CKD-MBD

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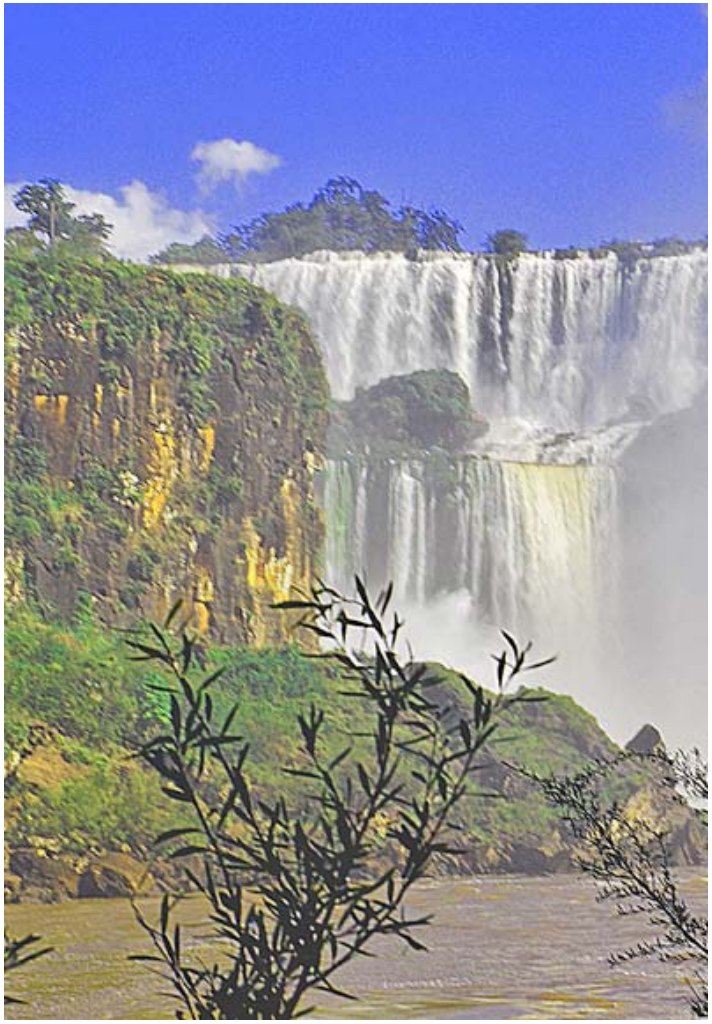
Baylor College of Medicine
May 23, 2007

Goals

- Understand the new definition that ties vascular calcification, mineral disorders and bone abnormalities together - CKD-MBD
- Understand new concepts on bone adaptation to CKD
- Be familiar with the therapies directed toward preventing extraskeletal calcification and low bone turnover syndrome

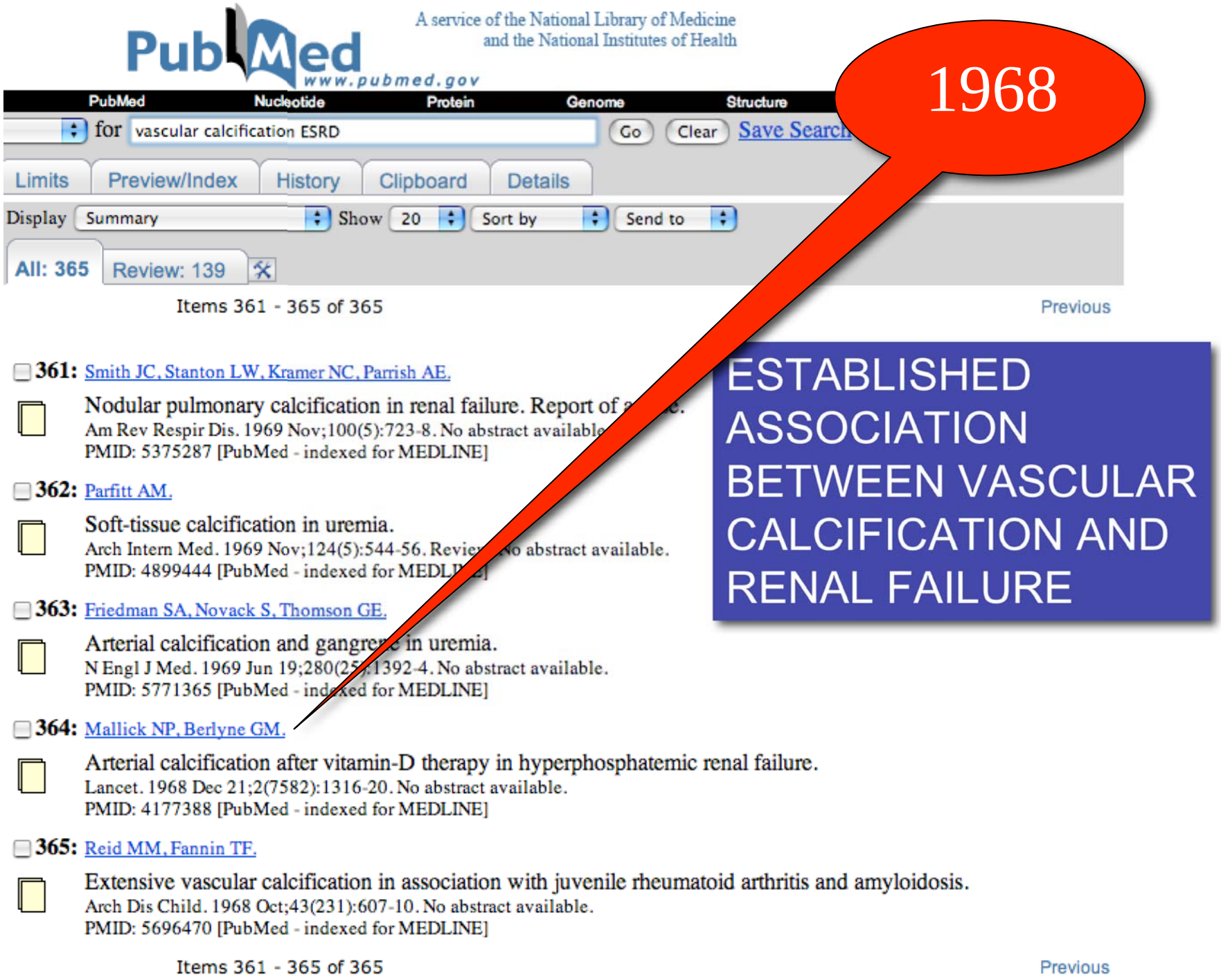


PHOTOS BY STEPHEN FADEM

Disclosures

I am either a consultant, on the speaker bureau, on the advisory board or conduct clinical trials for Abbott, Ortho Biotech, Amgen, Genzyme, ASH Medical, Diasorin, Shire or DaVita.

This talk is unsponsored.


PubMed
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PubMed Nucleotide Protein Genome Structure
for vascular calcification ESRD
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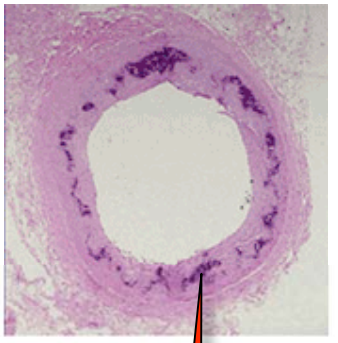
Limits Preview/Index History Clipboard Details
Display Summary Show 20 Sort by Send to
All: 365 Review: 139
Items 361 - 365 of 365
Previous
361: Smith JC, Stanton LW, Kramer NC, Parrish AE.
Nodular pulmonary calcification in renal failure. Report of a
Am Rev Respir Dis. 1969 Nov;100(5):723-8. No abstract available
PMID: 5375287 [PubMed - indexed for MEDLINE]
362: Parfitt AM.
Soft-tissue calcification in uremia.
Arch Intern Med. 1969 Nov;124(5):544-56. Revie
o abstract available.
PMID: 4899444 [PubMed - indexed for MEDL
363: Friedman SA, Novack S, Thomson GE.
Arterial calcification and gangrene in uremia.
N Engl J Med. 1969 Jun 19;280(25):1392-4. No abstract available.
PMID: 5771365 [PubMed - indexed for MEDLINE]
364: Mallick NP, Berlyne GM.
Arterial calcification after vitamin-D therapy in hyperphosphatemic renal failure.
Lancet. 1968 Dec 21;2(7582):1316-20. No abstract available.
PMID: 4177388 [PubMed - indexed for MEDLINE]
365: Reid MM, Fannin TF.
Extensive vascular calcification in association with juvenile rheumatoid arthritis and amyloidosis.
Arch Dis Child. 1968 Oct;43(231):607-10. No abstract available.
PMID: 5696470 [PubMed - indexed for MEDLINE]
Items 361 - 365 of 365
Previous
1968
ESTABLISHED ASSOCIATION BETWEEN VASCULAR CALCIFICATION AND RENAL FAILURE

Renal Osteodystrophy linkage to vascular calcification is not new

"Consideration is also given to the manifestations of soft-tissue calcification, both of the vascular and subcutaneous type, and to the effects of treatment"

- *Source: Eastwood, JB. Renal osteodystrophy - a radiological view, CRC Crit Rev Diagn Imaging. 1977 Apr;9(1):77-104.*

1985 - Uremic Arterial Disease



- Rabbit model of 9 months renal failure
- All major systemic arteries affected
- Medial degeneration without lipid accumulation
- No coronary stenosis
- Medial calcification in non-cholesterol-fed rabbits
- Uremic arterial disease different than atherosclerosis
  - *Acta Pathol Microbiol Immunol Scand [A]. 1985 Mar;93(2):81-8.Uremic arterial disease in rabbits with special reference to the coronaryarteries.Tvedegaard E, Falk E, Nielsen M*

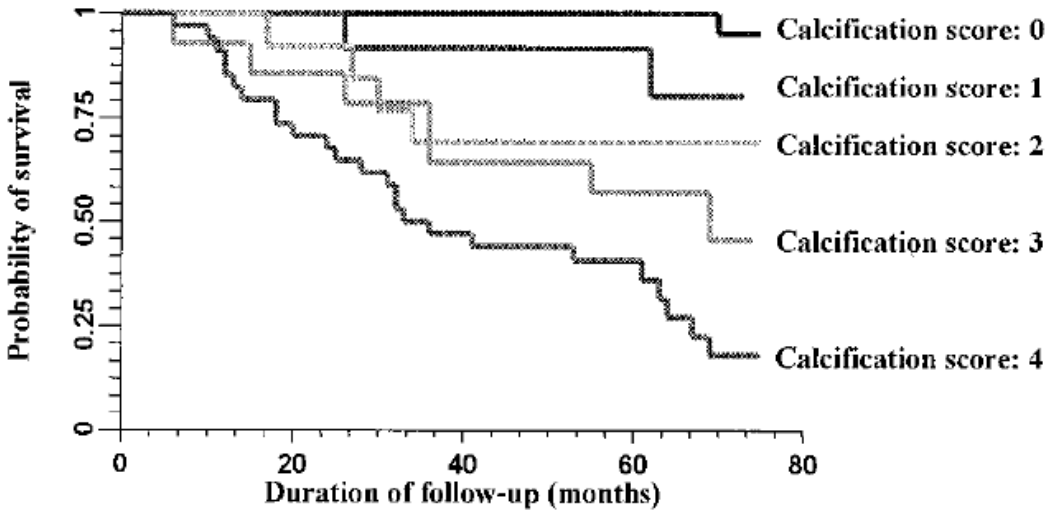
1987 Aortic and Mitral valve Calcification in ESRD

- Echocardiography in 87 patients
- 35 to 70 years old
- Maintenance dialysis 7.5 years
- 24 patients: aortic valve calcification
- 31 patients: mitral annular calcification
  - Source: Lancet. 1987 Oct 17;2(8564):875-7.Aortic and mitral valve calcification in patients with end-stage renal disease.Maher ER, Young G, Smyth-Walsh B, Pugh S, Curtis JR.

1990 - Pulse Wave Velocity - Aorta and large artery compliance in ESRD

- 90 control and 92 hemodilaysis patients
- Matched for age and MAP
- Aortic calcification - plain films and echo
  - PWV 1113±319 cm/sec in HD
  - 965 ± 216 cm/sec in Control (P=0.0016)
- Pulse Pressure
  - HD 76.6 ± 23.7 mg Hg
  - CS 63.9 ± 22 mg Hg (p=0.007)
  - *Source: Kidney Int. 1990 Jan;37(1):137-42.Aortic and large artery compliance in end-stage renal failure.London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, Chedid K,London AM.Centre Hospitalier Manhes, Fleury Merogis, France*

2001 - Longitudinal Study linking calcification with mortality



Probability of all-cause survival according to calcification score. Comparison between curves was highly significant (χ^2=42.66, P<0.0001).

Source: Hypertension. 2001 Oct;38(4):938-42.Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease.Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM.

Linkage of vascular calcification and bone

- J Am Soc Nephrol. 2003 Jun;14(6):1559-67. **BMP-7 is an efficacious treatment of vascular calcification in a murine model of atherosclerosis and chronic renal failure.**Davies MR, Lund RJ, Hruska KA.
- Kidney Int. 2002 Feb;61(2):638-47. **Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins.**Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, Fineberg N, Kopecky K
- Nephron. 2001 Dec;89(4):455-8.**Soluble osteopontin and vascular calcification in hemodialysis patients.**Nitta K, Ishizuka T, et al.

LDLR-/- 5/6 Nephrectomized Mice with Metabolic Syndrome

J Am Soc Nephrol 16: 917-928, 2005

LDLR-/- mice

- High fat, cholesterol diets, and normal kidneys
  - Decreased bone turnover, vascular calcification and hyperphosphatemia
- Added 5/6 nephrectomy
  - LBT worsened
- Treating with BMP-7
  - Corrected LBT, hyperphosphatemia and vascular calcification
- Decreased VC by reducing the serum $P0_4$ with a phosphate binder

