Forteo)
 - Abaloparatide - PTHrP analog (Tymlos)
 - Antisclerostin antibodies
 - Romosozumab, blosozumab

Therapy: High Turnover

STOP BONE LOSS

- **Reduce PTH**

- ★ Adequate Calcium, Magnesium, nl. Phos.
- ★ Calcitriol
- ★ Cinacalcet

- **Antiresorptives**

- ★ Bisphosphonates
- ★ Denosumab

Cinacalcet in Dialysis

- **BONAFIDE Study: 110 patients with high turnover**
 - ★ PTH >300, Ca \geq 8.4mg/dL, BSAP >20.9n/mL, + biopsy
 - ★ 6-12 mo: 2nd biopsy in 70.
 - ★ Median PTH decreased from 985 to 480
 - ★ NI histology in 20, 2 adynamic (PTH <150)
 - Behets GJ et al. Kidney International 2015;87:846

- **Secondary analyses of RCTs (ADVANCE and EVOLVE) show reduced fracture risk if PTH \geq 180pg/mL**
 - Komaba H, Fukagawa M. Semin. Dial. 2015;28:594

Bisphosphonates

- **~50% excreted by kidneys but clodronate, pamidronate and ibandronate are readily dialysable**
 - ★ 16 pts: PTH > 2x NI.
 - ★ Rx: Ibandronate 2mg q 4 weeks for 48 weeks
 - ★ Decreased turnover markers. Mean T scores: -3.08 to -2.78
 - Bergner R et al. J Nephrol. 2008;21:510

- ★ 13 pts: PTH >500, Ca >11mg/dL, P < 6mg/dL
- ★ Rx: Pamidronate 60mg IV q 2 months for 1 year
- ★ Slight decrease in Ca & P
- ★ BMD increased (mean 33%)
- Torregrosa JV et al. Kidney Int Suppl 2003;85:S88

Denosumab (Prolia)

- **2012: 55 people, varying levels of CKD do not affect pharmacokinetics of denosumab**
 - Block GA et al. J Bone Miner Res 27:1471
- **2012-3: 5 reports, 1 dose \rightarrow hypocalcemia, some severe with tetany**
- **2014: 5 women, 7men, iPTH >1,000, bone pain**
 - ★ 1 dose. At 6 mo. BMD LS +17.1%, FN +23.7%
 - Chen CL et al. J Clin Endocrinol Metab 99:2426
- **2015: 10 women, 1 man, T scores \leq -2.5**
 - ★ 1 dose + alfacalcidol + CaCO₃, LS +15%, FN 0%, Rad +5%
 - Hiramatsu R et al. Am J Kidney Dis 66:175

Denosumab (continued)

- **2014: Woman, age 39. Den for 2 yrs**
 - ★ T scores: LS -3.9 → -2.8 ,HIP -3.6 → -2.9
 - Dusilova Sulkova et al. ACTA MEDICA 57:30
- **2017: 17 men, Den for 1 year**
 - ★ BMD Radius: +2.6%, controls -4.5%
 - Takami H et al. Intl J Nephrology ID 6218129
- **2017: 12 pts, Den for 2 yrs**
 - ★ QUS T score -5.33 → -4.84
 - Festuccia F et al. J Nephrol 30:271

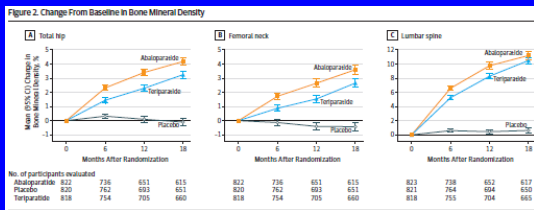
Therapy: Low Turnover

- **Anabolic: (FDA approved)**
 - ★ PTH 1-34: Teriparatide (Forteo)
 - ★ PTHrP 1-34: Abaloparatide (Tymlos)
- **Sclerostin inhibitors (not yet approved)**
 - ★ Romosozumab
 - ★ Blosozumab

Teriparatide

- **Review of 4 studies, 17 pts: 20mcg/day**
 - ★ Increased BMD of varying degrees
 - Sista SK, Arum SM. J Clin. Translat. Endocrinol 2016;5:32
- **Case reports with ABD on biopsy:**
 - ★ Repeat biopsy normalized
 - Palcu P et al. Am J Kidney Dis. 2015;65: 933
 - Lehmann G et al. NDT Plus 2009;2:49
- **Dosage 56.5mcg/week**
 - ★ 22 pts – AE in 10 mainly transient hypotension
 - Sumida K et al. Osteoporosis Int 2016;27:1441

Effect of Abaloparatide PTHrP 1-34 (Tymlos)