Eur J Clin Invest. 2006 Aug;36 Suppl 2:43-50

BMP-7 and VC in LDLR-/- mice

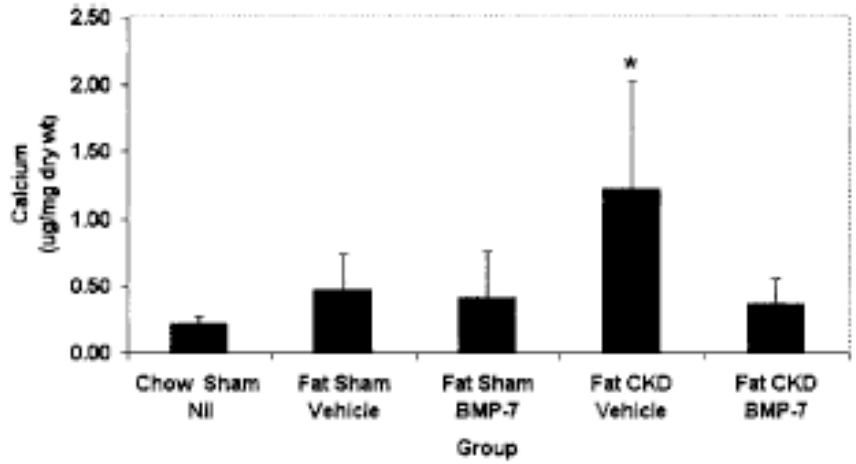
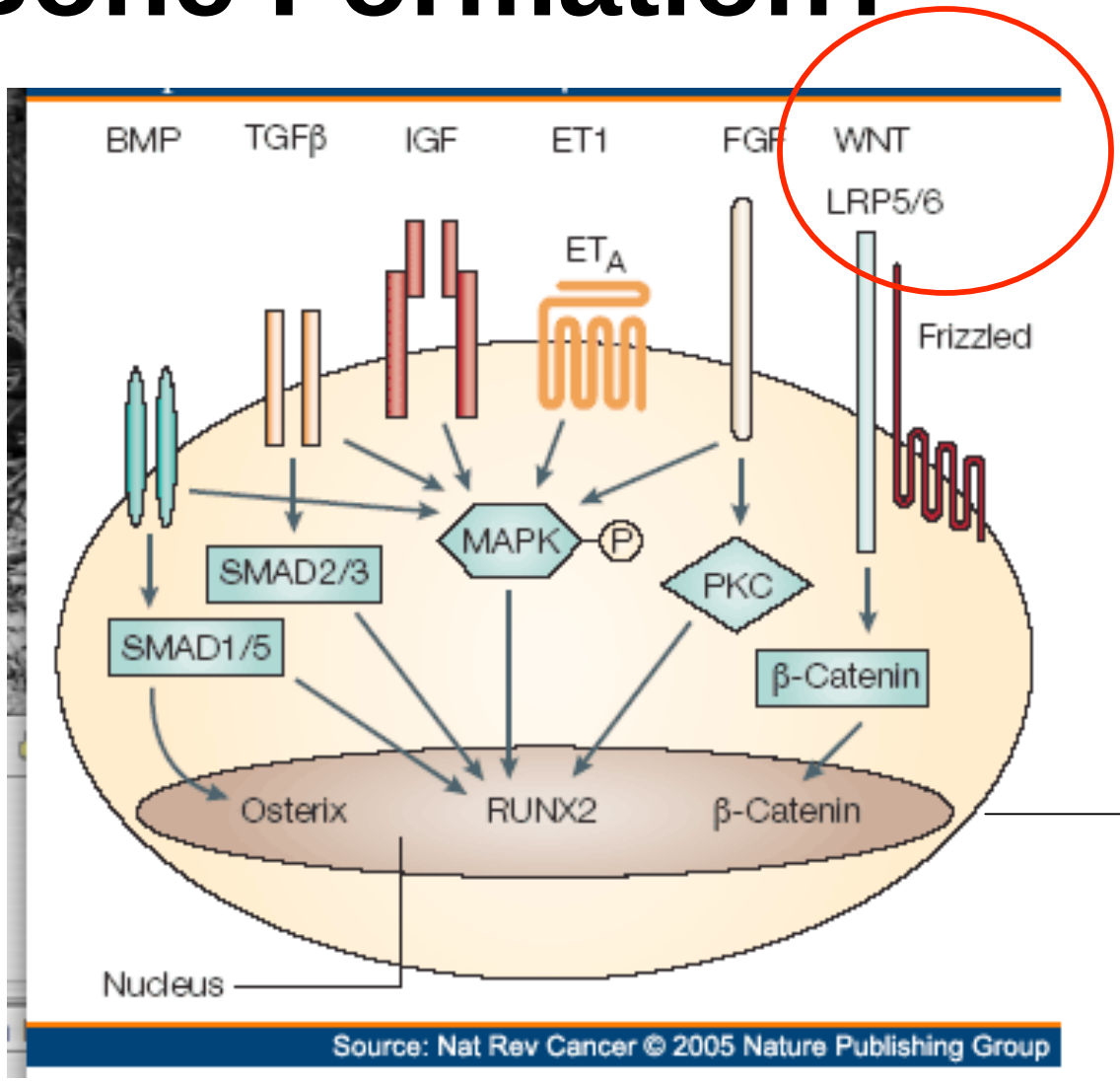


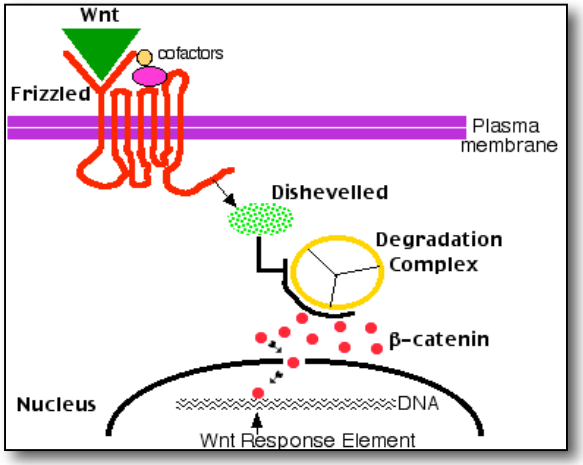
Figure 2. Chemical assessment of effect of BMP-7 on vascular calcification by treatment group. Total aortic calcium content measured in a 10% formic acid eluate of crushed. Data are mean ± SD. Trend is significant by ANOVA, $P = 0.008$. *Fat-fed uremic animals treated with vehicle have significantly higher levels than chow-fed sham controls. ($P < 0.01$, by Dunnetts post hoc test.) Fat-fed uremic animals treated with BMP-7 are indistinguishable statistically from control (chow sham animal).

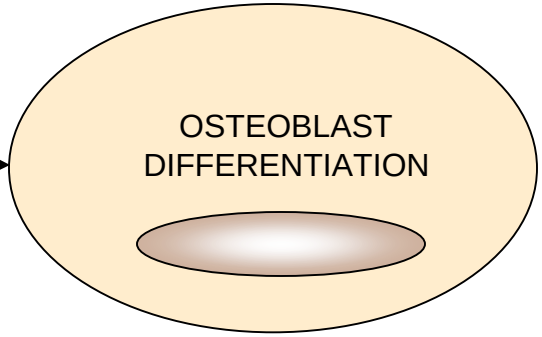
Vascular calcium deposition is blocked in fat-fed, uremic, LDLR-/-mice treated with BMP-7

J Am Soc Nephrol 14: 1559–1567, 2003

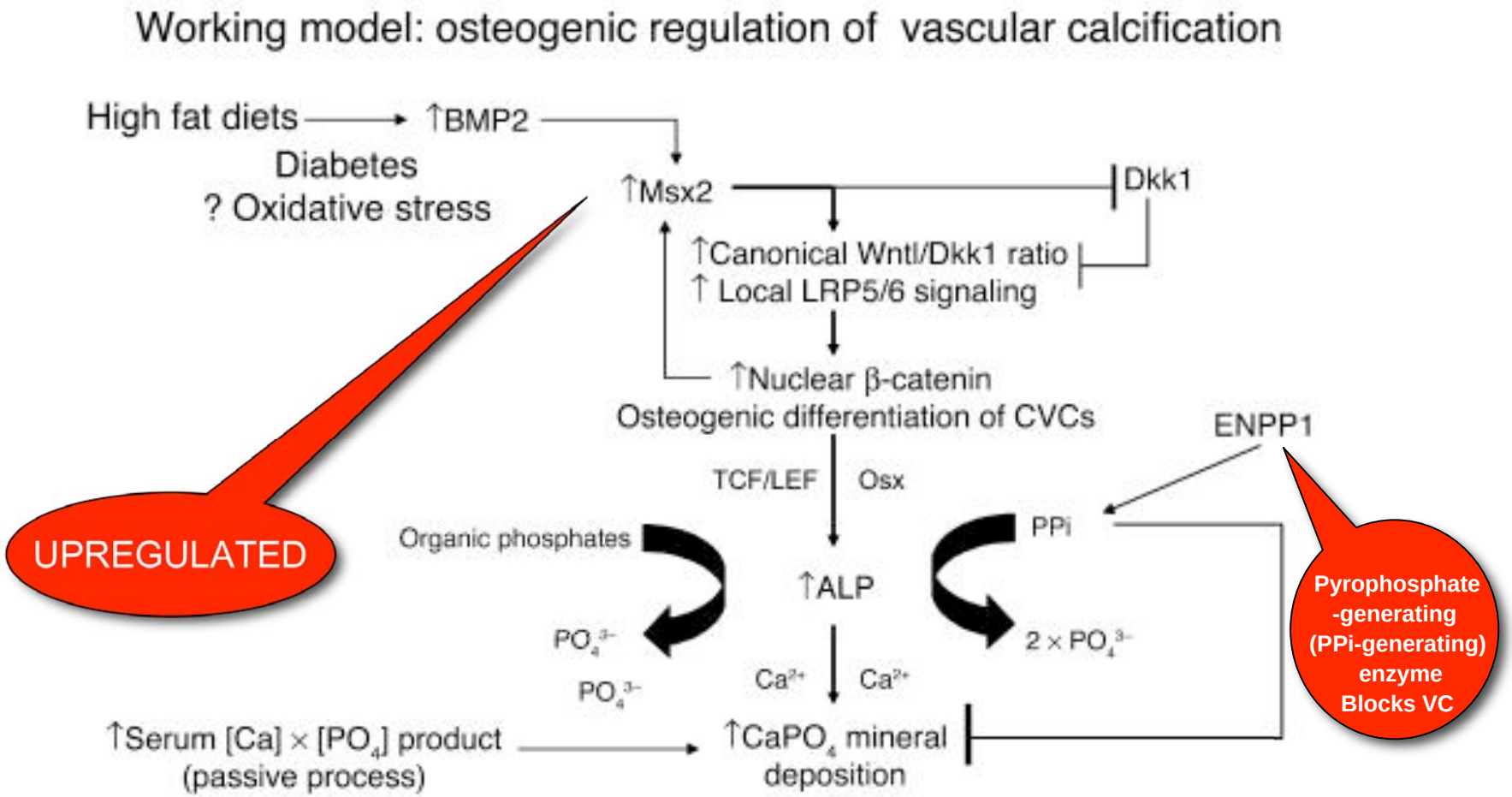
How the LDLR related to Bone Formation?





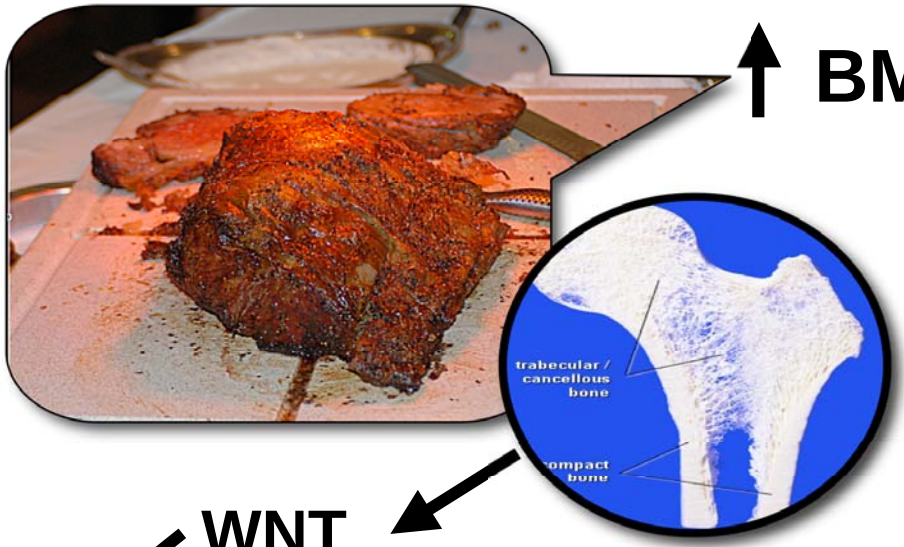


Mechanism of LDLR-/- VSMC Calcification

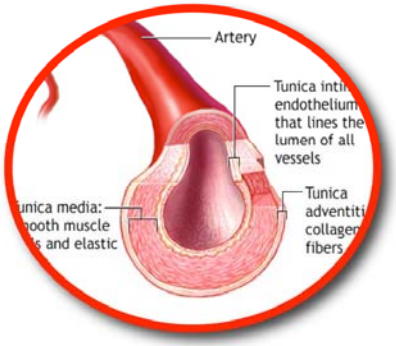


J Clin Invest. 2005 May 2; 115(5): 1210–1220.

Difference between blood vessel and bone is the MSX2 in adventitial fibroblasts



BMP2



MSX2

WNT

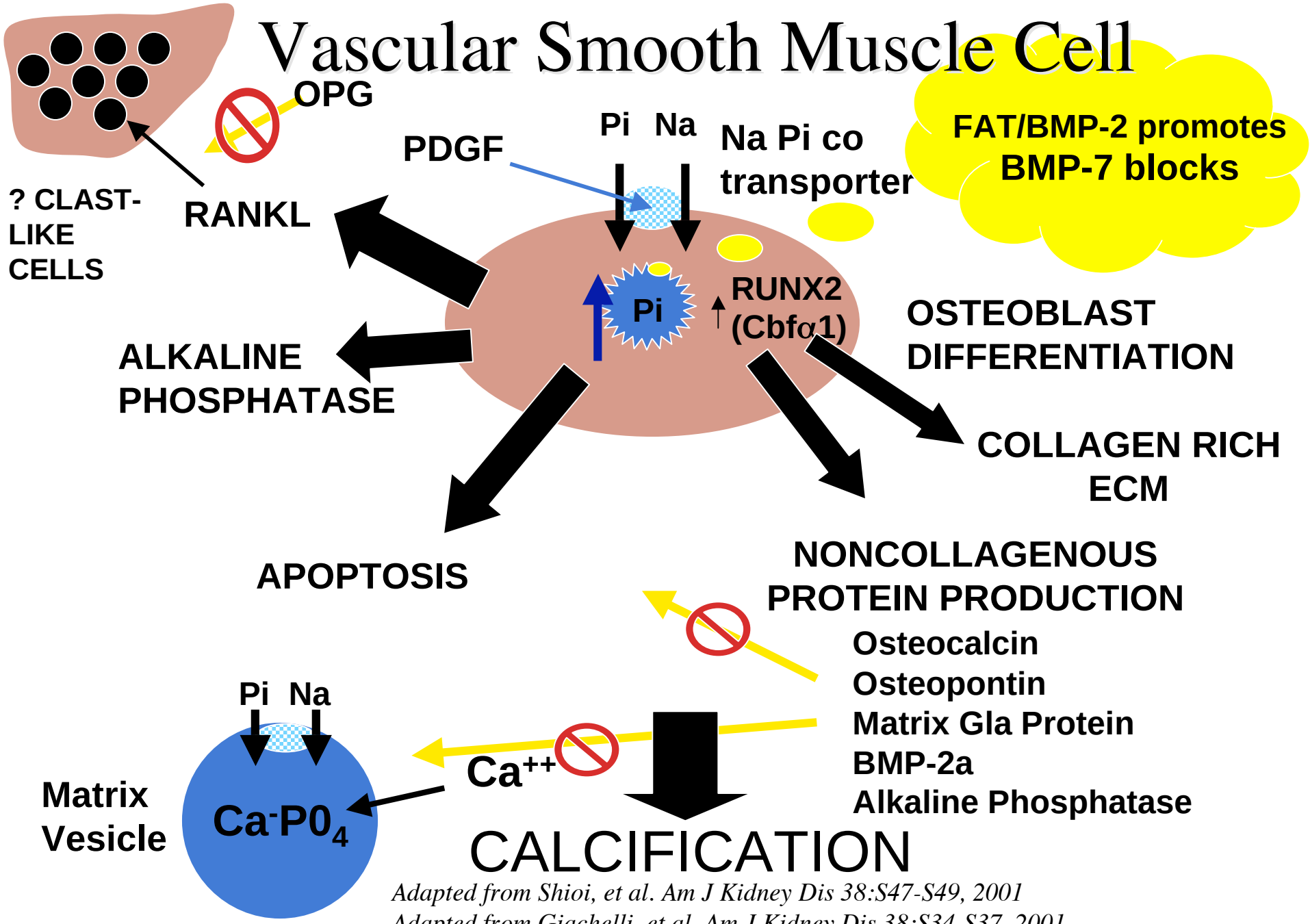
(WNT signaling does not occur because there is no LDL Co-receptor)

In LDLR -/- mice skeletonization decreases

LRP5/6 + WNT

RUNX2 (Cbfα1)

Osteoblastic vascular calcification

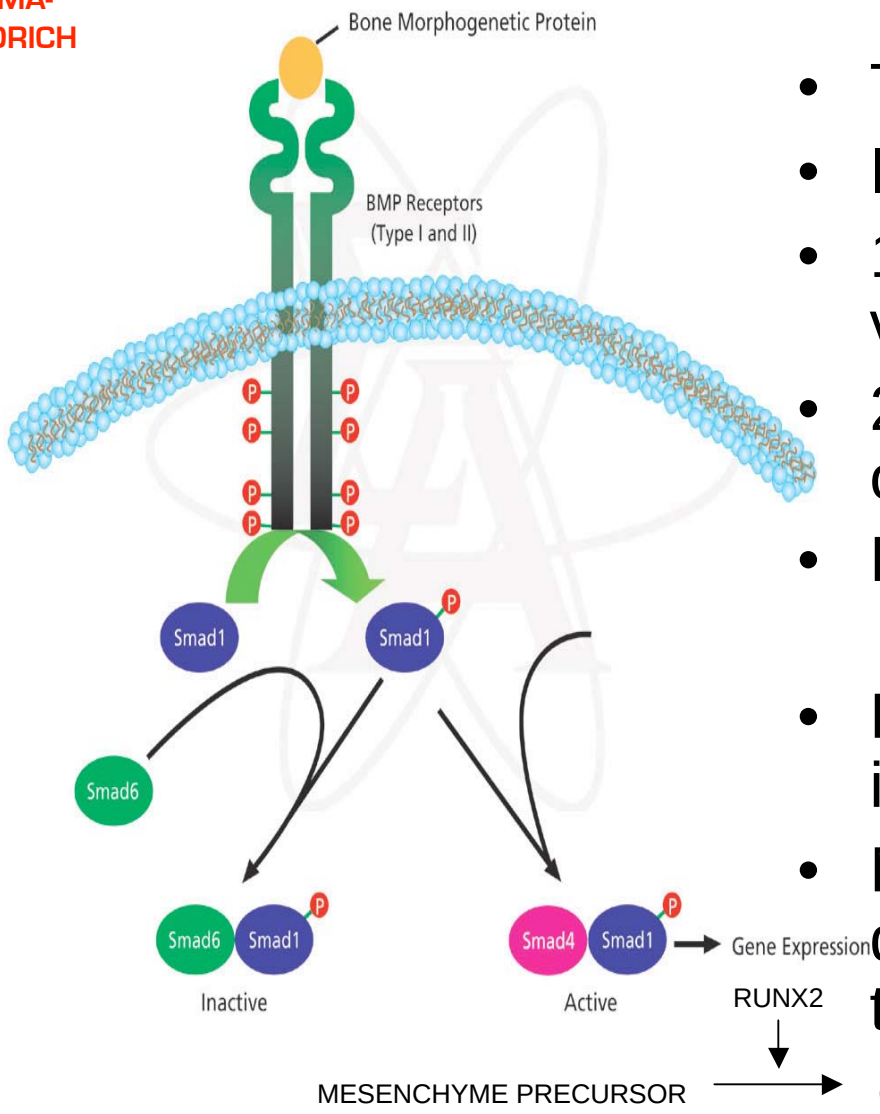


Adapted from Shioi, et al. Am J Kidney Dis 38:S47-S49, 2001
Adapted from Giachelli, et al. Am J Kidney Dis 38:S34-S37, 2001
Chen, et al. Kidney International 70:1046-1053, 2006

Bone Morphogenetic Protein Receptors

BMP-7

SIGMA-ALDRICH



- TGFß superfamily
- Induces SMAD
- 14 BMPS (BMP-2 induces vascular calcification)
- 20q13 (long arm, 13th band of chromosome 20)
- Holt-Oram - ⇑BMP-7
  - Nonapposable thumb, ASD
- BMP-7 downegulated early in kidney failure
- Maintains VSMC differentiation - blocks transformation to osteoblast

BMP ACTIONS

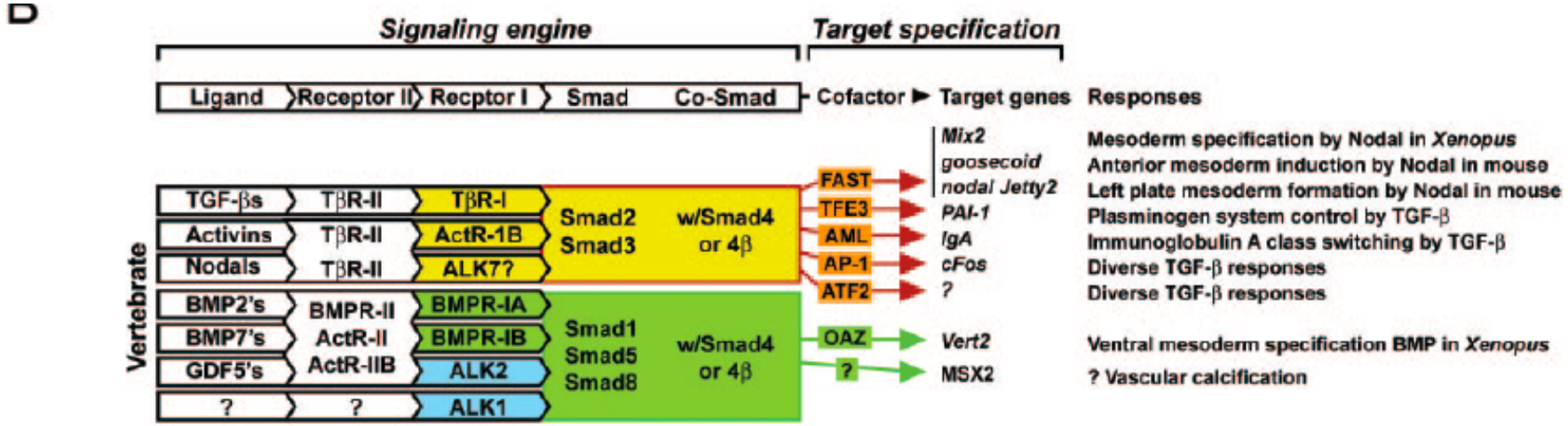


Figure 1. Putative BMP signaling mechanisms as related to vascular calcification. Adapted from Massagué J and Wotton D, the *EMBO J.* 2000;19:1745–1754.

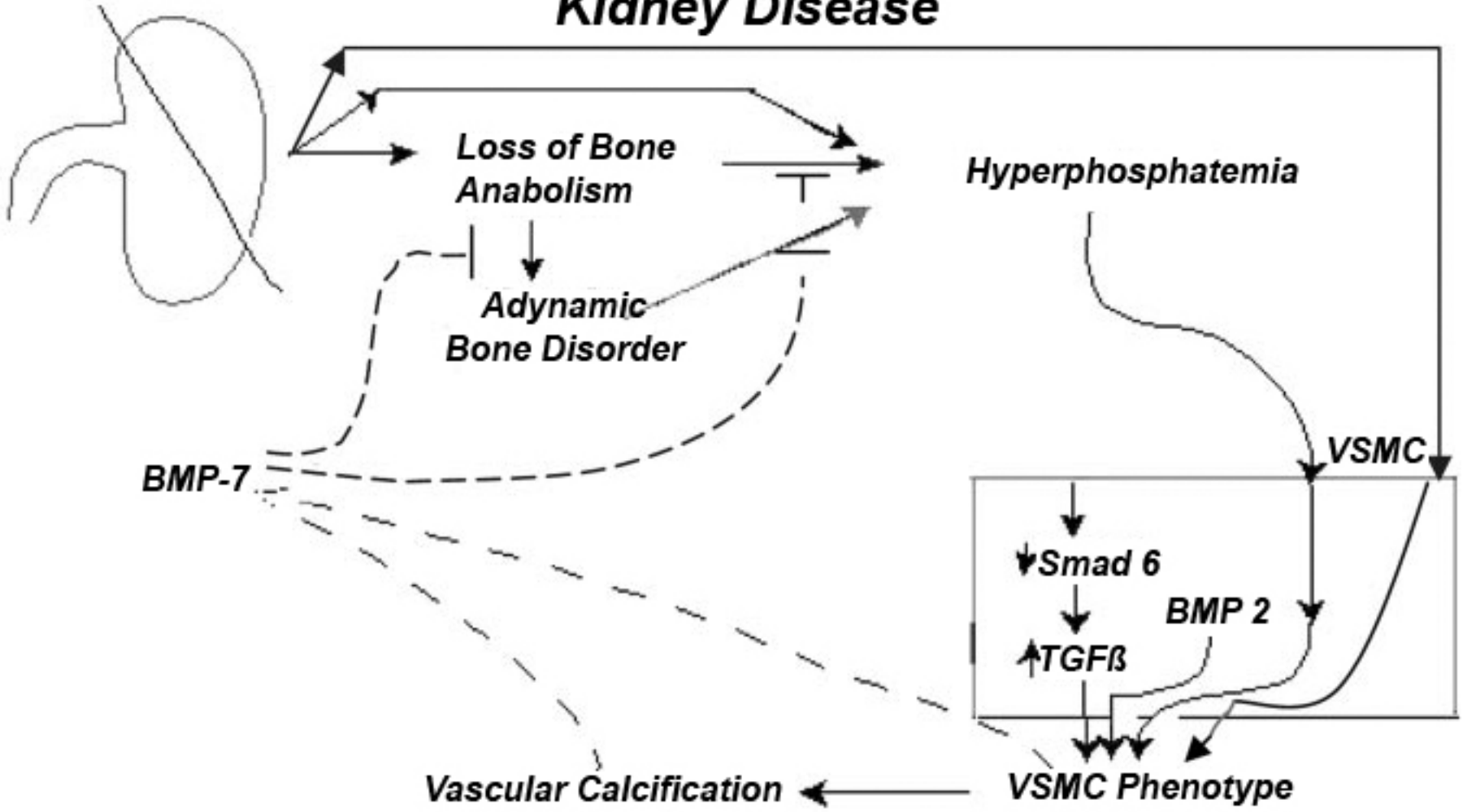
BMP2/BMP 7 - Needed for Osteoblast Differentiation
BMP7 - Blocks Vascular calcification

BMP-7 has great potential

- Blocks tubular epithelial cell de-differentiation,
- Blocks mesenchymal transformation and apoptosis
- Preserves glomerular integrity
- Inhibits injury-mediated mesangial matrix accumulation.
- Eliminates peritrabecular fibrosis
- Decreases bone resorption and restores normal rates of bone formation
- Increases the skeletal deposition of ingested phosphorus and calcium, preventing vascular calcification in CKD restoring osteocalcin expression to normal tissue-restricted sites.

Curr Opin Nephrol Hypertens. 2004 Jul;13(4):417-22.

Concept of the roles of the BMPs in Pathogenesis and Treatment of Vascular Calcification in Chronic Kidney Disease



Circ. Res. 2005;97;105-114


KDIGO
Kidney Disease
Improving Global
Outcomes
www.kdigo.org

Renal Osteodystrophy no longer works

- Strong relationship between mineral metabolism and CKD morbidity
- Osteodystrophy
  - Implies a bone disorder
  - 24 to 37 year old diaysis patients have the cv death rate 70 to 80 year olds
  - 99% of patients die of cardiovascular disease prior to reaching dialysis
- KDIGO establishes new classification in 2005

KDIGO

Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD-MBD and Renal Osteodystrophy

Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

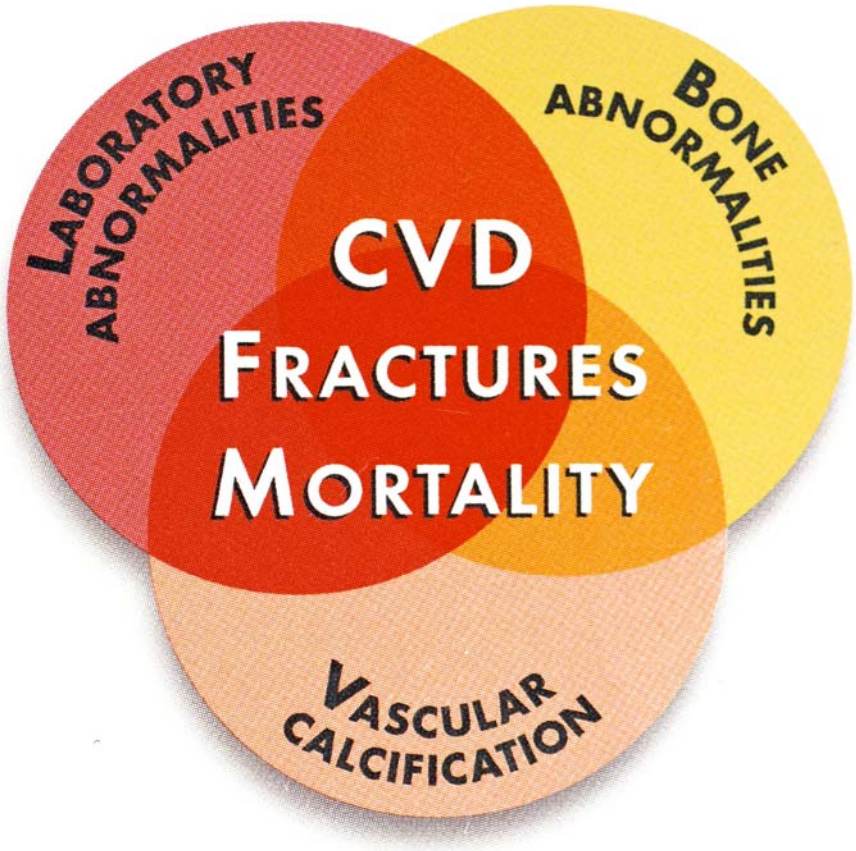
- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft tissue calcification

Definition of Renal Osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 69:1945-1953, 2006.

Chronic Kidney Disease–Mineral and Bone Disorder

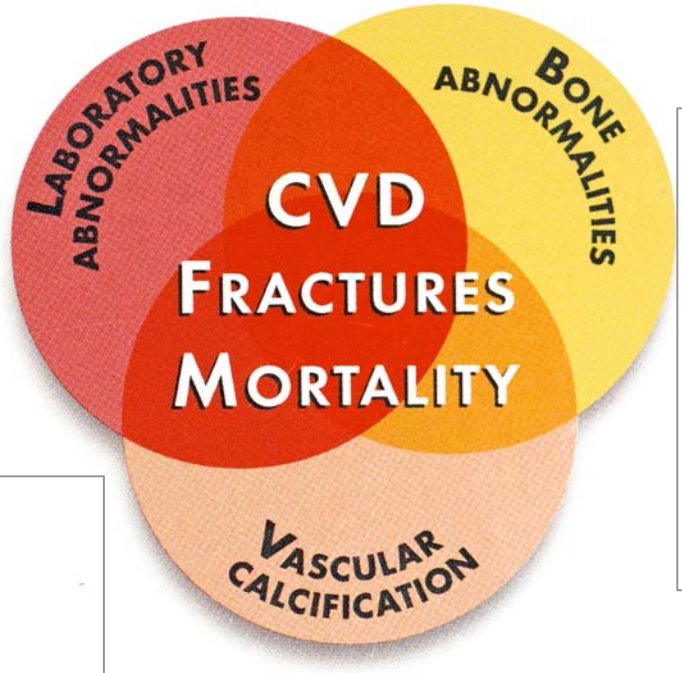


CKD-MBD

CKD-MBD

The broad syndrome that develops as a systemic disorder of mineral and bone metabolism caused by CKD

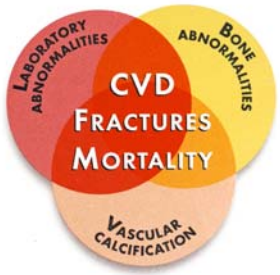
Laboratory
Calcium
Phosphorus
PTH
Vitamin D