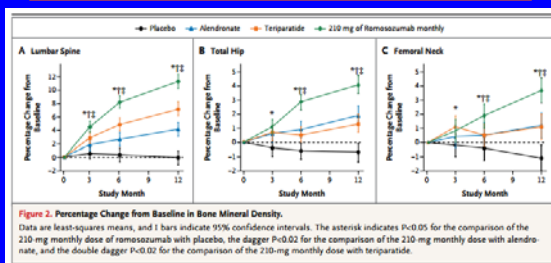


Miller PD et al. JAMA 2016 Aug;316(7):722-33

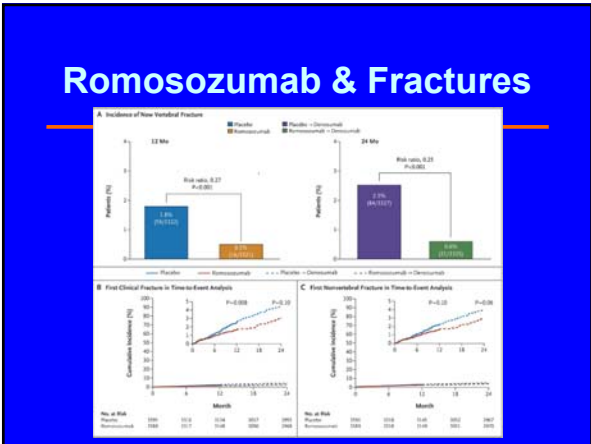
Targeting Wnt inhibitors

- The Wnt pathway stimulates osteoblast production
- Sclerostin and Dickkopf 1 inhibit Wnt
- Antibodies to sclerostin and Dickkopf 1 are in clinical trials

Sclerostin Antibody: Romosozumab



Cosman F et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. NEJM September 18, 2016



Challenge 5 Retain the Gain

When you stop
anabolic therapy,
you lose the gains
UNLESS
an antiresorptive is given

Monitoring

- **Usual: P, Ca, Mg, Vitamin D**
- **Turnover**
 - ★ PTH
 - ★ Alkaline phosphatase
 - ★ C- or N-telopeptide crosslinks
- **Bones**
 - ★ DXA spine, hip and radius

Challenge 6

**EXPECT
THE
UNEXPECTED**

Is it High or Low Turnover ?

- **Woman age 30 on HD since 2002.**
- **Severe back pain; DXA T -3.9**
- **2004: Unsuccessful transplant**
- **2008-2011: alendronate – no effect**
- **2y HPT controlled by calcitriol/paricalcitol**
- **2011: Normal Ca, PTH, low 25-OH-vit. D**
- **Rx: Denosumab, oral Ca, vitamin D**

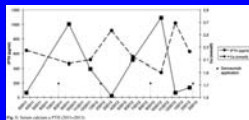
Dusilova Sulkova D et al. ACTA MEDICA (Hradec Kralove) 2014;57:30

Denosumab for 2 years

Tab. 2: Bone metabolism markers in the course of denosumab treatment.

	Ca (mmol/l)	PTH (pmol/l)	25(OH)D (nmol/l)	Osteocalcin (µg/l)	CTX (µg/l)
Reference range	2.15-2.51	1.6-6.9	>75 (recommended)	11-43	0.162-0.436
Before the 1st dose	2.40	5.5	31.6	154.1	1.600
Two months after 1st dose	2.26	39.3	not available	3.9	0.256
Before the 2nd dose	2.43	13.6	38.7	10.5	0.179
Before the 3rd dose	2.68	5.0	113.0	26.1	0.207
Before the 4th dose	2.63	7.0	60.8	33.9	0.724

Note: Serum samples taken in interdialysis period (during out-patient visit in tertiary centre).



T scores: Spine -3.9 to -2.8 Total hip -3.6 to -2.9

An unexpected PTH pendulum

- **Woman, age 68 with bone pain and fractures. BMD: T score - 4.7**
- **Low PTH and low alk. phos. Biopsy ABD**
- **Rx: Teriparatide 20mcg SC daily for 9 mo.**
 - **From 6-9 months: PTH 30 → 520**
- **Alk. Phos → 200, Biopsy: high turnover BMD T score - 3.4**
- **At 2 yrs: PTH 200-300 and bone metabolic parameters nl.**

• Giamalis P et al. Clin Kidney 2015;8:188

Summary

- **Maintain adequate nutrition & activity**
- **Control phosphate**
- **High normal ionized calcium and magnesium**
- **Adequate vitamin D/calcitriol**
- **With medications: monitor often**
 - ★ anticipate hypocalcemia with antiresorptives
 - ★ EXPECT UNEXPECTED CHANGES

GOAL OF THERAPY

PREVENT FRACTURES

THE END

for now!