Renal Osteodysdrophy
Turnover
Mineralization
Volume
Linear Growth
Strength

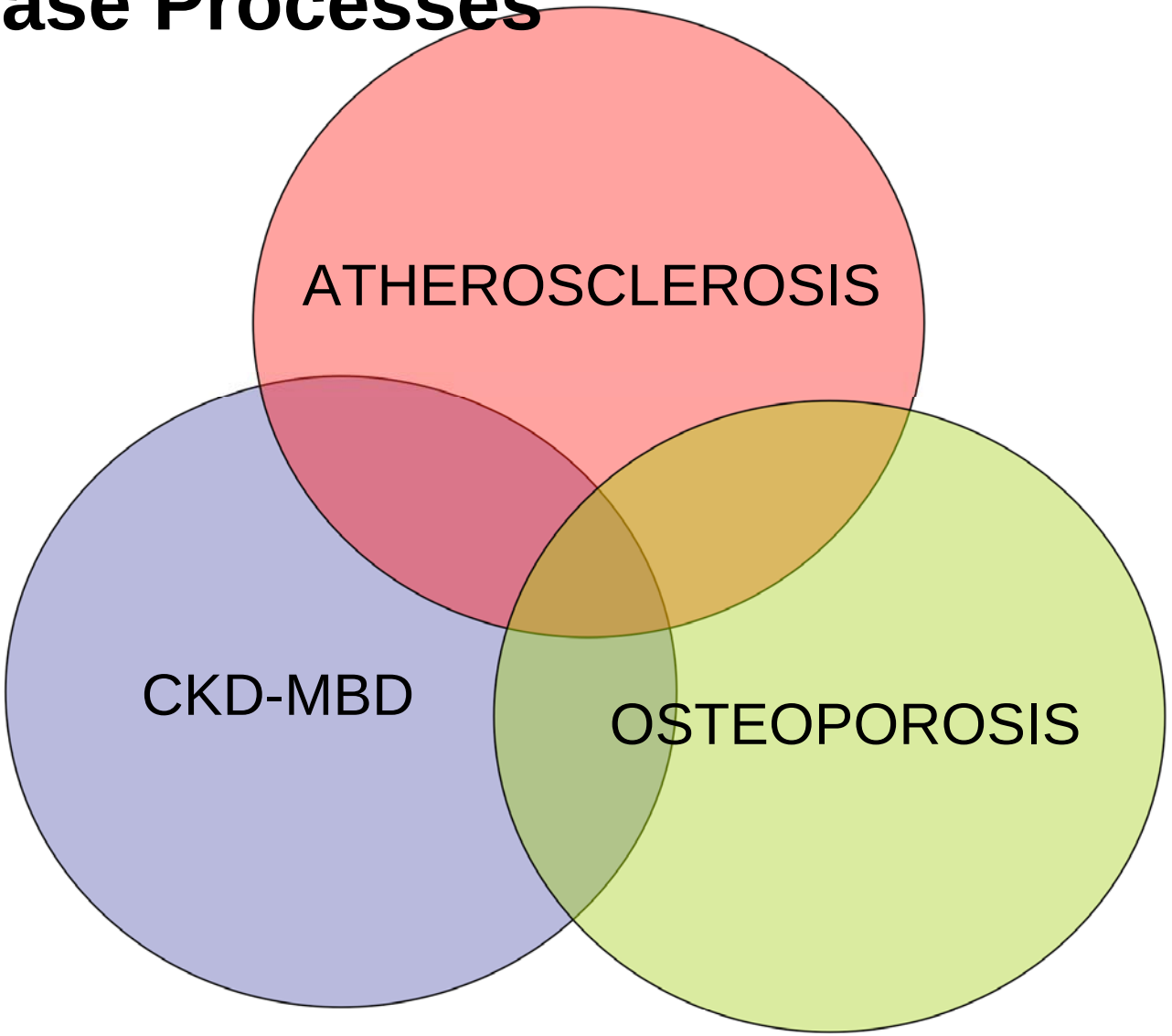
Calcification
X-ray
EBCT
Plethysmography

LBC - Evaluation in CKD



- Laboratory
  - PTH, Clacium, Phosphorus, alkaline phosphatase (total or bone specific), serum bicarbonate, vitamin D level
- Bone Biopsy Only if
  - High PTH and low alkaline phosphatase
  - Unexplained bone pain and fractures
- Calcification -
  - Soft Tissue Imaging
  - Pulse Pressure

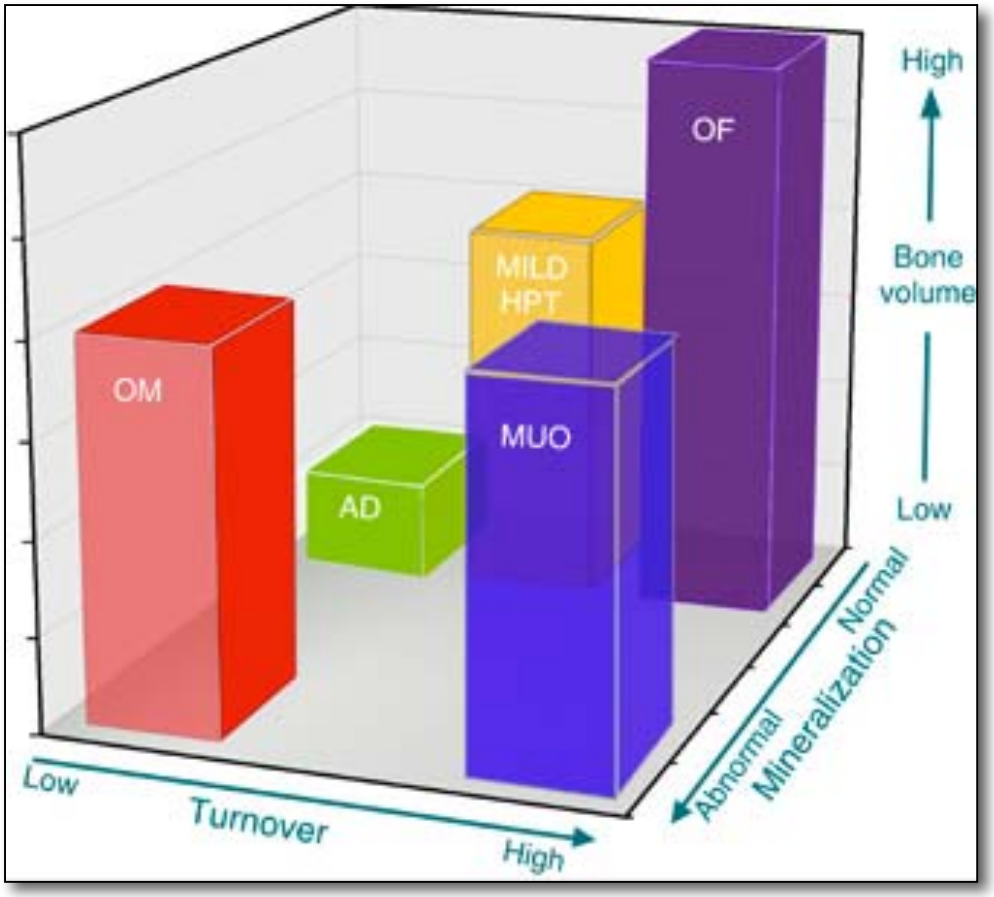
Vascular Calcification: Confounding Disease Processes



Case Study

- 54 year old African American Man on hemodialysis for 4 years. Hypertensive 20 years. Diabetes 10 years. L upper arm AVF.
  - Kt/V 1.3, BP 157/70 mm Hg,
  - Serum Phosphorus 6.1 mg/dL
  - iPTH 321 pg/L (Bayer Alexis Method)
  - Serum Calcium 10.2 mg/dL
  - Serum Albumin 4.1 g/dL
  - Sevelamer 800 mg, 3 with each meal
  - Doxercalciferol 3 mcg/treatment
  - Cinacalcet 30 mg each day

Bone Biopsy - TMV



Moe, S., et al., *Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO).* Kidney Int, 2006. **69**(11): p. 1945-1953.

1. OM - Osteo-malacia
2. MUO - Mixed uremic osteo-dystrophy
3. AD - Adynamic bone disease
4. HPT - Hyper-parathyroid-related
5. OF - Osteitis Fibrosa

Low Bone Turnover

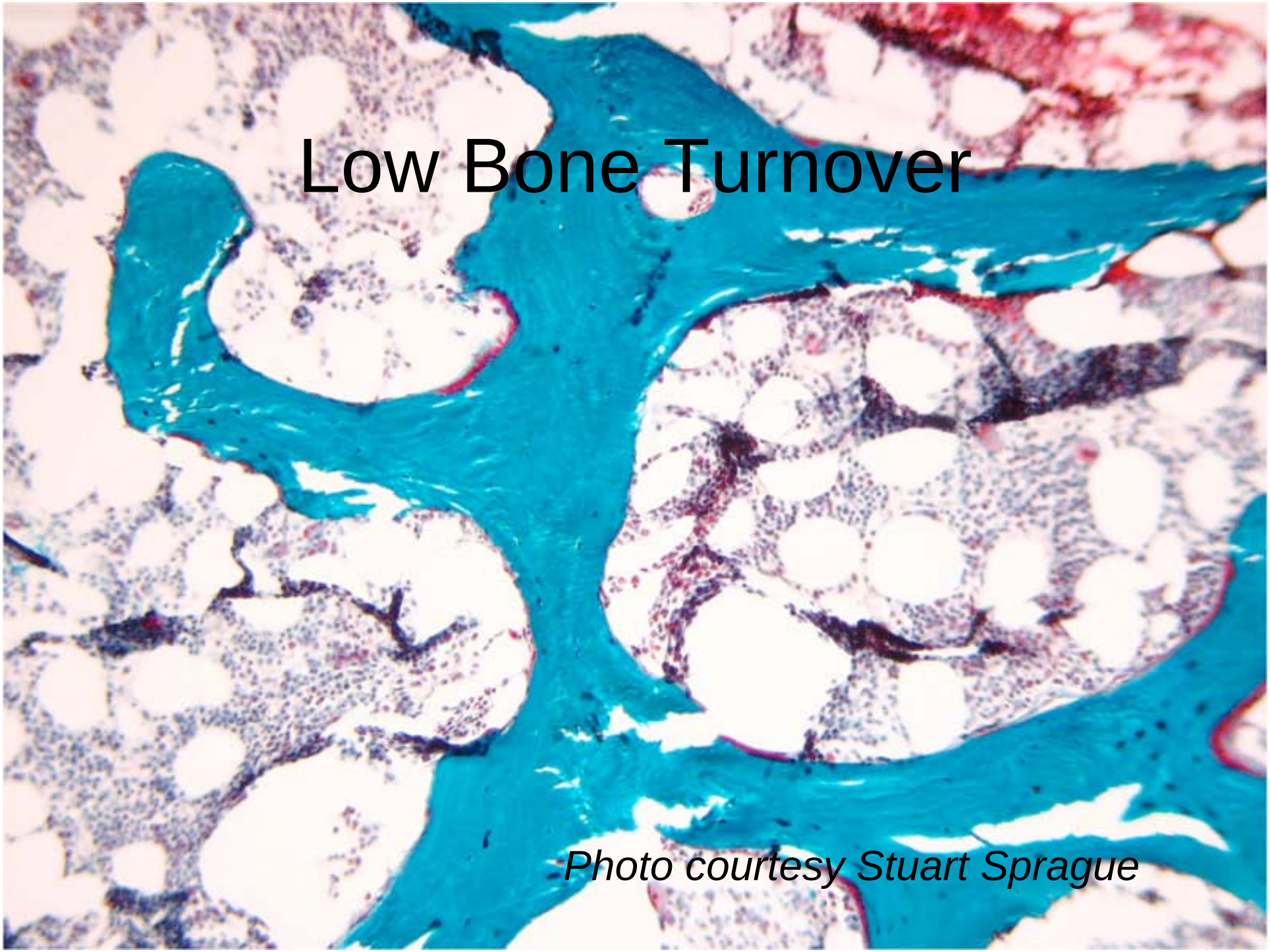
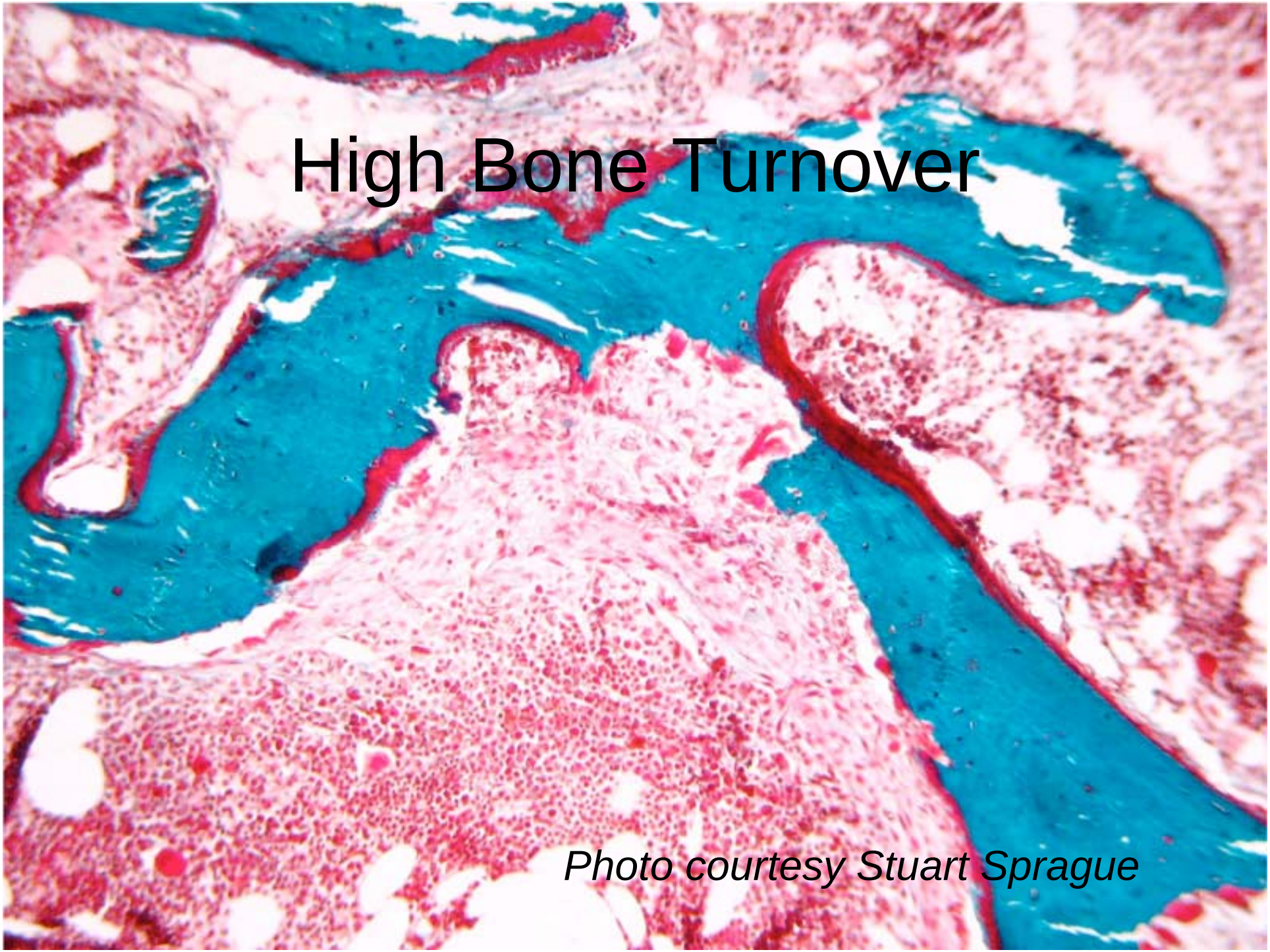


Photo courtesy Stuart Sprague

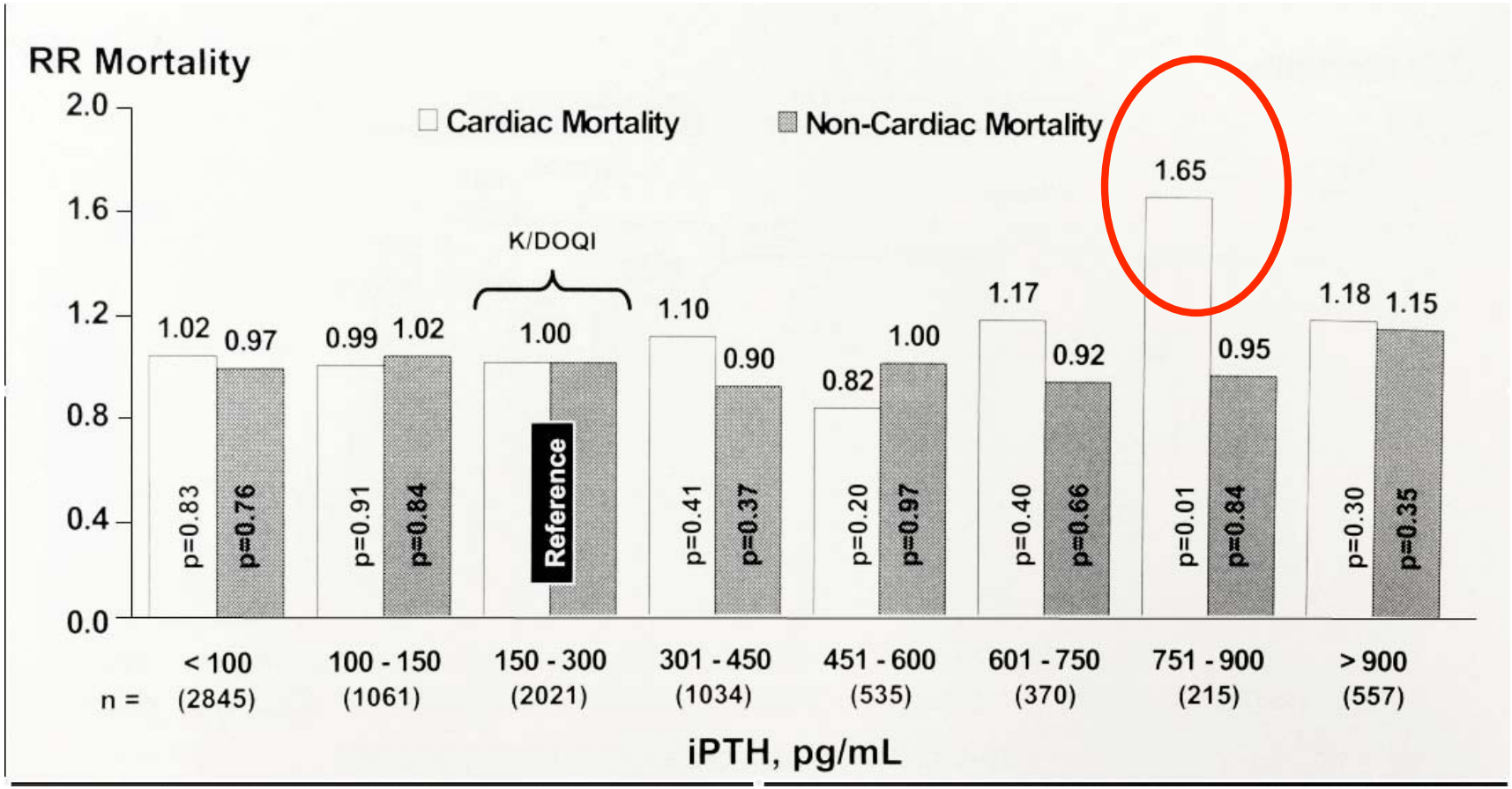

High Bone Turnover
Photo courtesy Stuart Sprague

iPTH levels between African Americans and Caucasians

- **76 ESRD patients (Caucasian = 48, African Americans = 28)**
- **histomorphometric measurement and iPTH levels**
- **Age, duration of dialysis, and calcium and phosphorus levels were similar between the two groups.**
- **iPTH levels**
  - **African American group - 534 pg/mL ± 79 vs.**
  - **Caucasian 270 pg/mL ± 46 (*P* < 0.01).**
- **iPTH levels with low bone turnover**
  - **African Americans 460 pg/mL ±115 vs**
  - **Caucasians 168 pg/mL ± 41**
- **Alkaline phosphatase levels**
  - **African American group 162mg/dL ± 31 vs.**
  - **Caucasian 144 mg/dL ± 43, (*P* < 0.01).**
- **Correlations between PTH levels and activation frequency**
  - ***r* = 0.60, *P* < 0.01 in Caucasians**
  - ***r* = 0.22, *P* = NS in African Americans.**

Kidney Int. 2003 Aug;64(2):737-42.

How aggressive should we be in managing PTH levels?



Compare PTH assay to K/DOQI standard

Table 1. Comparison of PTH assays to Allegro Assay

Assay	*PTH (ng/L)*	*PTH (ng/L)*	*PTH (ng/L)*	*Median Bias (%)*
Allegro intact PTH	150	300	1000	0
N-tact PTH IRMA	83	160	517	−44.9 (−68.0; −26.2)
PTH IRMA Immunotech	188	369	1216	23.9 (−6.1; 108.3)
ELISA-PTH	149	290	948	−1.6 (−24.3; 47.2)
Total intact PTH IRMA	134	262	857	−14.5 (−41.5; 23.5)
DSL PTH IRMA	323	638	2108	123.0 (53.1; 188.9)
DSL PTH ELISA	264	523	1734	79.6 (−8.0; 180.9)
Elecsys PTH	161	311	1011	7.3 (−13.8; 80.3)
Immulite 2000 intact PTH	212	410	1334	37.8 (3.8; 130.8)
PTH-ACS 180	185	374	1256	18.8 (−9.9; 69.4)
PTH Adviacentaur	168	342	1154	9.5 (27.6; 55.6)
Intact PTH advantage	174	339	1109	14.6 (−10.4; 72.2)
LIAISON N-tact PTH	111	223	748	−23.4 (−68.2; −1.9)
Ca-PTH IRMA	84	165	543	−44.8 (−65.6; −22.8)
BioIntact PTH advantage	109	214	704	−27.6 (−53.0; 12.5)

NOTE. Comparison of PTH assay concentrations in comparison to the *Allegro* assay at 3 concentrations (150 ng/L, 300 ng/L, and 1,000 ng/L). (Reproduced with permission.[37])

5/6 Nephrectomized Mice

- Chow fed
  - Developed secondary hyperparathyroidism
- Phosphate restricted and treated with calcitriol
  - Adynamic bone disease
  - depressions in osteoblast number, perimeters, bone formation rates, and mineral apposition rates

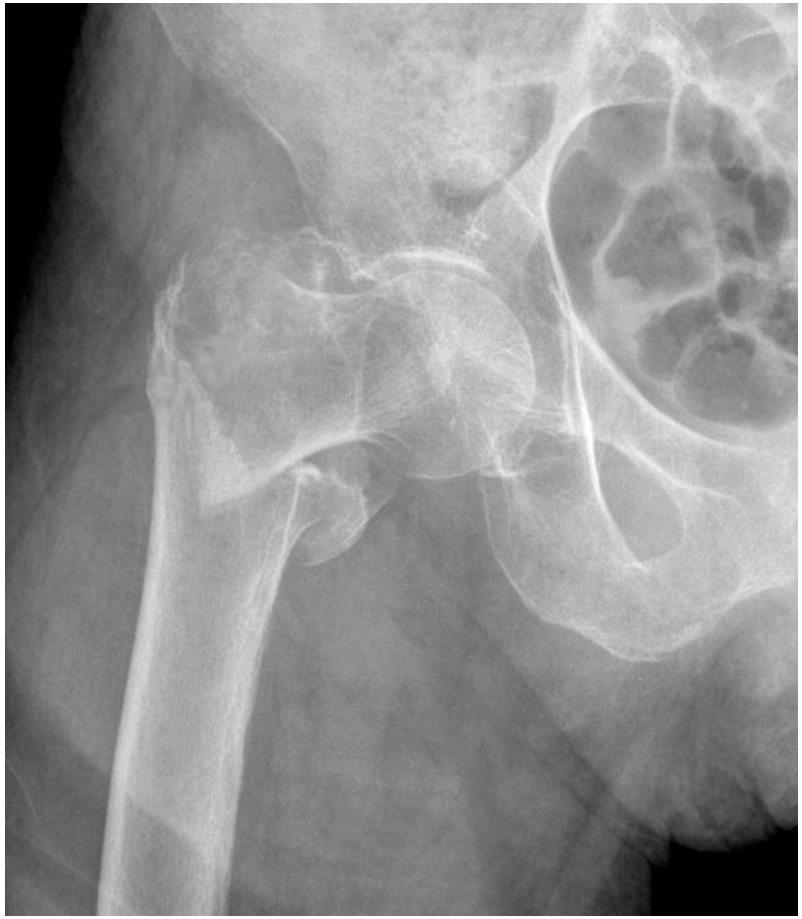
J Am Soc Nephrol. 2004 Feb;15(2):359-69

African Americans may be more resistant to PTH and have higher levels.
Suppressing the iPTH to accepted levels could lead to low bone turnover disease

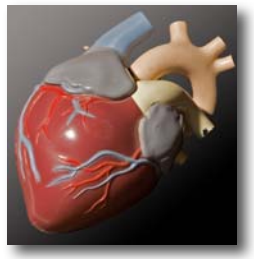
*Kidney International (2003) **64**, 737-742*

Pathological Fractures

- Dialysis Patients in their 40s
  - 80 fold higher risk of hip fracture
- Hip fracture
  - Double mortality
- Low or high PTH level
  - a risk factor for hip fracture

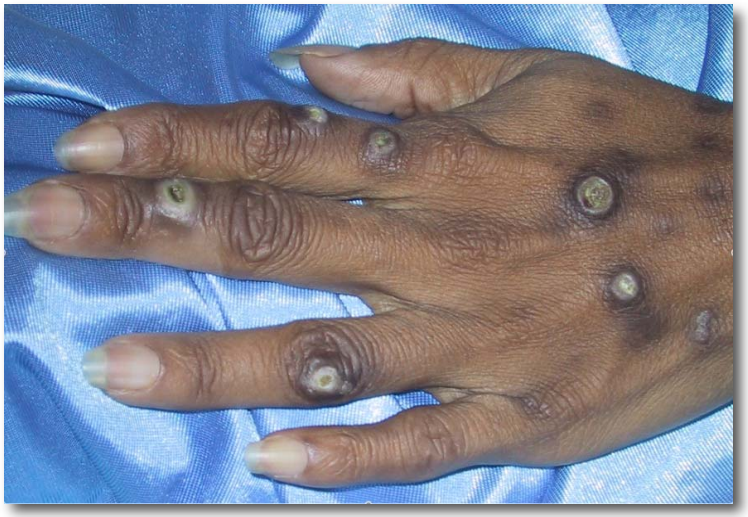


Vascular Calcification



- Associations with dialysis patients
  - Goodman, W.G., et al., *Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis.* N Engl J Med, 2000. **342**(20): p. 1478-83.
  - Raggi, P., et al., *Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease?* J Am Coll Cardiol, 2002. **39**(4): p. 695-701.
- Mortality associated with EBCT
  - Wayhs, R., A. Zelinger, and P. Raggi, *High coronary artery calcium scores pose an extremely elevated risk for hard events.* J Am Coll Cardiol, 2002. **39**(2): p. 225-30.
- 65% patients starting HD have vascular calcification. Patients with zero calcification at onset of HD do not progress
  - Block, G.A., et al., *Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis.* Kidney Int, 2005. **68**(4): p. 1815-1824.

Peripheral Vascular Disease



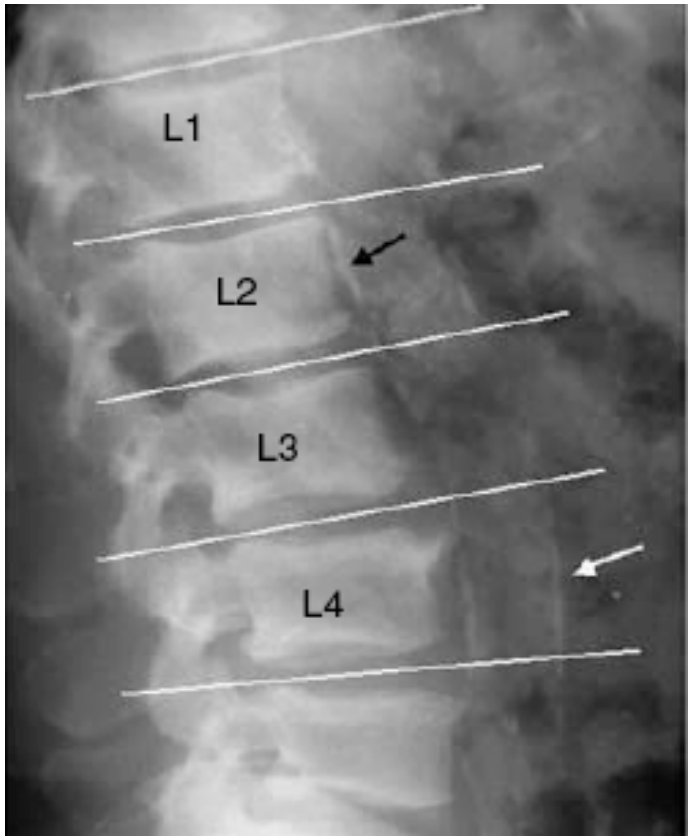
- Plain film femoral artery calcification related to increased all cause mortality
- Increased pulse wave velocity
- Increased pulse pressure
- Inverse relation to bone mineralization
  - Bone mineralizes at ages 25 to 25, then decreases,
  - accentuated in CKD
- Common in CKD

JASN, 2001. **12**(12): p. 2838-2847.
AJKD, 2002. **40**(3): p. 472-9.
Circulation, 2006. **114**(18): p. 1914-1922.

- Low bone turnover - greatest risk of vascular calcification
- Non calcium binders - may have role in decreasing calcification, increasing trabeculation
- Some patients never get vascular calcification

KI 2005. **68**(4): p. 1815-182

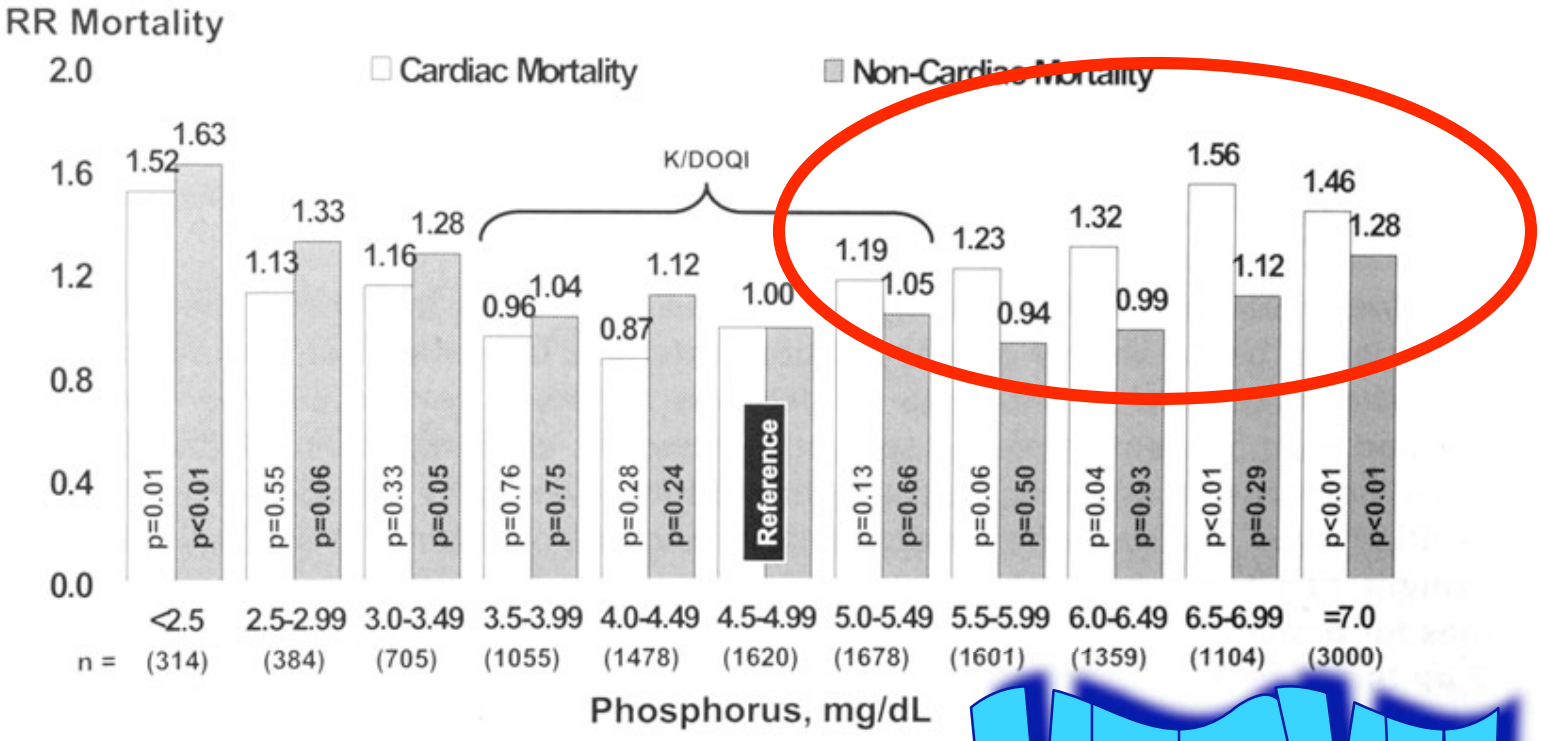
Abdominal Aorta X-ray Score



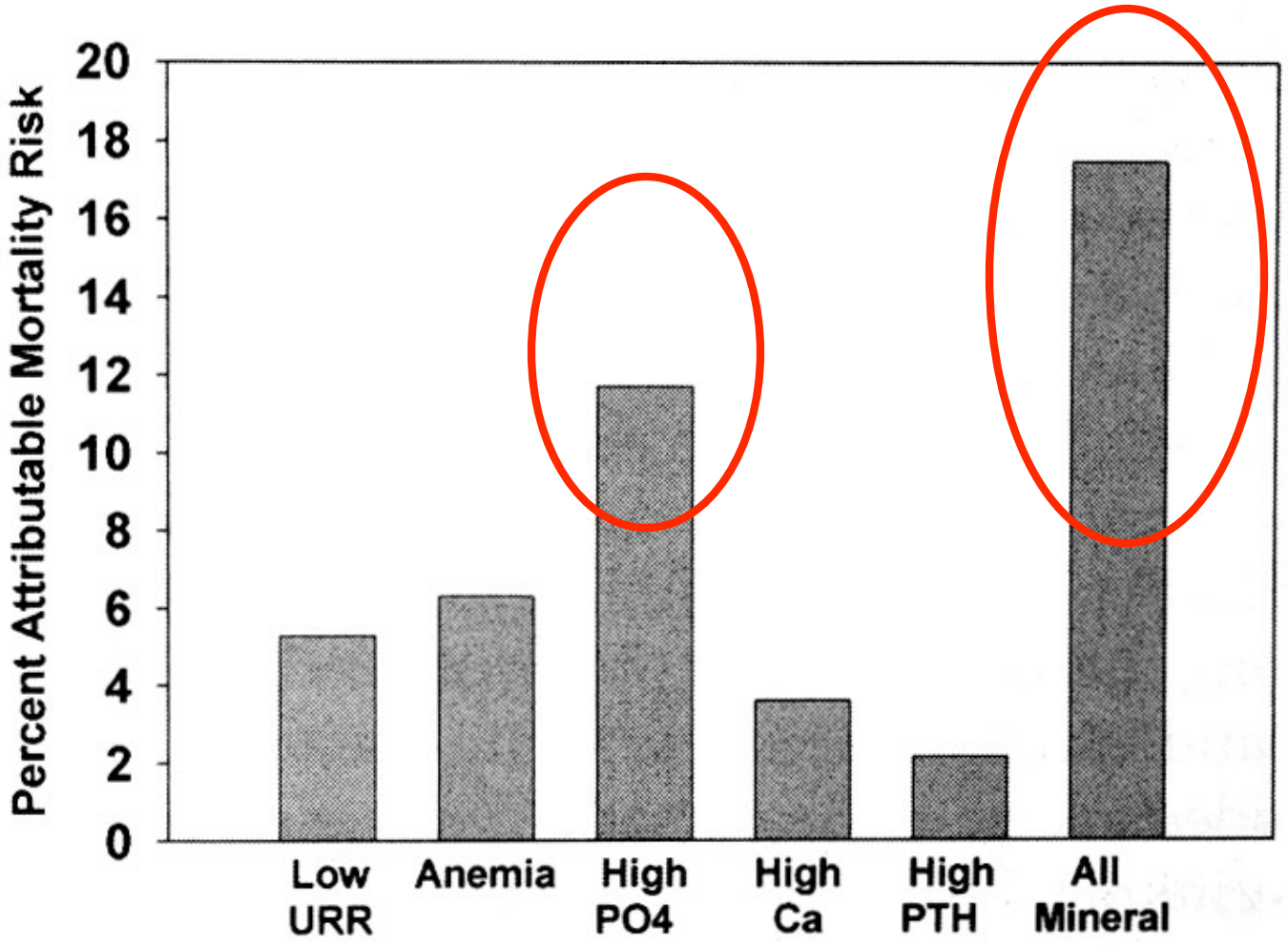
- Plain lateral x-ray of the lumbar spine
  - Aortic calcification >7
  - CACs on EBT > 1000
  - Aortic valve of 75.9
  - ($p < 0.001$)
- CAC Score > 100 (Valve)
  - Sensitivity 53%
  - Specificity 70%
- CAC Score > 100 (Xr >7)
  - Sensitivity 67%
  - Specificity 91%

Kidney International (2006) 70, 1623–1628.

How aggressive should we be in managing Phosphorus levels?



Laboratory Evidence



Moe S, Chertow G, CJASN 1:697, 2006

Phosphorus Risks in ESRD

10% higher risk at phosphorus concentrations of 6.4 to 7.5 mg/dL[9]

18% higher risk at phosphorus concentration of 6.6 to 7.8 mg/dL[4]

25% higher risk at phosphorus concentrations of 6.0 to 7.0 mg/dL[7]

28% higher risk at phosphorus concentrations of 6.5 to 7.0 mg/dL[8]

53% higher risk at phosphorus concentrations of 6.0 to 7.0 mg/dL[10]

54% higher risk at phosphorus concentrations greater than 6.0 mg/dL[11] 83% higher risk in CKD patients with P concentrations of 4.5 to 4.9 mg/dL.[12]

4 AJKD 31:607,1998
7 JASN 15:2208, 2004
8 KI 67:1179, 2005
9 JASN 16:1788, 2005
10 JASN 15:770, 2004
11 KI 70:351, 2006
12 JASN 16:520, 2005

Phosphorus in non dialysis

- Association with early atherosclerosis in patients with presumed normal kidney function (p=0.0003; N=294)

  Int J Cardiol, 1997. ***60****(1): p. 73-79.*

- CARE: Normal cr, PO_4 ≥ 3.5 gm/dL - adjusted mortality hazard ration of 1.27 (CI 1.02 to 1.59 p=0.03 for trend).

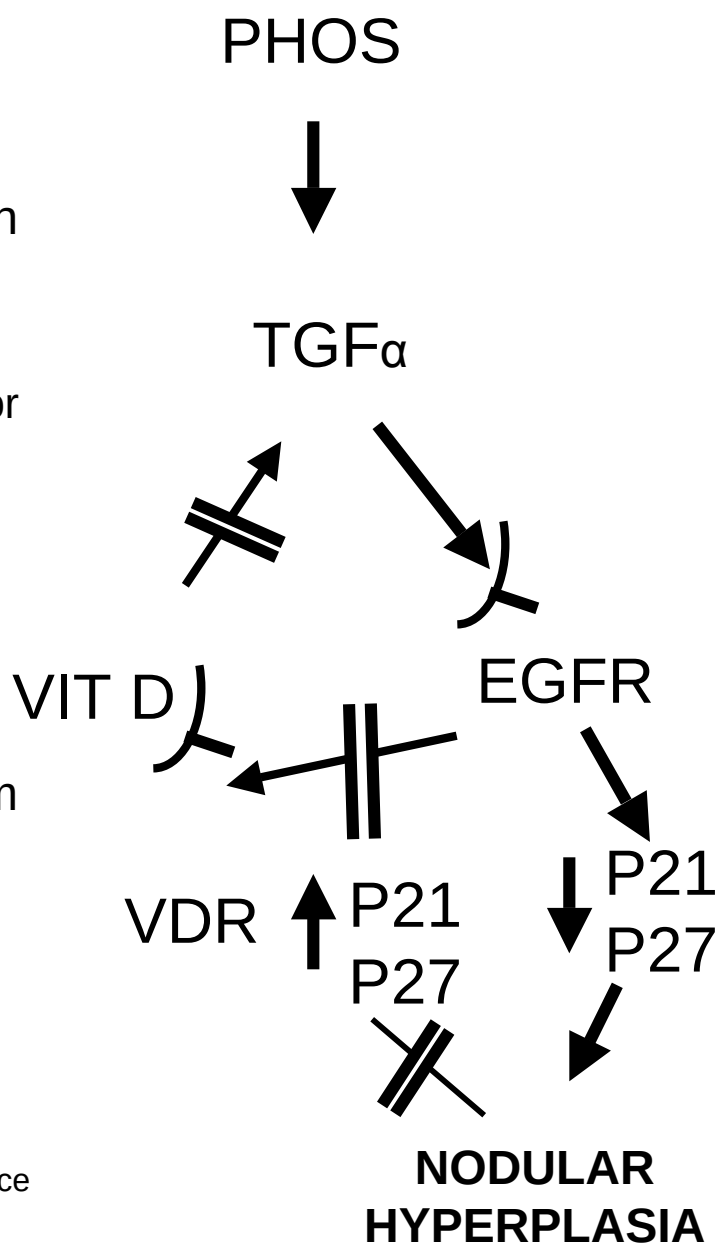
  Circulation, 2005. ***112****(17): p. 2627-33.*

- 8 VAMCs: (n=96,619 patients), 7021 non dialysis patients had creatinine levels > 1.2 mg/dL.
  - Serum $P0_4$ than 3.5 mg/dL associated with a significantly increased risk of death
  - Mortality rate increased linearly with 0.5 mg/dL serum $P0_4$ increments

    J Am Soc Nephrol 2005;16:520-8.

Phosphorus

- Directly influences the development of parathyroid hyperplasia and PTH secretion
- Indirectly influences vitamin D resistance.
  - Enhances expression of a potent growth promoter, TGFα (transforming growth factor alpha) and its receptor, EGFR, the epidermal growth factor receptor.
  - TGFα/EGFR expression and downstream signaling lead to severe parathyroid hyperplasia and vitamin D resistance.
- Lends insight into how vitamin D is less effective in controlling hyperparathyroidism when severe hyperphosphatemia is present.



Kidney International (2002) 62, 1472–1473
Nodular parathyroid growth: Role of vitamin D resistance
Adriana S Dusso

FGF-23 FACTS

- **What**
  - In FGF Family
  - FIBROBLAST GROWTH FACTOR 23;
  - 3 exons, 10 kb of genomic sequence
  - 251-amino acids contains an N-terminal 24-amino acid signal sequence
- **When**
  - FGF23 gene encodes mutant factor
    - autosomal dominant hypophosphatemic rickets
  - Tumor induced osteomalacia
  - -/- knockout mice
    - hyperphosphatemia and increased 1 alpha hydroxylase
- **Where**
  - lies in 54 kb telomeric of FGF6 12p13 (short arm, 13th band)
- **Why**
  - Essential for phosphorus metabolism
  - Essential for adaptation of hyperphosphatemia induced by CKD
  - Present in normal circulation
- **How**
  - Decreased Na dependent phosphate uptake in kidney cells
  - Decreases 1 a hydroxylase activity
  - Binds to Klotho - high affinity - Klotho essential for its function
  - Klotho generates receptor from FGF1
- **Breakdown**
  - cleaved between arg179 and ser180,
- **Measured**
  - sandwich ELISA for human FGF23, using 2 monoclonal antibodies to FGF23.

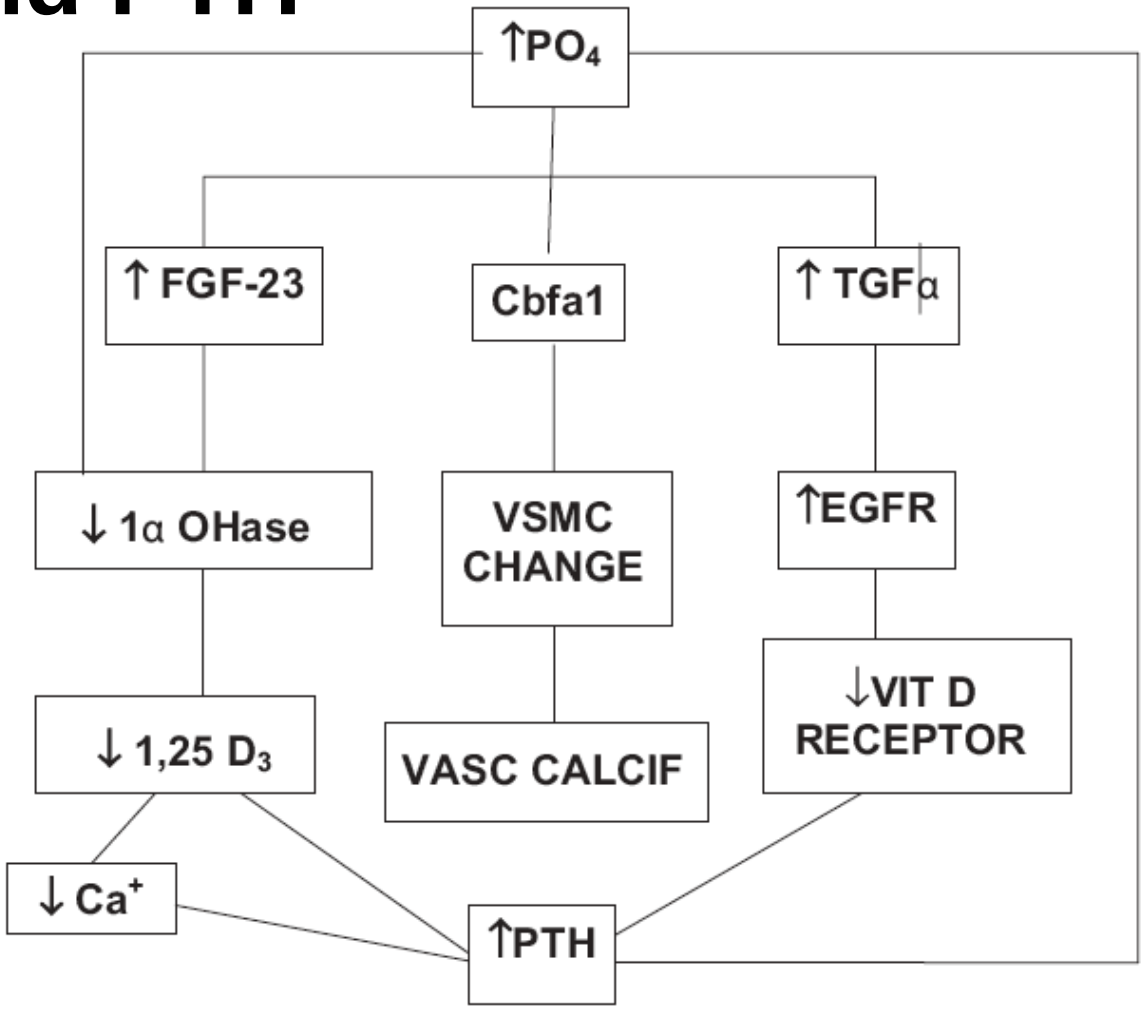
PHOSPHORUS STIMULATES FGF23 IN CKD

Source: Entrez Gene

Elevated Serum Phosphorus

- 30% ingested phosphorus excreted in the gastrointestinal tract, remaining 70% eliminated by the kidney.
- Phosphorus stimulates FGF-23 in CKD
  - This increase tubular excretion of $P0_4$, maintaining levels.
  - Decreases 1,α Hydroxylase - which decreases active vitamin D
  - Increased PTH synthesis
    - *J Clin Endocrinol Metab* 2006
- Serum $P0_4$ would rise sooner in CKD were it not for FGF-23
- Keeps serum phosphorus levels normal during moderate to severe CKD
- Phosphorus retention begins when these compensatory mechanisms are overcome by the decrease in kidney function (GFR 20-25 mL/min/1.73m^2).
- PTH corrects with dietary protein restriction (supplemented 0.3 g/kg/bw) in early CKD
  - *Combe C et al. Nephrol Dial Transplant 1993;8:412-8.*

Established relationships between $P0_4$ and PTH



Fadem, SZ and Moe, SM
Adv Chr Kidney Dis 14:44-35, 2006

Dietary $P0_4$ control

- 800 to 1,000 mg/day limits protein to below requirements
  - http://nutrinfo.org – Source: USDA
- Phosphorus - an additive to processed foods
  - Restructured meats, spreads, puddings and caramelized colas,
  - “Fast foods” and less expensive foods - burdensome to families
  - Polyphosphates and pyrophosphates are rapidly absorbed.
- Crossover study of graduate students,
  - Diet free of phosphate additives reduced the load by an average of 1,154 mg per day,
  - Maintained protein content

    J Nutr 1977;107:42-50
- Plant foods require phytase for phosphorus breakdown
  - Absent in humans
  - Phosphate absorption less complete

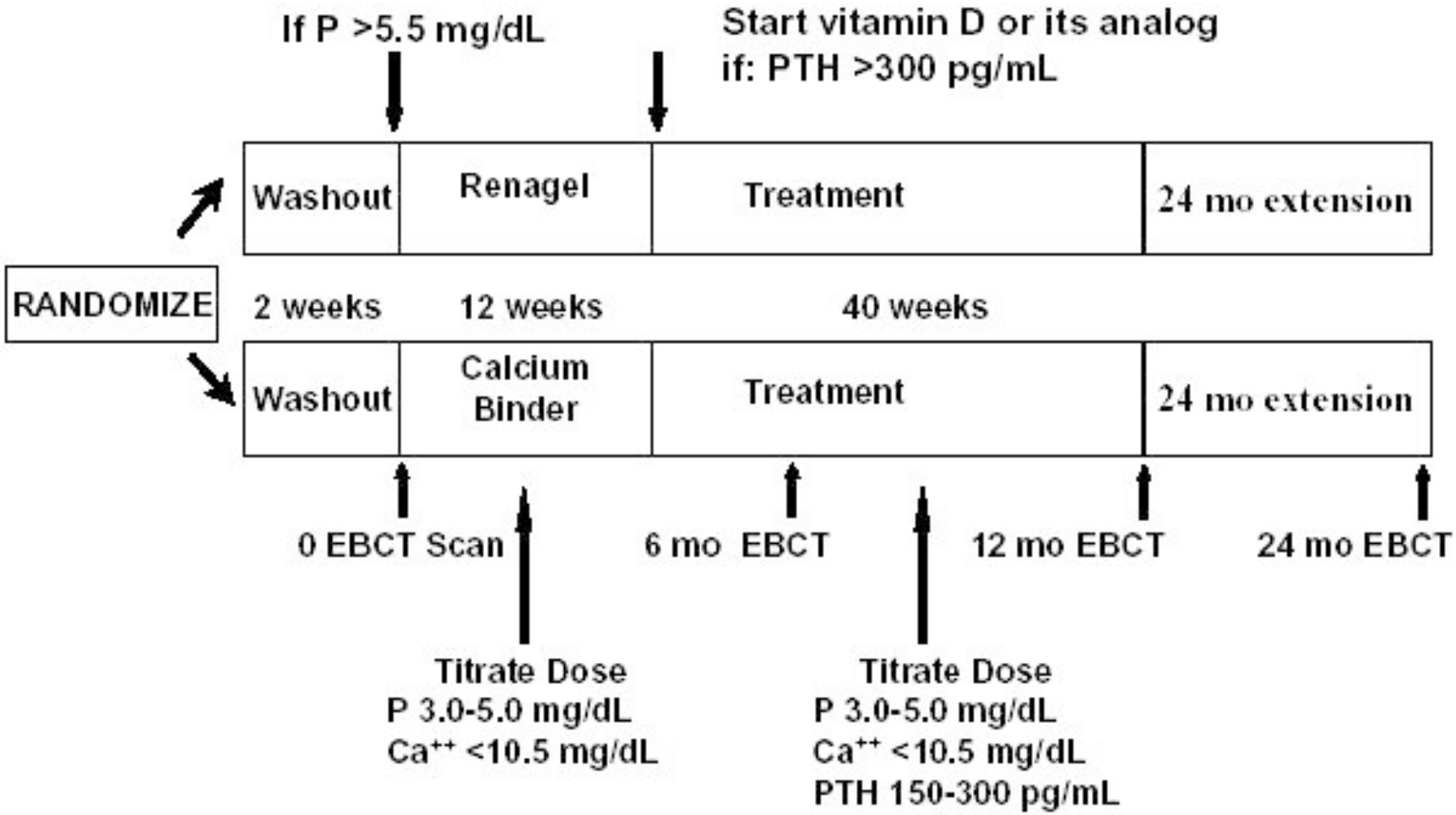
    Semin Dial 2003;16:186-8

A summary of therapy

- 1970s - Suppress PTH with oral vitamin D and control Serum P04 with aluminum
- Aluminum Toxicity lead to Calcium binders
- 1980s iv calcitriol lead to hypercalcemia
- 1990s vitamin D analogs
  - P04 mortality and Vascular calcification studies
- Late 1990s Sevelamer
- 2000s Lanthanum, Cinacalcet

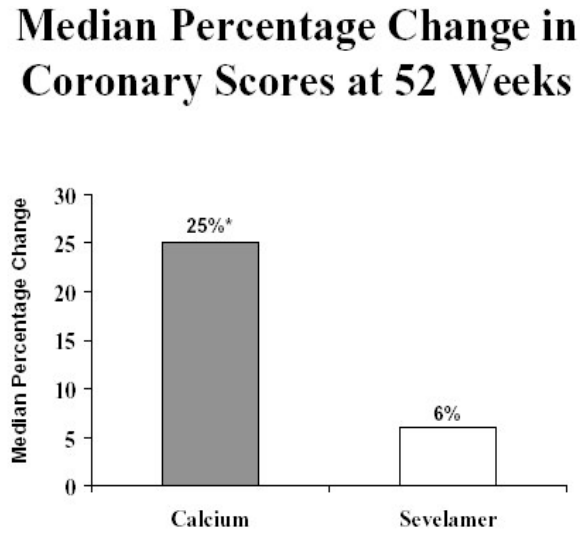
Am J Kidney Dis 42:96-107, 2003
Nephrol Dial Transplant 19:1902-1906, 2004
N Eng J Med 294:184-188, 1976
Contrib Nephrol 102:110-124, 1993
Am J Kidney Dis 33:694-701, 1999
Am J Kidney Dis 43:234-243, 2004
N Eng J med 350:1516-1525, 2004

Treat To Goal Study and Extension

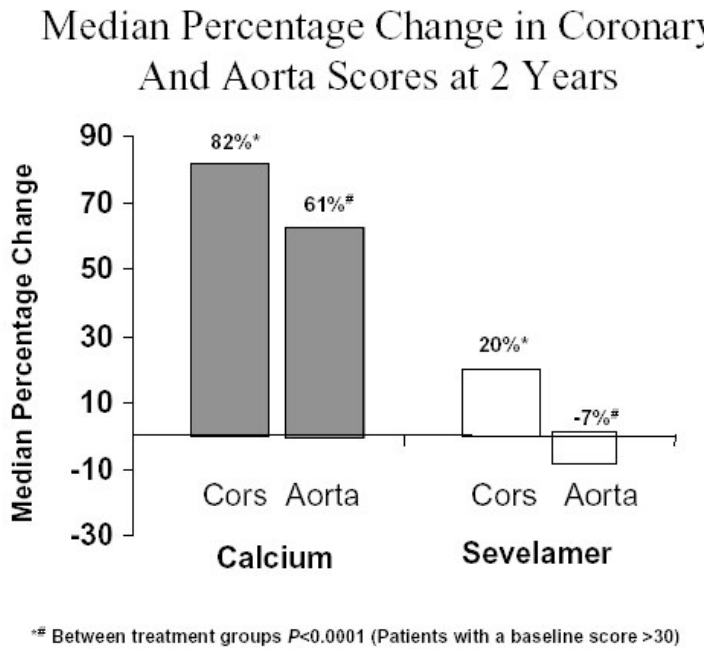


Chertow, GM, Burke, SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney International 2002;62:245-252

Lower $P0_4$ without raising Ca



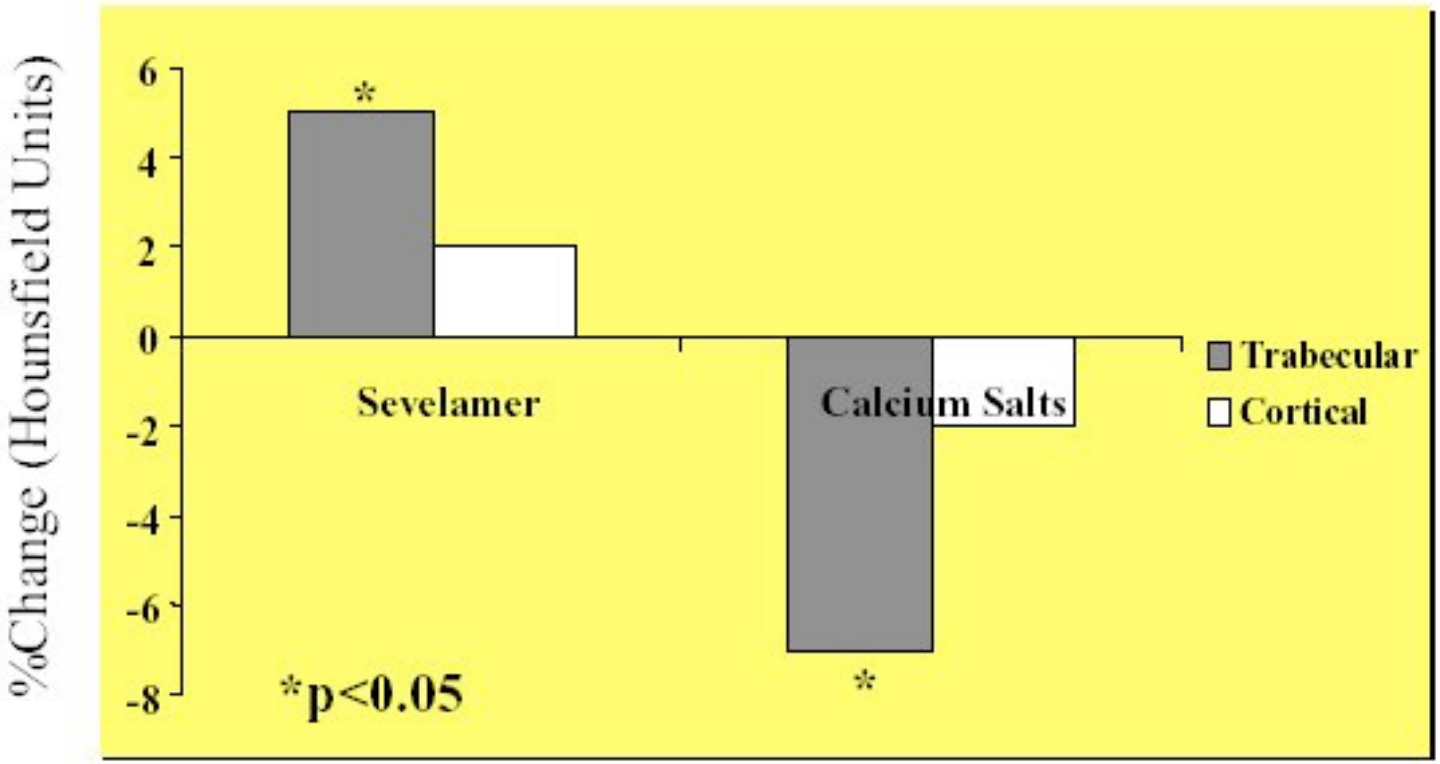
*Within treatment *P*<0.0001; between treatment groups *P*=0.02.
Patients with a baseline score >30.



*# Between treatment groups *P*<0.0001 (Patients with a baseline score >30)

Chertow, GM, Burke, SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney International 2002;62:245-252

Changes in Thoracic Vertebral Bone Density After 2 Years of Randomization



Nephrol Dial Transplant. 2005 Aug;20(8):1653-61. Two year comparison of sevelamer and calcium carbonate effects on cardiovascularcalcification and bone density.Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, Neumayer HH,Raggi P, Bommer J.

Sevelamer and Calcium Carbonate decrease kidney calcification in 5/6 nephrectomy rats

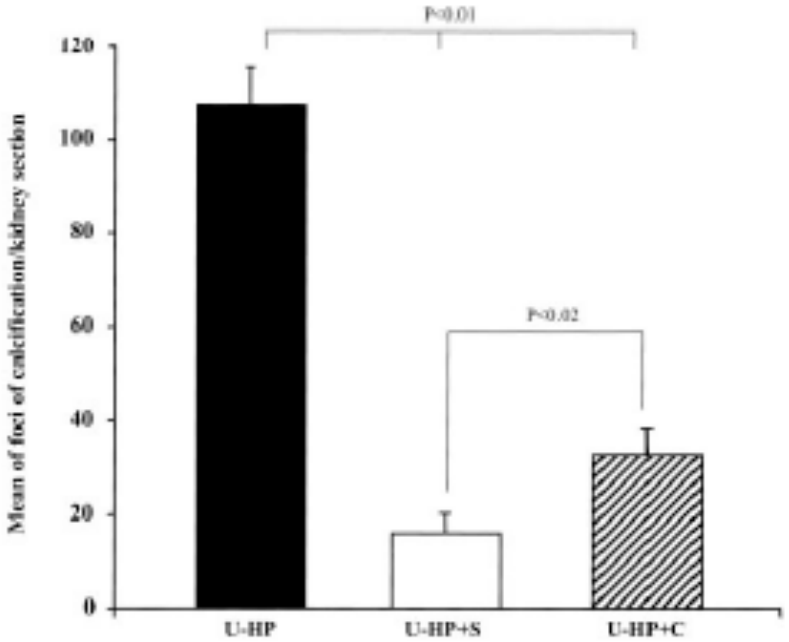
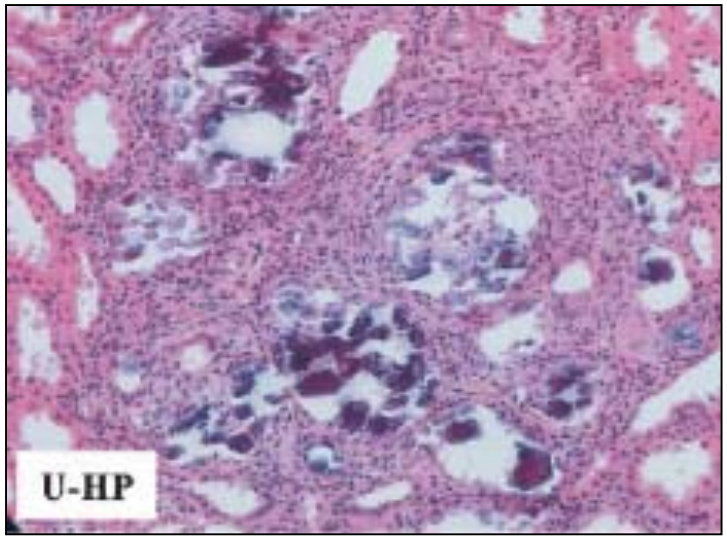


Figure 5. Effects of sevelamer and $CaCO_3$ on kidney foci of calcification. Mean of foci of calcification in remnant kidney tissue uremic (5/6-nephrectomized) rats undergoing one of the following experimental protocols for 3 mo: uremic control + high-phosphorus diet (U-HP) (closed bar); uremic + HP diet + 3% sevelamer (U-HP+S) (open bar); uremic + HP diet + 3% calcium carbonate (U-HP+C) (dashed bar). Results represent the mean and SEM from four sections/rat in five rats per group. *P* values were obtained by ANOVA and Bonferroni tests. Magnification, ×20.

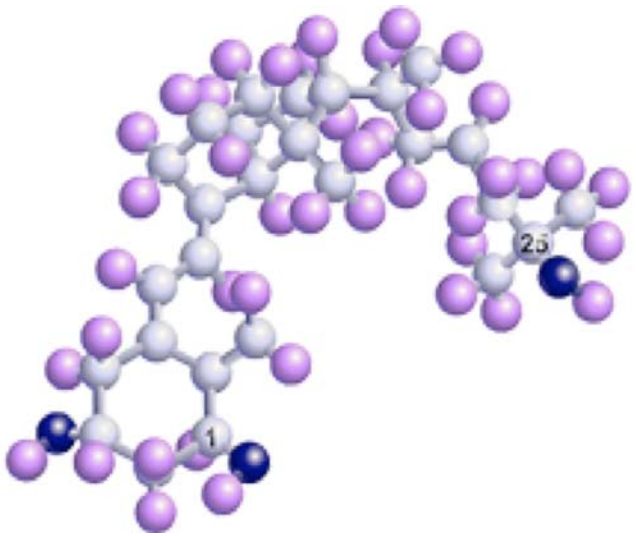


J Am Soc Nephrol 13: 2299–2308, 2002

Binder Studies

- **CARE Study - 8 week blinded study**
  - Calcium acetate more efficatious in controlling serum $P0_4$ than sevelamer
    - Kidney International 65:1914-1926, 2004
- **RIND Study 18 month trial**
  - 60 incident patients randomized to calcium binders - had progressive calcification
  - 54 to sevelamer HCL
    - Kidney International 68:1815-1824, 2005
- **LANTHANUM 6 weeks**
  - Significant drop in P04 in one week - 2250 mg/day
    - Clinical Nephrology 65:191-202, 2006

Vitamin D



- Vitamin D, especially the new analogs, confers a protective effect on patient survival
- Reasons
  - Inflammation
  - Renin-angiotensin system
  - Myocardium
  - Muscle
  - Bone (may also decrease bone pain)

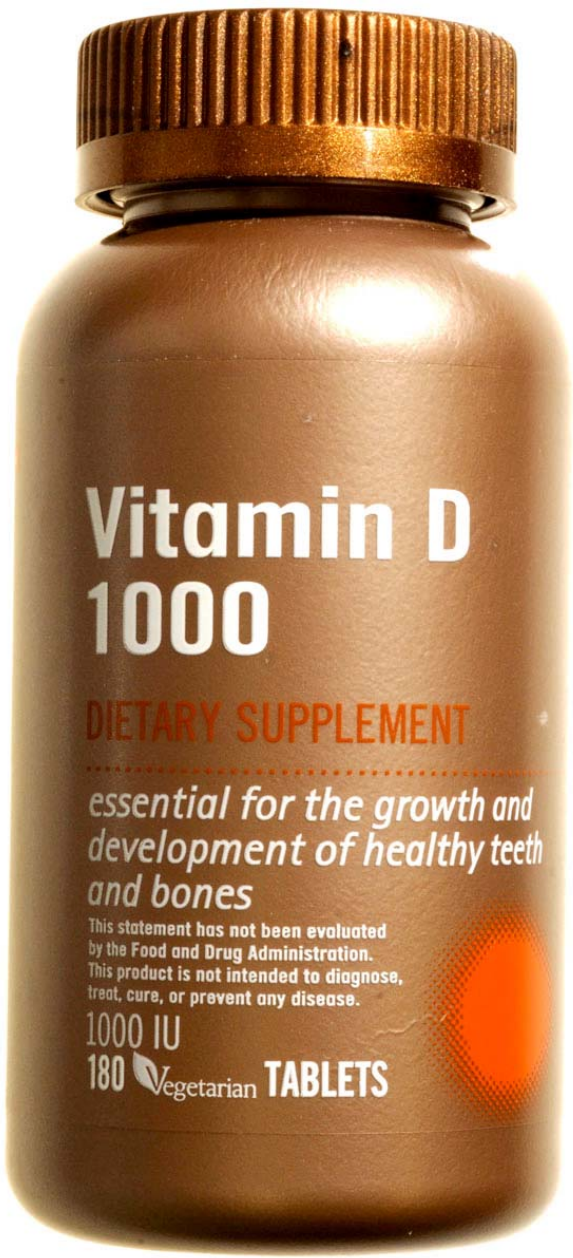
Prog Biophys Mol Biol 2006;92:4-8.
Kidney Int 2005;68:1973-81.
Hemodial Int 2005;9 Suppl 1:S25-9.

Vitamin D and Blood Pressure

- NHANES III survey
  - Representative sample of the US population between 1988 and 1994.
  - 12,644 participants with 25OHD levels and Blood Pressure measurements,
  - Systolic blood pressure was 2.7 mmHg lower (P=0.0005)
    - vitamin D levels ≥ 85.7 nmole/L compared with the lowest quintile <40.4 nmole/L when adjusted for BMI, age, sex and ethnicity.
  - Diastolic blood pressure changes were significant, but not when adjusted for BMI (p=0.013).
    - Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D and blood pressure in the Third Tational Health and Nutritional Examination Survey. Proc 13th Workshop on Vitamin D: 512006.
- Down-regulates renin production

Vitamin D Deficiency

- Calcidiol, 25(OH)D_3, low due to
  - Urban living
  - Cultural dress
  - Lack of sun explosure
  - Lack of physical activity
  - CKD population
- Limited studies evaluating the effects of supplementation with ergocalciferol or cholecalciferol
- Measure vitamin D_3 in CKD
- Treat with OTC Ergocalciferol



Exercise

- Weight bearing on bone mass - Astronauts
  - NASA Space Program
  - Trabecular bone loss was similar in space travel to that in prolonged bed rest.
- Weight-bearing exercise in postmenopausal women
  - slow or decrease a decline in bone mineral density
  - Increase trochanteric bone mineral content,
  - Reducing the risk of falls (15889312)
- Exercise in CKD - need for additional studies

Nocturnal Dialysis

mmol ($P < 0.01$)

Dietary Phosphorus Absorbed	10 and 30 mmol/day (310-930 mg/day)	100 to 210 mmol/week (3100 - 6510 mg/wk)
Conventional Hemodialysis	25.3 ± 7.5 (784.3 mg/L)	75.8 ± 22.5 (1,516 mg/L)
Nocturnal Hemodialysis	26.9 ± 9.8 (833.9 mg/L)	161.6 ± 59.0 (5,010 mg/L)

Weekly intake in ESRD around 1 gm/day
Only 40-80% absorbed
By fourth month patients were on no binders
Dietary Phosphorus intake doubled

Kidney International 53:1399-1404, 1998
Conversion from nephron.com

Nocturnal hemodialysis may slow vascular calcification

Yuen, D., et al., ***The natural history of coronary calcification progression in a cohort of nocturnal haemodialysis patients.*** **Nephrol Dial Transplant, 2006. 21(5): p. 1407-12.**

PTH caveats

- Higher PTH levels and adynamic bone disease in African Americans
- PTH may be a normal adaptation mechanism in CKD, and we may not want to over treat it
- DOPPS data does not show the strong association between PTH with mortality in K/DOQI range
- The measurement of PTH does not relate to the original Nichols Allegro assay with current Bayer Centaur or Roche Elecys assays
- Newer agents such as cinacalcet enable PTH suppression without hypercalemia
- Therefore, a high serum calcium level in a patient on cinacalcet who has a lowered PTH level could have low bone turnover disease, particularly if African American

Appendix

Aluminum hydroxide [1]
Calcium Carbonate [2]
Calcium Acetate [3]
Sevelamer [4 5]
Lanthanum [6 7 8 9 7 10 11]
Ferric citrate [12]
Magnesium [13 14]
Nicotinamide [15]
Combination binder therapy [11]
Ergocalciferol/Hydroxycholecalciferol [16]
Calcitriol [17 18 19 20 21]
Doxercalciferol [22 23 24 25 26 27 28 29]
Paricalcitol [19 30 31 32 33 34 35 36]
Cinacalcet [37 38 39 40 41 42]

1 A. C. Alfrey, A. Hegg, and P. Craswell, *Am J Clin Nutr* **33** (7), 1509 (1980).
2 E. Slatopolsky, C. Weerts, S. Lopez-Hilker et al., *N Engl J Med* **315** (3), 157 (1986).
3 W. Y. Qunibi, R. E. Hootkins, L. L. McDowell et al., *Kidney Int* **65** (5), 1914 (2004).
4 A. J. Bleyer, S. K. Burke, M. Dillon et al., *Am J Kidney Dis* **33** (4), 694 (1999).
5 R. Ramsdell, *Anna J* **26** (3), 346 (1999).
6 E. Slatopolsky, H. Liapis, and J. Finch, *Kidney Int* **68** (6), 2809 (2005).
7 A. J. Freemont, J. A. Hoyland, and J. Denton, *Clin Nephrol* **64** (6), 428 (2005).
8 M. Pennick, K. Dennis, and S. J. Damment, *J Clin Pharmacol* **46** (7), 738 (2006).
9 G. B. Spasovski, A. Sikole, S. Gelev et al., *Nephrol Dial Transplant* (2006); L. Feng, H. Xiao, X. He et al., *Toxicol Lett* **165** (2), 112 (2006).
10 W. F. Finn, *Clin Nephrol* **65** (3), 191 (2006).
11 M. Emmett, *Kidney Int Suppl* (90), S25 (2004).
12 W. C. Yang, C. S. Yang, C. C. Hou et al., *Nephrol Dial Transplant* **17** (2), 265 (2002).
13 J. A. Delmez, J. Kelber, K. Y. Norword et al., *Kidney Int* **49** (1), 163 (1996).
14 I. Zofkova and R. L. Kanceva, *Cas Lek Cesk* **136** (15), 459 (1997).
15 Y. Takahashi, A. Tanaka, T. Nakamura et al., *Kidney Int* **65** (3), 1099 (2004).
16 G. Sjoden, J. U. Lindgren, and H. F. DeLuca, *J Nutr* **114** (11), 2043 (1984); A. C. Looker, B. Dawson-Hughes, M. S. Calvo et al., *Bone* **30** (5), 771 (2002); A. Zadshir, N. Tareen, D. Pan et al., *Ethn Dis* **15** (4 Suppl 5), S5 (2005).

Appendix -2

17 K. J. Martin, H. S. Ballal, D. T. Domoto et al., *Am J Kidney Dis* **19** (6), 540 (1992).
18 I. B. Salusky, B. D. Kuizon, T. R. Belin et al., *Kidney Int* **54** (3), 907 (1998).
19 M. Teng, M. Wolf, E. Lowrie et al., *N Engl J Med* **349** (5), 446 (2003).
20 I. B. Salusky, *Pediatr Nephrol* **20** (3), 393 (2005).
21 F Tentori, WC Hunt, CA Stidley et al., *J Am Soc Nephrol* **16**, 279A (2005).
22 J. M. Frazao, L. Elangovan, H. M. Maung et al., *Am J Kidney Dis* **36** (3), 550 (2000).
23 J. M. Frazao, R. W. Chesney, and J. W. Coburn, *Nephrol Dial Transplant* **13 Suppl 3**, 68 (1998).
24 G. O. Sjoden, O. Johnell, H. F. DeLuca et al., *Acta Endocrinol (Copenh)* **106** (4), 564 (1984).
25 G. Sjoden, *Acta Orthop Scand Suppl* **217**, 1 (1985).
26 H. M. Maung, L. Elangovan, J. M. Frazao et al., *Am J Kidney Dis* **37** (3), 532 (2001).
27 M. S. Parisi, B. Oliveri, J. Somoza et al., *Clin Nephrol* **59** (6), 471 (2003).
28 Jack W. Coburn, Hla M. Maung, Logan Elangovan et al., *Am J Kidney Dis* **43** (5), 877 (2004).
29 H. F. DeLuca, *Biochem Pharmacol* **26** (7), 563 (1977).
30 K. J. Martin, E. A. Gonzalez, M. E. Gellens et al., *Am J Kidney Dis* **32** (2 Suppl 2), S61 (1998).
31 K. J. Martin, E. Gonzalez, J. S. Lindberg et al., *Am J Kidney Dis* **38** (5 Suppl 5), S57 (2001).
32 K. J. Martin and E. A. Gonzalez, *Am J Kidney Dis* **38** (6), 1430 (2001).
33 K. J. Martin and E. A. Gonzalez, *Am J Kidney Dis* **38** (5 Suppl 5), S34 (2001).
34 D. W. Coyne, M. Grieff, S. N. Ahya et al., *Am J Kidney Dis* **40** (6), 1283 (2002).
35 E. Slatopolsky, M. Cozzolino, and J. L. Finch, *Kidney Int* **62** (4), 1277 (2002).
36 D. Coyne, M. Acharya, P. Qiu et al., *Am J Kidney Dis* **47** (2), 263 (2006).
37 G. A. Block, *Kidney Int Suppl* (87), S131 (2003).
38 J. Cunningham, M. Danese, K. Olson et al., *Kidney Int* **68** (4), 1793 (2005).
39 W. G. Goodman, *Curr Opin Nephrol Hypertens* **14** (4), 355 (2005).
40 S. M. Moe, J. Cunningham, J. Bommer et al., *Nephrol Dial Transplant* **20** (10), 2186 (2005).
41 S. M. Moe, *Drugs* **65** (2), 282 (2005).
42 Sharon M. Moe, Glenn M. Chertow, Jack W. Coburn et al., *Kidney Int* **67** (2), 760 (2005).
43 G. A. Block, K. J. Martin, A. L. de Francisco et al., *N Engl J Med* **350** (15), 1516 (2004).

CKD-MBD

- **Parathyroid Hormone**
  - Epidemiology
  - Accuracy
  - Management
- **Bone Disease**
  - CKD Adaptation
  - Assessment
  - Management
- **Vascular Calcification**
  - Association with CKD-MBD
  - Assessment (Plain Films)
  - Management
- **Phosphorus Control**
  - Consequences
  - Management (Diet, Meds, Dialysis)
- **Vitamin D**
  - Vitamin D Deficiency
  - Vitamin D and Survival
  - Vitamin D in over suppression

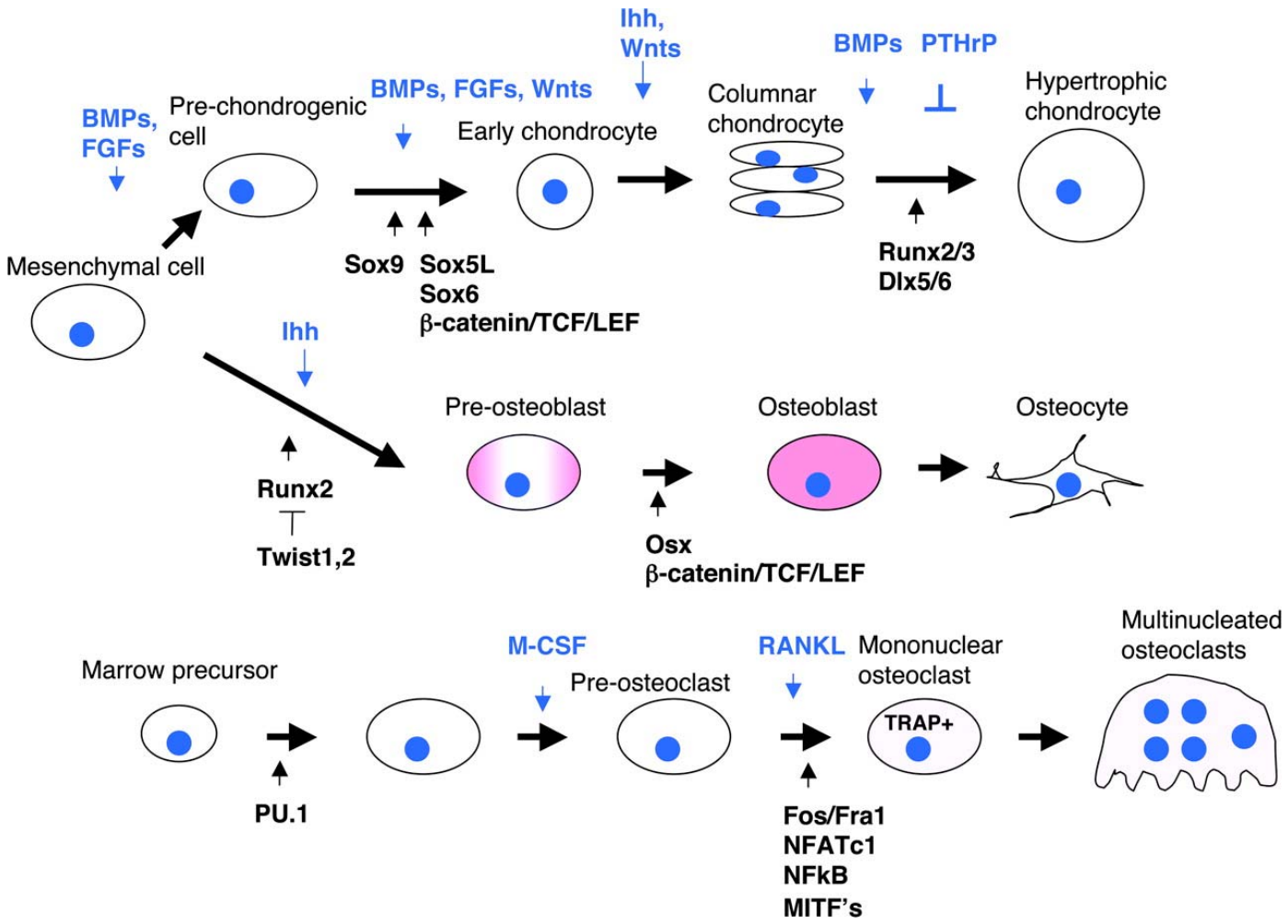
Take Away

- Vascular calcification plays a key role in CKD mortality
- Vascular calcification starts early
- We may be doing a disservice to patients by not emphasizing early phosphorus control and over suppressing PTH levels

- We should be offering nocturnal dialysis to more patients
- Vitamin D has non-skeletal functions that are ignored not only in CKD but in the general population


QUESTIONS?

FIG. 1. Differentiation of bone cells of three lineages and its regulation by transcription factors



Kobayashi, T. et al. Endocrinology 2005;146:1012-1017

Endocrinology